CLINICAL FACTORS WHICH INFLUENCE THE OPTIMUM MANAGEMENT OF PATIENTS WITH ACROMEGALY

A thesis submitted by

DR MARK SHERLOCK

For the degree of DOCTOR OF MEDICINE (M.D.)

At

THE ROYAL COLLEGE OF SURGEONS IN IRELAND

2011
Acknowledgments

There are many people who I would like to acknowledge who have provided support and assistance to me during this thesis.

Firstly, I have to thank my supervisor and mentor Professor Paul Stewart for all his help, encouragement, mentorship and guidance during my five years in Birmingham, which has continued after leaving his unit. Despite his onerous workload his door was always open and he has been supportive to me in terms of both clinical and research training and this thesis would not have been possible without him.

I would also like to thank Dr John Ayuk, Dr Andrew Bates and Professor Michael Sheppard who were involved in the initiation and maintenance of the West Midlands Pituitary Study Group and also helped with interpretation and analysis of data and critically reviewing the manuscripts, which were produced from this thesis. I would also like to thank all my clinical colleagues in the University of Birmingham, particularly Dr Andy Toogood, Professor Wiebke Arit, Professor Jayne Franklyn and Dr Jeremy Tomlinson. I would like to thank Dr Gareth Lavery whom I shared an office with for his friendship and good humour.

I would like to acknowledge the role of my RCSI supervisor, Professor Chris Thompson, who first ignited my interest in Endocrinology as a third year medical student and has mentored my personal and professional development since then.

I would like to acknowledge the role my parents (Ellen and Jim) have had, they have always supported me in my personal and professional life and also thank my sister (Audrey) and brother (James).
I would like to thank Dr Raoul Reulen and Professor Mike Hawkins of the Centre for Childhood Cancer Survivor Studies, Department of Public Health & Epidemiology, University of Birmingham, who patiently spent hours coaching me on statistical principles and trying to design novel methods of analysing risk factors for mortality in acromegaly. I am indebted to Ms Liz Jablonski who helped manage the database at the Queen Elizabeth Hospital, Birmingham, Mrs Maureen Brown who managed the database at the University Hospital of North Staffordshire and to the Department of Clinical Biochemistry, University Hospital Birmingham NHS Trust who helped greatly in the analysis of samples for this database.

The West Midlands Acromegaly Database was a collaboration between multiple centres and physicians and I would like to thank them all for their co-operation: J. A. Franklyn, A.A Toogood, N.J. Gittoes, R. Walsh, R. Mitchell, A. Johnson (Queen Elizabeth and Selly Oak Hospitals, Birmingham); R. Clayton (University Hospital of North Staffordshire); H. Connor (County Hospital, Hereford); P. Dodson (Heartlands Hospital, Birmingham); P. R. Daggett (Staffordshire District General Hospital), R. Ryder, S. Jones (City Hospital, Birmingham); D. Jenkins (Worcester Royal Infirmary); S. Walford, D. Singh (New Cross Hospital, Wolverhampton); J. Benn (Burton District Hospital); P. Davies (Sandwell Hospital); Andrew MacLeod (Telford District General Hospital); T. Harvey, and A. D. Wright (Manor Hospital, Walsall).

I am indebted to all the patients with acromegaly in the West Midlands region and hope that the results of this thesis will be of benefit to them.

On a personal level, I would like to thank Niamh for everything over the years and for agreeing to leave her beloved Dublin and come with me to Birmingham so that I could do this work. She has supported me through everything and shown unbelievable patience!
To anyone else who has helped me with this thesis (and there are too many to mention individually), a big thank you.
Summary

Acromegaly is a rare disabling disease characterised by excess growth hormone (GH) secretion and circulating insulin like growth factor-I (IGF-I) concentrations. In addition to significant morbidity, acromegaly is associated with increased mortality, which has been demonstrated in a number of retrospective studies with standardised mortality ratios (SMR) between 1.3 and 3 (comprising over 5,000 patients and 1,000 deaths).\(^{1-9}\)

Optimum management of patients with acromegaly requires appropriate investigation, treatment and defining targets for therapy that are associated with a reduction in overall morbidity and mortality in these patients. Due to the rare nature of this disease studies are often small and studies related to mortality are often multicentre (a limitation due to different growth hormone and IGF-I assays used in each centre).

With this in mind the West Midlands Acromegaly database was established in 1990 as a collaboration between 16 West Midland Endocrine centres and is centrally located at the Queen Elizabeth Hospital in Birmingham. The West Midlands region has an overall population of 5.7 million. To ensure optimum patient ascertainment, all patients with a diagnosis of acromegaly in each of the referral centres were flagged by physicians. Also, all patients with an elevated GH or IGF-I measurement in the Regional Endocrine laboratory at Selly Oak Hospital Birmingham were also flagged and their case notes assessed for a diagnosis of acromegaly. The Regional Endocrine laboratory at Selly Oak Hospital Birmingham is the regional centre for GH and IGF-I assays these assays, therefore all samples in the study were analysed here. Follow up biochemical and clinical data was recorded in the database. With this data the aims of this thesis were as follows:
1. Does a basal fasting GH reliably predict the nadir GH during an OGTT or mean GH during a GHDC in the assessment of disease activity during follow up in patients with acromegaly?

2. What is the degree of discordance between disease activity measured by GH and IGF-I values?

3. Does exposure to radiotherapy have any effect on the above relationships?

4. To evaluate the role of baseline prolactin concentrations (and tumour immunohistochemical staining), prior surgery or radiotherapy and pituitary hormonal deficiencies in the response of GH and IGF-I to dopamine agonist therapy and somatostatin analogue therapy.

5. Assess the relative efficacy of dopamine agonist therapy compared to somatostatin analogue therapy in patients with acromegaly, in routine clinical practice.

6. To determine the efficacy of SSA in clinical practice compared to that observed in clinical trials (and the relative efficacy of subcutaneous versus long acting preparations of SSA).

7. To assess the role of radiotherapy on mortality in patients with acromegaly

8. To assess the role of hypopituitarism (in particular the effect of individual pituitary axis deficiency) and their replacement on mortality

9. To assess the targets for GH and IGF-I which normalize mortality and assess newer ways of assessing the role of GH/IGF-I in mortality in acromegaly.
# Index

List of Figures | 1  
List of Tables | 4  
Published Manuscripts arising from this thesis | 6  
Selected abstracts arising from this thesis | 6  

## Chapter 1 – Introduction  

1.1 Epidemiology of Acromegaly  
1.2 Historical background  
1.3 Clinical features of Acromegaly  
1.4 GH and IGF-I physiology  
1.4.1 Regulation of GH secretion and synthesis  
1.4.1.1 Growth Hormone Releasing Hormone  
1.4.1.2 Somatostatin  
1.4.1.3 Pulsatile GH release and factors influencing GH release  
1.4.2 Insulin like Growth Factor-I  
1.5 Somatotroph adenoma pathogenesis  
1.6 Diagnosis of Acromegaly  
1.6.1 GH in the diagnosis of Acromegaly  
1.6.2 IGF-I in the Diagnosis of Acromegaly
1.7 Treatment options in Acromegaly
21
1.7.1 Surgery for Acromegaly
21
1.7.1.1 History of Pituitary Surgery for Acromegaly
21
1.7.1.2 Surgical classification and planning
22
1.7.2 Radiotherapy for acromegaly
23
1.7.2.1 Radiotherapy techniques
23
1.7.2.2 Pituitary Radiotherapy for Acromegaly
24
1.7.2.3 Mortality following pituitary radiotherapy
25
1.7.2.3.1 Introduction
25
1.7.2.3.2 Cerebrovascular morbidity and mortality following pituitary radiotherapy
25
1.7.2.3.3 Hypopituitarism following pituitary radiotherapy
26
1.7.2.3.3 Mechanisms of radiation injury
27
1.7.2.3.4 Secondary oncogenesis following pituitary radiotherapy
29
1.7.3 Medical therapy for acromegaly
30
1.7.3.1 Introduction
30
1.7.3.1 Somatostatin Receptor Ligand (SRL) therapy
32
1.7.3.1.1 Somatostatin receptor interaction
32
1.7.3.1.2 Pharmacological aspects
32
1.7.3.1.3 Biochemical control
33
1.7.3.1.3.1 Subcutaneous octreotide
33
1.7.3.1.3.2 Long-acting SRL
34
1.7.3.1.4 Antitumoral effects
35
1.7.3.1.5 Primary Medical Therapy
37
1.7.3.1.6 Pre-operative somatostatin analogue therapy
38
1.7.3.1.7 Adverse effects of SRL therapy
39
1.7.3.2 Dopamine agonists
39
1.7.3.2.1 Bromocriptine
40
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7.3.2.2</td>
<td>Cabergoline</td>
<td>40</td>
</tr>
<tr>
<td>1.7.3.2.3</td>
<td>Predictive value of hyperprolactinemia</td>
<td>41</td>
</tr>
<tr>
<td>1.7.3.2.4</td>
<td>Adverse effects of dopamine agonists</td>
<td>42</td>
</tr>
<tr>
<td>1.7.3.2.5</td>
<td>Tumor shrinkage on dopamine agonist therapy</td>
<td>43</td>
</tr>
<tr>
<td>1.7.3.3</td>
<td>Pegvisomant</td>
<td>43</td>
</tr>
<tr>
<td>1.7.3.3.1</td>
<td>Introduction</td>
<td>43</td>
</tr>
<tr>
<td>1.7.3.3.2</td>
<td>Efficacy of pegvisomant</td>
<td>44</td>
</tr>
<tr>
<td>1.7.3.3.3</td>
<td>Use in SRL-treatment resistance</td>
<td>46</td>
</tr>
<tr>
<td>1.7.3.3.4</td>
<td>Tumor growth while taking pegvisomant</td>
<td>46</td>
</tr>
<tr>
<td>1.7.3.3.5</td>
<td>Adverse effects of pegvisomant</td>
<td>47</td>
</tr>
<tr>
<td>1.7.3.4</td>
<td>Newer agents for the treatment of Acromegaly</td>
<td>48</td>
</tr>
<tr>
<td>1.7.3.4.1</td>
<td>Pasireotide (SOM230)</td>
<td>48</td>
</tr>
<tr>
<td>1.7.3.4.2</td>
<td>Chimeric molecules</td>
<td>50</td>
</tr>
<tr>
<td>1.7.3.5</td>
<td>Conclusions</td>
<td>50</td>
</tr>
<tr>
<td>1.8</td>
<td>Morbidity associated with Acromegaly</td>
<td>51</td>
</tr>
<tr>
<td>1.8.1</td>
<td>Cardiovascular morbidity in acromegaly</td>
<td>51</td>
</tr>
<tr>
<td>1.8.1.1.</td>
<td>Acromegalic Cardiomyopathy</td>
<td>51</td>
</tr>
<tr>
<td>1.8.1.2.</td>
<td>Cardiac Valve disease in acromegaly</td>
<td>52</td>
</tr>
<tr>
<td>1.8.1.3</td>
<td>Rhythm disturbances in acromegaly</td>
<td>54</td>
</tr>
<tr>
<td>1.8.1.4</td>
<td>Hypertension in acromegaly</td>
<td>54</td>
</tr>
<tr>
<td>1.8.1.5</td>
<td>Atherosclerosis and endothelial dysfunction</td>
<td>55</td>
</tr>
<tr>
<td>1.8.2</td>
<td>Respiratory Complications of Acromegaly</td>
<td>55</td>
</tr>
<tr>
<td>1.8.3</td>
<td>Metabolic complications of acromegaly</td>
<td>57</td>
</tr>
<tr>
<td>1.9</td>
<td>Mortality in Acromegaly</td>
<td>58</td>
</tr>
<tr>
<td>1.9.1</td>
<td>Studies of mortality in acromegaly</td>
<td>58</td>
</tr>
<tr>
<td>1.9.2</td>
<td>Impact of GH levels on mortality in acromegaly</td>
<td>62</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1.9.3</td>
<td>Impact of IGF-I levels on mortality in acromegaly</td>
<td>65</td>
</tr>
<tr>
<td>1.9.4</td>
<td>Assay variability in studies of mortality in acromegaly</td>
<td>66</td>
</tr>
<tr>
<td>1.9.5</td>
<td>Role of pituitary radiotherapy on mortality in acromegaly</td>
<td>67</td>
</tr>
<tr>
<td>1.9.6</td>
<td>Role of pituitary dysfunction on mortality in acromegaly</td>
<td>68</td>
</tr>
<tr>
<td>1.9.7</td>
<td>Cancer mortality in acromegaly</td>
<td>68</td>
</tr>
<tr>
<td>1.9.8</td>
<td>Other factors influencing mortality in acromegaly</td>
<td>70</td>
</tr>
<tr>
<td>1.10</td>
<td>Mortality in Hypopituitarism</td>
<td>72</td>
</tr>
<tr>
<td>1.10.1</td>
<td>Introduction</td>
<td>72</td>
</tr>
<tr>
<td>1.10.2</td>
<td>All cause mortality in hypopituitarism</td>
<td>74</td>
</tr>
<tr>
<td>1.10.3</td>
<td>Specific cause mortality</td>
<td>78</td>
</tr>
<tr>
<td>1.10.3.1</td>
<td>Vascular death</td>
<td>78</td>
</tr>
<tr>
<td>1.10.3.1.1</td>
<td>Insulin sensitivity</td>
<td>80</td>
</tr>
<tr>
<td>1.10.3.2</td>
<td>Lipid abnormalities</td>
<td>81</td>
</tr>
<tr>
<td>1.10.3.3</td>
<td>Blood pressure</td>
<td>82</td>
</tr>
<tr>
<td>1.10.3.4</td>
<td>Vascular structure and function</td>
<td>83</td>
</tr>
<tr>
<td>1.10.3.2</td>
<td>Malignancy</td>
<td>84</td>
</tr>
<tr>
<td>1.10.3.3</td>
<td>Respiratory and Respiratory tract infections</td>
<td>85</td>
</tr>
<tr>
<td>1.10.4</td>
<td>Role of ACTH deficiency and glucocorticoid replacement</td>
<td>86</td>
</tr>
<tr>
<td>1.10.4.1</td>
<td>Dosage of glucocorticoid replacement</td>
<td>86</td>
</tr>
<tr>
<td>1.10.4.2</td>
<td>Mode of glucocorticoid delivery</td>
<td>88</td>
</tr>
<tr>
<td>1.10.4.3</td>
<td>Tissue metabolism of glucocorticoids</td>
<td>89</td>
</tr>
<tr>
<td>1.10.4.4</td>
<td>Role of GH deficiency and replacement</td>
<td>90</td>
</tr>
<tr>
<td>1.10.5</td>
<td>Role of TSH deficiency and replacement</td>
<td>92</td>
</tr>
<tr>
<td>1.10.6</td>
<td>Role of Sex steroid deficiency and replacement</td>
<td>93</td>
</tr>
<tr>
<td>1.10.7</td>
<td>Role of underlying aetiology in mortality in hypopituitarism</td>
<td>94</td>
</tr>
<tr>
<td>1.10.8</td>
<td>Other factors contributing to mortality in hypopituitarism</td>
<td>95</td>
</tr>
<tr>
<td>1.11</td>
<td>Aims</td>
<td>96</td>
</tr>
</tbody>
</table>
Chapter 2 - Study Design, Methods and Participants

2.1 Participants

2.2 GH Assays

2.2.1 GH assay used in this study

2.2.2 GH Assays general description

2.2.3 Comparability of GH assay results

2.2.4 Factors contributing to GH assay heterogeneity

2.3 IGF-I Assays

2.3.1 IGF-I Assays used in this study

2.3.2 IGF-I Assays – General Description

2.4 Diagnosis of ACTH Deficiency

2.5 Diagnosis of TSH deficiency

2.6 Diagnosis of hyperprolactinaemia

2.7 Diagnosis of FSH and LH deficiency

2.8 Statistical Methods

2.8.1 Standardised Mortality Ratios (SMRs)

2.8.2 Poisson regression

2.8.3 Other Statistical Methods

2.9 Descriptive Statistics

2.9.1 Therapy received

2.9.2 Endocrinology at baseline

2.9.2.1 IGF-I at baseline

2.9.2.2 GH at baseline

2.9.2.3 Relationship between GH and IGF-I at baseline

2.9.2.4 Pituitary function at diagnosis
Chapter 3 - Monitoring disease Activity using GH and IGF-I in the follow up of 501 patients with Acromegaly

3.1 Abstract
3.2 Introduction
3.3 Patients and methods
3.3.1 Patients
3.3.2 Endocrine Evaluation
3.3.3 Statistical Analysis
3.4 Results
3.4.1 The association between basal fasting GH and nadir GH during OGTT /mean GH during GH
3.4.2 Discordance between disease activity as assessed by GH values and IGF-I status
3.4.3 Changes in relationship between basal GH and nadir/ mean GH on OGTT/ GHDC and IGF-I in patients receiving radiotherapy as assessed by GH values and IGF-I status.
3.5 Discussion
3.6 Conclusion
Chapter 4 - Medical therapy in patients with Acromegaly; predictors of response and comparison of efficacy of dopamine agonists and somatostatin analogues.

4.1 Abstract
4.2 Introduction
4.3 Aims of Study
4.4 Patients and Methods
4.4.1 Patients
4.4.2 Endocrine Evaluation
4.4.3 Statistical Analysis
4.5 Results
4.5.1 Dopamine agonist group
4.5.2 Somatostatin analogue group
4.5.3 Effect of Pituitary Hormone deficiency on response to medical therapy
4.6 Discussion
4.6.1 Dopamine agonists
4.6.2 Somatostatin Analogue Therapy
4.6.3 Pituitary Hormone Deficiency
4.7 Conclusions
Chapter 5 - ACTH deficiency, higher doses of hydrocortisone replacement and radiotherapy, are independent predictors of mortality in patients with acromegaly.

5.1 Abstract

5.2 Introduction

5.3 Patients and methods

5.3.1 Patients

5.3.2 Endocrine evaluation

5.3.3 Statistical Analysis

5.3.3.1 Standardised Mortality Ratios

5.3.3.2 Poisson regression

5.4 Results

5.4.1 Overall group

5.4.2 The effect of pituitary irradiation on mortality

5.4.3 The effect of pituitary hormone deficiency on mortality

5.4.4 The effect of hydrocortisone dose on mortality

5.5 Discussion

5.6 Conclusions
Chapter 6 - A Paradigm Shift in the monitoring of patients with Acromegaly: Last available growth hormone overestimates

6.1 Abstract
6.2 Introduction
6.3 Patients and Methods
6.3.1 Patients
6.3.2 Endocrine evaluation
6.3.3 Statistical Analysis
6.3.3.1 External analysis – Standardized Mortality ratios
6.3.3.2 Internal analysis – Poisson regression
6.4 Results
6.4.1 Mortality
6.4.2 Comparison of last available vs. time-dependent (instantaneous) GH on mortality
6.4.3 Mortality based on ranges of GH
6.4.4 Comparison of last available vs. instantaneous IGF-I
6.4.5 The Effect of cumulative GH on mortality
6.5 Discussion
6.5.1 Impact of GH levels on mortality in acromegaly
6.5.2 Impact of IGF-I levels on mortality in acromegaly
6.6 Conclusion

Chapter 7 - Conclusions and General Discussion
List of Figures

Chapter 1 – Nil

Chapter 2

Figure 2.1 - Referral Centres in West Midlands Acromegaly Database.

Figure 2.2 - Distribution of IGF-I at diagnosis in patients with acromegaly.

Figure 2.3 - Distribution of GH at diagnosis in patients with acromegaly.

Figure 2.4 - Relationship between GH and IGF-I at baseline.

Figure 2.5 - Distribution of prolactin concentrations at diagnosis.

Chapter 3

Figure 3.1 - Correlation between basal GH and GH nadir/ mean during oral glucose tolerance test (OGTT) and growth hormone day curve (GHDC) in all patients.

Figure 3.2 - Altman-Bland analysis of comparison between basal GH and GH nadir during oral glucose tolerance test (OGTT) (3.2a) and basal GH and mean GH during growth hormone day curve (GHDC) (3.2b).

Figure 3.3 - Correlation between mean and basal GH during GHDC in radiotherapy naïve patients (3.3a) and patients following radiotherapy (3.3b) and nadir and basal GH during OGTT in radiotherapy naïve patients (3.3c) and patients following radiotherapy (3.3d).

Figure 3.4 - Effect of radiotherapy on discordance between GH and IGF-I during oral glucose tolerance test.
Figure 3.5 - Algorithm for assessment of GH in the follow up of patients with acromegaly.

Chapter 4

Figure 4.1 - Effect of prior radiotherapy on percentage reduction of GH to dopamine agonist therapy.

Figure 4.2 - Effect of prior surgery on percentage reduction of GH and IGF-I to dopamine agonist therapy.

Figure 4.3 - Effect of elevated prolactin on percentage reduction of GH and IGF-I to dopamine agonist therapy.

Figure 4.4 - Effect of Dopamine agonist and somatostatin analogue therapy on the percentage reduction in GH and IGF-I.

Figure 4.5 - Effect of prior radiotherapy on percentage reduction of GH and IGF-I to somatostatin analogue therapy.

Figure 4.6 - Effect of prior surgery on percentage reduction of GH and IGF-I to somatostatin analogue therapy.

Chapter 5 – Nil

Chapter 6

Figure 6.1(a) - Clinical course of 3 patients (A, B, C) demonstrating that not all patients will arrive at the same last available GH level by similar clinical courses.

Figure 6.1(b) - Shows the difference in cumulative GH exposure (as assessed by area under the curve) between the 3 patients.
Figure 6.2 - A single patient may contribute years of follow up at a particular GH level to many different levels of GH using the instantaneous GH method.

Chapter 7 – Nil
List of Tables

Chapter 1

Table 1.1a. Studies assessing disease specific mortality rates in patients with acromegaly (pre year 2000).
Table 1.1b. Studies assessing disease specific mortality rates in patients with acromegaly (post year 2000).
Table 1.2 - The role of GH and IGF-I on mortality in acromegaly.
Table 1.3 - Studies assessing the role of pituitary radiotherapy in mortality in patients with acromegaly.
Table 1.4 - Relative prevalence of individual pituitary axis deficiency (and replacement) in studies assessing mortality in hypopituitarism.
Table 1.5 - Standardized mortality ratios for all cause and specific cause mortality for the published studies in hypopituitarism.

Chapter 2 – Nil

Chapter 3

Table 3.1 - The predictive value of basal GH indicating degrees of disease activity with respect to GH nadir on OGTT and mean GH on GHDC.

Table 3.2 - Discordance between disease activity as assessed by GH (basal or nadir / mean GH during OGTT/ GHDC) and IGF-I values.

Table 3.3 - Effect of radiotherapy on predictive value of basal GH compared to nadir/ mean GH OGTT or GHDC.

Table 3.4 - Effect of radiotherapy on the discordance between disease activity assessed by GH and IGF-I concentrations.
Chapter 4

Table 4.1 - Comparison between baseline prolactin, GH and IGF-I levels depending on medical therapy, surgery and radiotherapy.

Chapter 5

Table 5.1 - Cause of death in all patients (n=501, deaths 162) compared to the general population.
Table 5.2 - Effect of radiotherapy on mortality in patients with acromegaly. External analysis compared to the general population.
Table 5.3 - Cause of death in acromegaly cohort divided according to radiotherapy exposure.
Table 5.4 - Effect of pituitary axis deficiency of mortality compared to the general population.
Table 5.5 - Effect of pituitary axis deficiency of mortality.
Table 5.6 - Effect of increasing dose of hydrocortisone replacement of mortality in patients with acromegaly compared to the general population.

Chapter 6

Table 6.1 - All cause mortality in patients with acromegaly according to whether a patient was above or below arbitrary GH cut off.
Table 6.2 - All cause mortality in patients with acromegaly according to range of GH, using two methods of analysis.
Table 6.3 - All cause mortality in patients with acromegaly according to the level of IGF-I using two methods of analysis.
Table 6.4 - All cause mortality in patients with acromegaly according to quartile of IGF-I using two methods of analysis.
Table 6.5 - Effect of level of cumulative exposure to GH on all cause mortality and effect of radiotherapy on this effect.
Published Manuscripts arising from this thesis:


Selected abstracts arising from this thesis:

1. **Mark Sherlock**, Raoul C Reulen, Aurora Aragon Alonso, John Ayuk, Mike M Hawkins, Michael C Sheppard, Andrew Bates, Paul M Stewart. Follow up GH levels but not IGF-I are useful in predicting mortality in acromegaly;
however current targets for GH may be too high. **Oral presentation at the Irish Endocrine Society, 2009.**

2. **Mark Sherlock**, Raoul C Reulen, Aurora Aragon Alonso, John Ayuk, Mike M Hawkins, Michael C Sheppard, Andrew Bates, Paul M Stewart. Follow up GH levels but not IGF-I are useful in predicting mortality in acromegaly; however current targets for GH may be too high. **Oral presentation at the Endocrine Society Meeting, Washington, 2009.**


Chapter 1

Introduction
1.1 Epidemiology of Acromegaly

Acromegaly is a rare condition characterised by chronic supraphysiological GH secretion with resultant excess production of IGF-I, which is due to a pituitary adenoma in 99% of cases. Acromegaly may rarely be due to a hypothalamic tumor secreting GHRH or ectopic GHRH secretion from a carcinoid tumor. The incidence of acromegaly is 3-4 per million per year, with a prevalence of approximately 60 per million. There is no difference in race, gender or ethnicity in patients with the condition. The mean age at diagnosis of acromegaly is approximately 44 years but the range encompasses the entire lifespan with GH hypersecretion being recorded from infancy to old age. Due to the insidious nature of the disease and its symptoms, the average delay between onset of symptoms or changes in photographic appearances to diagnosis averages 8 years (range 6.6-10.2 years).

1.2 Historical background

Acromegaly was first described as a clinical syndrome by Pierre Marie in 1886 who described visceromegaly and enlarged pituitaries at the autopsy of two patients he treated at the Salpetriere hospital in Paris. He subsequently reported a case series of 48 patients with acromegaly, many derived from previous case histories of patients described by other physicians. One such case was described by Verga in 1864 as prosopectasia and is believed to be the first case of a pituitary tumour described. Pierre Marie had no definite ideas regarding the aetiology of acromegaly. However, around the same time Souza-Leite published his thesis in 1890 which described seven cases of acromegaly and described an enlarged sella turcica with a pituitary ranging in size from a pigeon's egg to that of an apple, however, he did not make the link and felt the pituitary enlargement was in parallel
to the visceromegaly seen in other organs. In 1887 Oscar Minkowski was the first to suggest that this pituitary enlargement was the cause of the acromegaly (but he was unsure if this pituitary enlargement was the cause of the visceromegaly or reflected the visceromegaly elsewhere in the body). Massalango in 1892 and Benda in 1900 both suggested that the pituitary was the cause of the disease. However, it was only in 1909 that Harvey Cushing showing clinical improvement following partial hypophysectomy, that the pituitary was definitively shown to be the origin of this disease. Cushing was not the first person to perform neurosurgery on a patient with acromegaly as in 1893 Caton and Paul from Liverpool operated on a lady with acromegaly to relieve pressure (removal of part of the skull vault) but the pituitary was not operated on.

1.3 Clinical features of Acromegaly

The clinical features of acromegaly can range from subtle signs to florid features and depends on the duration and severity of the disease. If growth hormone excess occurs before the closure of epiphyseal growth plates then accelerated growth and gigantism occurs (this bone growth is often further exacerbated by co-existing gonadotrophin deficiency thus reducing the effect of sex steroids on fusion of long bone epiphysis). If the GH excess occurs following fusion of epiphyseal plates then longitudinal growth is not a feature and the patient develops signs of acromegaly.

Local tumour effects include compression of normal pituitary tissue with resultant hypopituitarism (with resulting signs and symptoms) and hyperprolactinaemia (this can be due to stalk effect or co-secretion of prolactin from GH secreting tumour). Other local tumour effects include visual field defects, cranial nerve palsies and headaches.
Classical clinical signs of acromegaly include those of acral overgrowth, soft tissue swelling, carpal tunnel syndrome, acanthosis nigricans, skin tags, proximal myopathy, frontal bossing, visual field disturbance (if due to a macroadenoma with suprasellar extension), macroglossia, interdental splaying, jaw malocclusion and dental indentation of the tongue, prognathism, goitre and osteoarthritis.

Clinical symptoms include arthralgias, headaches, renal colic, hyperhydrosis, symptoms of obstructive sleep apnoea and a history of diabetes mellitus, hypertension and respiratory and cardiac failure.

1.4 GH and IGF-I physiology

1.4.1 Regulation of GH synthesis and secretion

The primary source of circulating GH is the somatotrophs of the anterior pituitary gland however it is also synthesised in other tissues including reproductive tissues, lymphoid tissues and the gastrointestinal tract. GH secretion from the anterior pituitary gland is pulsatile and is composed of two parts, regular GH pulses that account for the majority of the GH mass released, superimposed upon low-level tonic GH secretion. GH pulses occur approximately every three hours and have a diurnal pattern, the majority of GH being released at night particularly during slow wave sleep (sleep stages 2 and 3). Normal GH secretion is characterised by minimal basal secretion and highly regulated secretory episodes. 70-80% of GH measurements during a 24-hour period are below the level of detection of conventional immunoassays. The ultradian rhythm of GH secretion is generated by a co-ordinated interaction between GHRH and somatostatin. There are many other physiological regulators of GH secretion including stress, exercise, nutritional
status, body composition, glycaemic control, hormones, neurotransmitters and neuropeptides. 

GH has a short plasma half-life of 14 minutes and circulates bound to two circulating binding proteins, a high affinity 60-kd and low affinity 20-kd binding protein. The 60-kd BP corresponds to the extracellular domain of the hepatic GH receptor. The main functions of these BP is to dampen down the oscillations in GH associated with the pulsatile nature of GH release and to prolong the half life of GH by decreasing its renal clearance.

The pulsatility of GH secretion is a product of the action of two hypothalamic hormones GHRH and somatostatin on the somatotroph. For a detailed review of the regulation of GH synthesis and secretion see Giustina and Veldhuis.

1.4.1.1 Growth Hormone Releasing Hormone (GHRH)

GHRH is a peptide hormone, which is synthesised in the arcuate and ventromedial nuclei of the hypothalamus and is then released into the hypophyseal portal circulation. There are 2 isoforms of GHRH found in the hypothalamus; GHRH_{1-40} and GHRH_{1-44} (the first part of the peptide sequence being identical with modifications to the C-terminal). It is also synthesised in a number of other tissues, particularly the gut that accounts for the majority of the GHRH measured in serum.

GHRH has a half life in the circulation of 6.8 minutes as it is inactivated by a circulating dipeptidylaminopeptidase. It acts via the GHRH receptor, a seven transmembrane, G protein linked receptor (a member of the secretin family of G-coupled receptors) present on the somatotroph and promotes both GH synthesis and release. The importance of GHRH in the control of GH synthesis and secretion has been highlighted by elegant experiments using passive immunization.
with antibodies against GHRH in rodents \(^{20}\) or the acute and chronic infusion of a GHRH antagonist \(^{21,22}\) both of which abolish GH synthesis, secretion and pulsatility.

### 1.4.1.2 Somatostatin

Somatostatin is a cyclic peptide of 14 amino acids and is synthesised in many tissues and acts as both a hormone and a neurotransmitter \(^{23}\). In the hypothalamus somatostatin is synthesised in the periventricular and paraventricular nuclei. The axons of the periventricular nuclei project to the median eminence and terminate near the portal capillaries \(^{23}\) where somatostatin is released into the portal circulation. The main effect of somatostatin on the somatotroph is to inhibit GH release without inhibiting GH synthesis \(^{19}\). There are 5 somatostatin receptor subtypes, somatostatin action at subtype 5 appears to be the most important inhibitor of GH release \(^{24,25}\), however it also inhibits TSH release from thyrotrophs \(^{23,24}\) and prolactin release from lactotrophs in female animals \(^{24,26}\). In addition to its direct effects on GH release somatostatin has been identified as a neurotransmitter implicated in the regulation of sleep patterns and appetite \(^{23}\), which can both have an indirect effect on GH release.

### 1.4.1.3 Pulsatile GH Release and Factors influencing GH release

GHRH and somatostatin work in tandem to produce the characteristic pulsatile 24-hour GH profile. Blocking the effect of GHRH by passive immunization using anti-GHRH antibodies or GHRH receptor antagonists abolishes the pulsatility and greatly reduces the tonic component of GH secretion \(^{19,20,27}\). Somatostatin appears to modulate the amplitude of the GH pulse. In humans and rodents the GH
response to exogenous GHRH is variable \(^{28,29}\), however immunization against somatostatin in rats removes this variability \(^{28}\). This led to the hypothesis that a GH peak occurs when a GHRH peak coincides with a somatostatin nadir, this is supported by human studies which show abrupt, consistent and repeatable GH secretion following withdrawal of an intravenous somatostatin infusion \(^{30}\). In sheep and rats direct sampling of the hypophyseal portal vessels have demonstrated a significant relationship between GH release and GHRH pulses however a clear relationship with somatostatin nadirs was not always evident \(^{17,31}\).

GH exerts a negative feedback on its own secretion via GH receptors expressed by somatotrophs in the anterior pituitary and in multiple hypothalamic nuclei (arcuate, dorsomedial, paraventricular and periventricular) which produce GHRH and somatostatin \(^{32,33}\). In vitro studies have shown that GH stimulates somatostatin release from cultured rat hypothalami \(^{34}\). This negative feedback is rapid, within three hours of administration of exogenous GH the GH secretion in response to GHRH is inhibited (prior to a significant change in IGF-I), indicating that GH itself has a negative feedback on its own secretion \(^{35}\).

IGF-I also inhibits GH release \(^{36}\), an infusion of recombinant IGF-I leading to a drop in mean GH from 6.3 +/- 1.6 : 0.59 +/- 0.07micrograms/litre after 120 minutes (GH secretion rates decreased with a t1/2 of 16.6 minutes). This effect is probably via a direct effect of IGF-I on the IGF-I receptor in the pituitary rather than at the hypothalamic level or due to the insulin like metabolic actions of IGF-I. In cultured rat pituicytes, IGF-I down regulated GH mRNA expression, inhibited the 3-fold increase in GH mRNA induced by 1nM GHRH and reduced the amount of GH released \(^{37}\). The hypothalamic effects of IGF-I are uncertain, it has been shown to increase somatostatin mRNA synthesis and peptide release from incubated rat hypothalami \(^{36,39}\), however the effects of IGF-I on GHRH are less clear, increasing GHRH in one study \(^{38}\) and decreasing in another \(^{40}\).
1.4.2 Insulin like Growth factor-I (IGF-I)

IGF-I is a growth hormone dependant growth factor produced in a number of tissues but predominantly in the liver. IGF-I circulates attached to a number of IGF binding proteins (IGFBP 1-6), which are regulated by GH to varying degrees. The most biologically important of these binding proteins is IGFBP-3.\(^1\)

In healthy subjects without hypothalamic pituitary disease serum IGF-I levels are constant during the daytime and fall by 30% at night\(^2\) just before the onset of the nocturnal rise in GH secretion and rise progressively thereafter until 1100-1200 hours at which time they plateau. Nutritional status plays an important role in the synthesis and release of IGF-I, fasting over several days causes a rapid decrease in serum IGF-I which is rapidly returned to normal on refeeding.

IGF-I levels are also dependant on a number of other hormone factors including sex steroids (which may play an important role in age dependant decrease in IGF-I and will be discussed in detail later), thyroxine and glucocorticoids. Hypothyroidism is associated with a decrease in IGF-I, replacement of thyroxine leads to an increase in IGF-I and an increase in GH response to GHRH\(^3\). Glucocorticoids (dexamethasone 2mg twice daily for 4 days) cause an elevation in IGF-I with a smaller but significant increase in IGFBP3, no change in IGF-II and a decrease in IGFBP1 and 2\(^4,5\).

1.5 Somatotroph adenoma pathogenesis

A broad spectrum of changes in growth factor levels can induce a cascade of genetic events, which ultimately lead to pituitary cell transformation, and the genesis of a somatotroph adenoma. Genetic changes in somatotroph adenomas can also occur on the background of chromosomal instability, epigenetic alterations and mutations\(^6\). A number of genes have been implicated including mutations of
the alpha subunit of the stimulatory G protein which confers constitutive activation of cAMP in approximately 40% of somatroph tumours \(^{46}\). Expression of a proapoptotic factor, growth arrest and DNA damage-inducible (GADD) 45 g protein has also been reported to be lost in growth hormone secreting adenomas \(^{47}\).

Hypothalamic and paracrine GHRH and somatostatin as well as growth factors facilitate the expansion of the population of somatotroph tumour cells \(^{8}\). Over expression of the pituitary tumour transforming gene protein (PTTG) has been reported in growth hormone secreting adenomas (the expression in one study correlates with tumour size) \(^{48}\). To investigate this link, mice with targeted pituitary transgenic over-expression of nuclear regulatory proteins were developed, these mice develop growth hormone expressing pituitary tumours \(^{48,49}\).

There are four clinical genetic syndromes, which have provided key insights into the molecular basis of pituitary tumourogenesis: Multiple endocrine neoplasia type 1 (MEN1), Carney complex, familial acromegaly and McCune-Albright syndrome. MEN1 is caused by germline mutations in MEN1 (menin) gene and rarely cyclin-dependant kinase inhibitor CDKN1B. Carney Complex is due to genetic defects in one of the regulatory subunits of PKA (regulatory subunit type 1 alpha (PRKAR1A)). Familial acromegaly is caused by a mutation in the aryl hydrocarbon receptor-interacting protein (AIP). McCune-Albright syndrome results from a somatic mutation in the adenylate cyclise-stimulating G alpha protein (GNAS complex locus, GNAS) \(^{50}\). Other rare causes of acromegaly include excess GHRH by hypothalamic tumours or ectopic secretion of GH or GHRH by neuroendocrine tumours. In patients with GHRH secreting tumours there is generalised somatotroph hyperplasia with maintenance of GH pulsatility however the amplitude and frequency of GH pulses are greater than normal thus leading to supraphysiological levels \(^{51,52}\). The development and proliferation of somatotrophs are largely determined by a gene called the Prophet of Pit-1 (PROP1), which controls the
embryonic development of cells of the Pit-1 (POUF1) transcription factor lineage. Pit-1 binds to the GH promoter within the cell nucleus leading to the development and proliferation of somatotrophs and growth hormone transcription. However, it must be highlighted at this point that the vast majority of patients with acromegaly have sporadic tumours.

1.6 Diagnosis of Acromegaly

The majority of cases of acromegaly are diagnosed by either an internal medicine physician or general practitioner. Other healthcare professionals who frequently raise the possible diagnosis of acromegaly include ophthalmologists (visual field disturbances), gynaecologists (menstrual irregularities and infertility), dentists (inter-dental spacing, malocclusion and tempuro-mandibular joint syndromes) 53, rheumatologists (osteoarthritis), orthopaedic surgeons (carpal tunnel syndrome), sleep disorder/ respiratory physicians (obstructive sleep apnoea) 2,8.

1.6.1 GH in the diagnosis of Acromegaly

To understand the rationale behind the diagnostic criteria and diagnostic tests used in acromegaly one must fully understand GH physiology in normal subjects (see section 1.4). Normal GH production from the pituitary gland is pulsatile with the maximal production occurring at night in harmony with sleep stages and GH secretion is suppressible by glucose loading 1.

The majority of GH values throughout the day fall between 0.1-0.2µg/litre in normal subjects with six to ten secretory bursts during the day when GH reaches values between 5 and 30µg/litre. Therefore a random GH is of very little value in determining if a patient has acromegaly (unless the GH is unmeasurable) 54. Another more labour intensive approach, which takes into account the pulsatile
nature of GH secretion, is to measure GH frequently over a 24-hour period and compare to GH profiles in normal subjects. For the diagnosis of acromegaly this has a number of limitations; it is resource and time heavy, there is a need for age, BMI and probably gender specific GH reference ranges for this test\(^1\). The gold standard diagnostic test for acromegaly is the 75 g glucose OGTT with glucose and GH measurements every 30 minutes for 120 minutes. An acute glucose load will normally lead to an acute suppression of GH secretion, thus in acromegaly as there is autonomous GH secretion from a pituitary adenoma which is not under the control of normal physiological cues GH does not suppress indeed it may often be paradoxically elevated during an OGTT. However, it should be noted that the OGTT has limited use in patients who are in a catabolic state such as stress, liver and renal failure, uncontrolled diabetes mellitus, obesity, pregnancy, patients on oestrogen replacement or in tall pubertal adolescents as GH values may be falsely elevated\(^8,54\). The recent consensus guidelines for diagnosis of acromegaly states there must be a clinical suspicion of acromegaly, failure to suppress GH to \(<1\mu g/litre\) during an OGTT and an elevated IGF-I\(^{55}\). The cut-off level for GH suppression during an OGTT is a topic of much controversy as many of the original studies to determine this level used older assays, which may not be as sensitive as currently available assays. In recent years the use of higher sensitivity IRMA, immunofluorometric, chemiluminescence, immunoradiometric assays have been associated with significantly lower nadir GH during OGTT in healthy controls than was previously thought (ranging from 0.029-0.25\(\mu g/litre\))\(^{56-59}\), there was also a gender difference noted in some studies). Therefore with the use of more sensitive assays the cut off for physiologically normal GH suppression may decrease over time, as these assays can detect much lower levels of GH compared to older RIA and have redefined normality during an OGTT. However, it may be some time
before we have adequate follow-up data to assess GH cut-offs using these newer assays.

1.6.2 IGF-I in the Diagnosis of Acromegaly

IGF-I has been used as a marker of disease activity in acromegaly for approximately 30 years. Some authors would argue that a single IGF-I level is an appropriate, precise and cost effective first-line investigation test for the detection of acromegaly, this is particularly true before treatment has begun as IGF-I levels are invariably above the age related reference range. IGF-I has a long half life of 18-20 hours and the level remains stable throughout the day, therefore it is an ideal screening test. IGF-I levels have been shown to correlate with mean GH levels (in a curvilinear fashion, IGF-I levels showing a parallel rise with GH until a GH concentration of 10-20ng/ml, following which the IGF-I concentrations plateau) and clinical features of acromegaly. Multiple physiological factors have an impact on IGF-I concentrations including age, gender, IGF-BP, nutrition, oestrogen status and replacement route, liver and renal failure. Another possible marker of acromegaly is IGF-BP3 as these levels are directly correlated with IGF-I and are not found to overlap between normal subjects and patients with acromegaly.
1.7 Treatment options in Acromegaly

1.7.1 Surgery for Acromegaly

1.7.1.1 History of Pituitary Surgery for Acromegaly

The first attempt to operate successfully on a patient with acromegaly was reported in 1893, however the pituitary was not reached and the skull base was decompressed instead. Successful surgery for pituitary disease, via a nasal/ sinus surgery, was first performed in Vienna by Dr Schloffer in 1907 which was associated with lower mortality and morbidity than the transcranial approach. Harvey Cushing pioneered and refined the transphenoidal approach for several pituitary diseases. However, towards the end of his career (1927) Harvey Cushing had started to operate transcranially for pituitary tumours given the high recurrence rate and that by this stage the mortality for craniotomy had decreased significantly due to technical advances. Such was Harvey Cushing’s importance in the world of neurosurgery that the majority of neurosurgeons changed practice also around this time. There were a few surgeons who continued to develop the transphenoidal technique namely Dr Dott of Edinburgh, Dr Guiot of France and Dr Hardy of Montreal who introduced the concepts of microsurgery and microadenoma removal with preservation of normal pituitary function and with this the modern era of transphenoidal surgery for acromegaly began in the 1970’s.

The goals of surgical therapy (similar to other therapies for acromegaly) include normalisation of GH secretion and IGF-I concentrations, control of compressive symptoms from tumour, preservation (and restoration in some cases) of normal pituitary function and prevention of recurrence (current recurrence rates following successful surgery are approximately (0-19%)\textsuperscript{71-74}.
Surgical classification and planning

Pituitary tumours are classified by size and invasiveness with a microadenoma being <10mm and a macroadenoma >10mm. Invasion of surrounding structures is important as it has a significant impact on success of surgery and rates of recurrence. The commonest approach is the transphenoidal/ ethmoidal (over 90% of cases), as it is minimally invasive and produces little in the way of trauma or discomfort; furthermore it has low morbidity and is effective with excellent surgical results. The surgical success rate for microadenomas ~70% and ~50% for macroadenomas. Apart from tumour size and invasiveness the main factor determining success of surgery is the experience of the surgeon performing the operation. In a study in Manchester when 73 patients were operated on by 9 different surgeons fewer than 20% of patients achieved a GH <5mU/L. Similarly, in Birmingham the success rate was low at 33% when eight surgeons were involved. Conversely, the results from Oxford, Newcastle, and St Bartholomews in London who had only one surgeon operating on all patients with acromegaly reported success rates between 42-56%. A Japanese study revealed a doubling of success rates from 37-81% when a single surgeon operating on all patients. Similarly, the proportion of patients in Birmingham achieving a GH concentration <5mU/L doubled from 33% to 66% when a single surgeon performed all operations. The Oxford group also report an improvement in results of a single surgeon as his experience grew over 20 years. Therefore, there is very good evidence that these operations should be performed by surgeons who have experience in pituitary surgery and operate frequently on such patients.
1.7.2 Radiotherapy in Acromegaly

1.7.2.1 Radiotherapy techniques

Conventional radiotherapy (CRT) is the most frequently used method of radiation therapy for pituitary tumours. It is most frequently used in patients who have large remnants with evidence of progression following surgery or if surgery does not lead to normalisation of hormone excess. The techniques used for CRT include high energy CRT with opposed lateral fields, 360° rotational fields, moving arcs and 3 field techniques (2 lateral fields and a vertex field)\(^\text{83}\). The lesion is defined with MRI/CT and 3-D treatment planning with field conformation, and possibly non-polar irradiation is usually recommended\(^\text{84}\). During planning a custom mask is made using a thermoplastic mesh, which attaches directly to the radiotherapy treatment machine. This mask will limit mobility and minimises head rotation and chin tilt variation. To account for the larger variation in positioning in 3D-CRT than is seen in SRS a set up error margin is included in the planned treatment volume that results in a significantly larger radiation target compared to SRS\(^\text{85}\).

Radiation doses range from 45-50Gy at 180-200cGy fractions\(^\text{86-88}\). Fractionated conventional radiotherapy in the form of small doses in 25-30 fractions over 5-6 weeks\(^\text{85}\), modern stereotactic techniques can limit exposure to tissues surrounding the tumour. Due to the fact that stereotactic radiosurgery (SRS) is only a relatively new therapy the majority of data regarding efficacy and potential adverse effects of radiotherapy is derived from studies assessing the use of CRT.

Stereotactic radiosurgery (SRS) can divided into Gammaknife radiation therapy, Linear accelerator based and proton beam therapy. Gammaknife radiation therapy (GK, Elekta, Stockholm, Sweden) using multiple cobalt-60 gamma radiation emitting sources. Linear accelerator based SRS (linac) in which energy is accelerated, shaped and delivered in the form of electrons, or photons. Proton beam therapy which uses heavy charged protons and has the added advantage of leading to less
excess radiation deposition to surrounding tissue. While CRT for pituitary tumours is delivered in multiple small fractions over a number of weeks, SRS is delivered as a single treatment with the patient immobilised after careful stereotactic imaging planning.

1.7.2.2 Pituitary Radiotherapy for Acromegaly

Surgery remains the first choice therapy for acromegaly, however adjuvant therapy is often required as it renders GH to safe levels in only 40-80% depending on the tumour size and surgical expertise and as such should only be operated on by experienced surgeons. Medical therapy with long acting SSA will lower GH and IGF-I levels in approximately 90% of patients however only ~50% will achieve GH levels <2.5μg/litre, which depends heavily on pre treatment levels. Conventional radiotherapy has been used in acromegaly for over 30 years and has been shown to be effective in lowering GH levels. However, most of the older studies have been in small numbers of patients and have used old GH cure criteria and did not assess IGF-I concentrations, IGF-I physiology is known to be altered following radiotherapy. These studies may also have been prone to selection bias as patients followed up regularly and for long durations may have been patients with more active disease. In a study of 884 patients who had received radiotherapy for acromegaly in the UK acromegaly database mean GH levels decreased from 13.5 to 5.3ng/ml after 2 years, 2.0ng/ml by 10 years and 1.1ng/ml by 20 years. 22% achieved a GH <2.5ng/ml after 2 years, 60% by 10 years and 77% by 20 years. The IGF-I levels fell in parallel with GH with 63% of patients having a normal level by 10 years, this is in keeping with other reports. The single most important factor in eventual success of radiotherapy appears to be the pre radiotherapy GH/IGF-I concentration. There is contradictory evidence that despite good GH control radiotherapy is of little use in normalising IGF-I, however
this study was smaller numbers and in particular in the follow up group, as well as technical differences in radiotherapy administered.

1.7.2.3 Mortality following pituitary radiotherapy

1.7.2.3.1 Introduction

Conventional radiotherapy (CRT) is the most frequently used method of radiation therapy for pituitary tumours. It is most commonly used in patients who have large remnants of pituitary adenomas with evidence of progression following surgery or if surgery does not lead to normalization of hormone excess. Surgery remains the primary therapy of choice for all pituitary tumours with the exception of prolactinomas. However, radiotherapy has been shown to be efficacious adjuvant treatment for both tumour and endocrine control. Due to the fact that stereotactic radiosurgery (SRS) is only a relatively new therapy the majority of data regarding efficacy, potential adverse effects of radiotherapy and in particular effect of radiotherapy on mortality are derived from studies were CRT was used; this review will focus predominantly on studies which used CRT.

1.7.2.3.2 Cerebrovascular morbidity and mortality following pituitary radiotherapy

Increased cerebrovascular disease and death have been reported in a number of studies following pituitary irradiation. In a series of 156 patients with non-functioning pituitary adenoma (NFPA), increased cerebral infarction rates were found in patients administered higher doses of radiotherapy. In a study assessing the role of pituitary radiotherapy in the development of cerebrovascular accidents (CVA) in 331 patients who received pituitary radiotherapy for a number of underlying diagnoses, it was reported that patients who received radiotherapy had a relative risk of CVA of 4.1 (CI 3.6-4.7) compared to the general population. On
multivariate analysis the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared to biopsy or no operation, higher doses of radiotherapy and an underlying diagnosis of acromegaly. In a further study, Brada et al. assessed cerebrovascular mortality in 344 patients who had received radiotherapy (79% also had transcranial or transsphenoidal surgery), cerebrovascular disease accounted for 26% of all deaths [33 deaths compared to 8 deaths expected (RR 4.11, (CI 2.84 – 5.75)], with an even further increase in female patients [RR 6.9, (CI 4.29-10.6)] compared to males [RR 2.4, (CI 1.24-4.2), p=0.002]. Surgery also plays a role in the increased cerebrovascular mortality reported in this studies as patients with prior surgery had an increase RR compared to those with no surgery or biopsy alone [RR 5.19, (CI 3.5-7.42) vs. [RR 1.33, (CI 0.27-3.88), p=0.02], but there may be several confounders which may have led to this increase.

1.7.2.3.3 Hypopituitarism following pituitary radiotherapy

Over 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiency within the following decade. The classic pattern of pituitary hormone deficiency to radiotherapy of GH (100% at 5 years), gonadotrophin (91% at 5 years), ACTH (77% at 5 years) then TSH deficiency (42% at 5 years) is not always seen and deficiencies may occur in any order. As deficiencies can occur at any time point even up to 20 years later long term testing is required. With conventional RT the speed of onset of hypopituitarism is related to the total and fractional doses of radiotherapy and the rate of hypopituitarism increases from time of irradiation.

A number of studies have described an increased mortality in patients with hypopituitarism compared to age and sex matched controls. In these studies, the increased mortality was predominantly due to cardiovascular and
cerebrovascular mortality. In total nearly 1900 patients have been included in these
studies and approximately 50% had radiotherapy: in 2 studies radiotherapy was not
associated with increased mortality $^{116,118}$ and in the 3rd study it was not possible to
investigate the link as nearly all patients had radiotherapy [304/344 (88.4%) received
radiotherapy with an overall cerebrovascular mortality RR of 3.39 (2.27,
4.99), men 2.64 (1.44-4.42) and women 4.91, (2.62-8.4)] $^{117}$. In the largest series in
the literature, Tomlinson et al $^{119}$ reported that radiotherapy significantly increased
mortality with an SMR of 2.32 (1.7-3.14, p=0.004) in the radiotherapy group
compared to 1.87 (1.62 -2.16) in the general cohort of patients with hypopituitarism.
In particular, patients who had received radiotherapy had an elevated
cerebrovascular risk [SMR 4.36 (2.48 – 7.68), p=0.001]. Erfurth et al $^{120}$ compared
radiation regimens and duration of symptoms of hypopituitarism in 342 patients
treated with surgery and radiotherapy. They compared 32 patients who had died
from cerebrovascular disease to 62 matched patients from the cohort who had not
died from cerebrovascular accidents. They found no significant difference between
the two groups for a number of irradiation parameters such as maximum absorbed
dose, maximum biological equivalent dose, field size and number of fractions. The
only difference found was a longer duration of symptoms of hypopituitarism in the
cerebrovascular mortality group. They concluded that untreated hormone
deficiency may be more directly implicated in cerebrovascular mortality than
radiotherapy per se. The increase in cerebrovascular mortality following
radiotherapy has also been described in patients with acromegaly.

1.7.2.3.3 Mechanisms of radiation injury

Radiation injury to the vasculature was first described over 100 years ago $^{121}$ and
has subsequently been reported to be one of the commonest adverse effects of
therapeutic radiotherapy. Radiotherapy leads to damage of both large and small
vessels, with a predilection to smaller vessels as endothelial cells are radiosensitive. In capillaries and sinusoids irradiation can lead to focal cytoplasmic degeneration, vacuolation and irregular projections of the cytoplasm to the vessel lumen. In the early stages this leads to increased capillary permeability and intracellular oedema. This may be followed by platelet and fibrin thromboses leading to the detachment of endothelial cells from their basement membrane which may ultimately lead to necrosis of the endothelial cell and wall rupture with resulting loss of a segment of microvessel. Less severe damage often results in permanent dilatation and teleangectasia, there may also be compensatory endothelial cell proliferation which if the insult is not significant can re-establish microvascular segments. Arteriolar lesions can also occur, this is most commonly in the form of myointimal proliferation, which leads to narrowing of the lumen, foamy macrophage plaques may also develop (particularly likely to be due to radiation if they occur in arterioles measuring less than 100mM in diameter). Fibrin may accumulate in the media or intima of arteriole leading to fibrinoid necrosis or the media may be replaced by dense collagen rich tissues leading to hyalinisation of the media. Also, some studies have shown an acute lymphocytic vasculitis affecting the media, intima and adventitia of medium sized arteries localised to the radiation field leading to fibrinous exudate and occasionally thrombosis. In arteries measuring more than 100mM lesions are observed less frequently than in smaller vessels, these lesions are similar to those seen in atherosclerosis, however, as the patients are often young and the plaques are limited to the radiation field then one can assume they may be secondary to the radiation therapy.

These changes may be clinically important as seen in patients with pituitary radiotherapy who have increased risks of cerebrovascular death but also in other patient groups who receive radiotherapy. A recent retrospective analysis of 4,665
Hodgkin's patients who had irradiation to the heart followed up for 7 years revealed a RR of 2.56 (CI 1.11-5.93) for myocardial infarct, whereas those treated with chemotherapy alone had no increase. Another study assessing 2,232 Hodgkin's patients (79% >40Gy), followed up for 9.5 years the RR for MI in patients treated with radiotherapy alone 3.8 (CI 2.8 - 4.8). This RR increased with the latency period and was highest in patients who had been treated with radiotherapy prior to the age of 20.

1.7.2.3.4 Secondary oncogenesis following pituitary radiotherapy

Secondary oncogenesis following pituitary radiotherapy is a controversial area. It is impossible to calculate the true incidence of tumours arising following pituitary radiotherapy as most of the literature are case reports or cross sectional studies. Another factor to take into account is that patients with pituitary disease receive disproportionately frequent imaging, which historically took the form of recurrent CT scans and in more recent years MRI; a more appropriate control group might be patients treated with surgery alone rather than normal population controls as they also undergo regular surveillance imaging. In some studies the incidence of secondary neoplasm is as high as 1-2% occurring with a latency of 8-15 years. One study has estimated an incidence of extracranial tumours in NFA patients 3.9 fold that of the general population irrespective of whether the patient had radiotherapy or not, therefore having a pituitary adenoma may lead to some underlying increased susceptibility to tumourogenesis. Secondary intracranial tumours (most commonly gliomas or meningioma) due to pituitary irradiation are now rarer due to newer techniques which expose a smaller volume of cranial tissue to radiation.
1.7.3 Medical therapy for acromegaly

1.7.3.1 Introduction

Patients with the rare disease, acromegaly, have excess growth hormone (GH) secretion and increased circulating levels of insulin like growth factor 1 (IGF-I). The disease is associated with increased morbidity and premature mortality; reported standardized mortality ratios range between 1.3 and 3.0.\textsuperscript{53,71,75,132-138} This increase in mortality has been reported to be reduced if GH levels can be decreased to <2.5 \( \mu g/l \)\textsuperscript{133,134,136,137} and IGF-I levels are normalised.\textsuperscript{75,139} Life expectancy of patients with acromegaly has also increased over the past few decades,\textsuperscript{135} probably because of improvements in the surgical and pharmacological management of this condition.

Therapy for acromegaly is targeted at reducing excess morbidity and mortality by decreasing levels of GH and IGF-I, ameliorating symptoms and decreasing any local compressive effects of the pituitary adenoma. Currently, the therapeutic options for acromegaly include surgery, radiotherapy and medical therapies such as dopamine agonists, somatostatin receptor ligands (SRLs) and the GH receptor antagonist pegvisomant. Medical therapy is used predominantly as secondary therapy for persistent or recurrent acromegaly following noncurative surgery, although it can be used as primary therapy for patients in whom surgery is not an option or as short-term therapy before surgery. Consensus guidelines have described the optimal management and the role of medical therapy in treating patients with acromegaly.\textsuperscript{140}

A number of important issues need to be mentioned before interpreting the data with regard to medical therapies in patients with acromegaly.
• Acromegaly is a rare condition and as such the numbers in studies may be relatively small and studies are often multicenter

• There is appreciable heterogeneity in study design, patient characteristics and patient selection between studies, so direct comparison and meta-analysis may be difficult

• Patients who receive the drug as primary therapy should be differentiated from those who receive the drug as secondary therapy

• Large variations exist between studies in the number of patients who have had surgery and radiotherapy prior to medical therapy; this point is important as it effects the subsequent response to therapy both from the perspective of hormone hypersecretion and tumor shrinkage

• In studies that assess the effect of therapy on tumor shrinkage, wide variation exists in criteria for tumor shrinkage

• Duration of therapy and follow-up differs between studies and, as such, they may not be comparable, as some therapies function better the longer the patient receives them; furthermore, the effect of radiotherapy increases with time following therapy

• In studies assessing the efficacy of somatostatin receptor ligand (SRL), therapy may be with short-acting octreotide or one of the long-acting SRL preparations and, as such, direct comparison and meta-analysis may be difficult

• In studies using SRLs, selection bias may exist because in some studies patients will have shown response to short-acting SRL therapy as an entry criteria for the study
1.7.3.1 Somatostatin Receptor Ligand (SRL) therapy or Somatostatin Receptor Analogue Therapy (SSA)

1.7.3.1.1 Somatostatin receptor interaction

Somatostatin is a cyclical peptide with a short half-life (2–3 min) that is synthesized in many tissues, including the hypothalamus. When synthesized in the hypothalamus, it plays a key role in GH secretion by inhibiting GH release but not synthesis via its action on somatostatin receptors (SSR). Although SSR1, 2, 3 and 5 are all expressed on GH-secreting pituitary adenomas, SSR2 and SSR5 are more abundantly expressed than the other types. In vitro and in vivo studies have shown that expression of SSR2 correlates well with the GH-lowering effect of octreotide, which suggests that the main GH-lowering effect of the SRL octreotide is through SSR2. Although SSR5 is expressed at higher levels compared with SSR2, no correlation was found between the expression level of SSR5 and effects of SRL (including octreotide) on GH secretion in cultured pituitary adenomas from patients with acromegaly. Feelders et al. have reviewed the area of somatostatin receptor specificity in detail.

1.7.3.1.2 Pharmacological aspects

Subcutaneous octreotide is administered as a thrice-daily injection as its half-life is 2 h; this multiple daily dosing regimen has limitations, including issues with compliance and therapeutic escape prior to the next dose. The starting dose is usually 100 mg three times per day, which can be increased in increments to a maximum of 500 mg three times per day. The first long-acting formulation to be synthesized was octreotide long-acting release. This formulation of octreotide is delivered by microspheres, which leads to an increase in the serum level of the
drug on day 1 post-injection followed by a lag in drug concentrations from day 2–6, which then increase to a prolonged plateau phase lasting from days 11 to 40 after injection.  

The second long-acting SRL synthesized was lanreotide, which is available in two formulations: lanreotide sustained release and lanreotide autogel. Lanreotide sustained release is lanreotide incorporated into a biodegradable polymer microparticle, which leads to a rapid release of the drug 1–2 h after injection followed by a prolonged drug release phase peaking 2 days later. Lanreotide sustained release has a mean half-life of 5 days and, therefore, injections are required every 10–14 days. Lanreotide autogel is a depot preparation of lanreotide in a supersaturated aqueous solution.

Lanreotide autogel has a peak concentration on day 1 but has a longer half-life (25 days) than lanreotide sustained release. The elimination of SRLs, such as octreotide or lanreotide, from the body is predominantly via biliary secretion.

1.7.3.1.3 Biochemical control

1.7.3.1.3.1 Subcutaneous octreotide

In a study by Vance et al., treatment with subcutaneous octreotide lead to a decrease in GH and IGF-I levels in 94% and 92% of patients with acromegaly, respectively. This reduction lead to a normalization of IGF-I in 46% of patients and a GH level of <5 µg/l in 45% of patients and was associated with a reduction in tumor size of >20% in 44% of patients. In a study by Ezzat et al., 21% of patients on 250 mg subcutaneous octreotide three-times daily and 16% of patients on 100 mg three-times daily achieved a GH level of <2 µg/l. IGF-I level was normalized in 68% of patients in the 250 mg group and in 55% in the 100 mg group. Tumor
shrinkage of >1 mm in diameter occurred in 37% in the 250 µg group and in 19% in the 100 µg group during the 6-month treatment period. 151

These studies had limitations that included a non-age-adjusted reference range for IGF-I, open labeling and variable dose escalation (or fixed dose in the study by Ezzat et al.) 150,151. A number of studies have reported no difference in efficacy between subcutaneous and long-acting SRLs. 152-154 However, subcutaneous SRL therapy has been replaced by long-acting SRL therapy owing to improved compliance and patient preference, but it should be noted that long acting SRL therapy may be considerably more expensive (depending on dose of short-acting SRL used).

1.7.3.1.3.2 Long-acting SRL

An analysis of prospective studies has reported that long-acting SRLs reduce GH levels to <2.5 µg/l and normalize IGF-I levels in 48–52% and 42–68% of patients with acromegaly, respectively. 155 A 5 year prospective study of 45 patients with acromegaly treated with long-acting SRLs as first-line therapy reported GH control in 100%, IGF-I control in 97.8% and tumour shrinkage of 74.9% in the octreotide LAR group and 78.2% in the lanreotide group. 156

Direct comparison of different formulations of SRLs used in clinical trials is difficult for a number of reasons as have been described in the introduction. Another key factor is duration of therapy as there is evidence that control of acromegaly by SRLs may improve with time, independent of dosage change and, therefore, if studies are of different duration that may not be comparable. 157,158 In two of the largest studies to assess the efficacy of octreotide long-acting release, 66–75% of patients achieved IGF-I levels within the normal reference range and 70–72% achieved GH levels <2.5 µg/l. 91,157
The findings of these studies may be limited by therapeutic and selection bias, as in the study by Lancræjan et al.\textsuperscript{91} patients were selected on the basis of known responsiveness to subcutaneous octreotide and in the study by Cozzi et al.\textsuperscript{157} only patients with $>$20% decrease in GH and IGF-I remained in the study for its full duration. Baldelli et al. have assessed the efficacy of lanreotide-sustained release. In this study, GH and IGF-I levels were controlled in 77% and 63% of patients, respectively, and 22% of patients had clinically significant tumor shrinkage of $>$20% in volume.\textsuperscript{159} Verhelst et al. have also assessed the efficacy of lanreotide sustained release; these researchers found that GH was $<$2.5 µg/l in 45% of patients, IGF-I levels were in the normal reference range in 44% and 36% had clinically significant tumor shrinkage $>$25% volume.\textsuperscript{160}

The question as to which long-acting SRL is most efficacious and the data comparing octreotide long-acting release and the different preparations of lanreotide is beyond the scope of this thesis but has been extensively reviewed recently by Murray and Melmed.\textsuperscript{146}

1.7.3.1.4 Antitumoral effects

The antitumor effects of SRLs have been extensively reviewed by Bevan in 2005.\textsuperscript{161} The mechanisms by which SRLs inhibit growth and proliferation of tumor cells are complex and include cell cycle arrest, induction of apoptosis and decreased angiogenesis.\textsuperscript{161} Losa et al.\textsuperscript{162} compared Ki-67 staining (a marker of cell cycling) in 39 patients treated with SRLs and 39 controls who were not treated preoperatively with SRLs, who were matched for age, sex, tumor size and extension and reported a decreased Ki-67 index with no increase in apoptosis in the treated patients, which suggests that SRLs have important antiproliferative effects. Further evidence comes
from Danila et al. who have reported that inhibition of cell proliferation by SRLs occurs independently of inhibition of GH secretory pathways.  

The studies that have assessed changes in tumor size following SRL therapy have used different imaging modalities (CT and MRI) and different assessments of tumor shrinkage (tumor diameter or volume). These differences between the studies make comparison of results difficult. Most studies define a 10–25% reduction in tumor volume as clinically significant tumor shrinkage. Studies that have assessed tumor shrinkage include those involving patients on short-acting or long-acting SRLs and those receiving SRLs as a primary or secondary therapy. In the review by Bevan, 217 of 478 patients (45%) who received SRL therapy had a reduction in tumor size. The reduction in tumor size was more prevalent in the primary medical therapy group (51%) than the secondary therapy group (27%).

Predictors of tumor shrinkage in patients receiving SRL therapy include prior exposure to surgery and radiotherapy; specifically, patients who have received radiotherapy and are surgery naïve have the greatest shrinkage. Data are conflicting with regard to the initial size of the tumor in relation to the amount of shrinkage that occurs with SRL therapy. Some researchers report that microadenomas are more likely to shrink than larger adenomas, whilst others report that macroadenomas are more likely to shrink than smaller adenomas.

Furthermore, other groups report no association between initial tumor size and the subsequent amount of shrinkage following SRL therapy. A few studies have suggested that patients who have a biochemical response also have a tumor volume response. In the patients in whom GH levels decreased by >50%, 58% had tumor shrinkage. This is compared to 29% in the patient group who had <50% reduction in GH levels. Verhelst et al. reported the greatest tumor shrinkage in patients with the greatest IGF-I response to SRL therapy. By contrast,
a number of studies did not show any relationship between biochemical response and tumor response.\textsuperscript{157,168,169}

1.7.3.1.5 Primary Medical Therapy

Primary medical therapy unlike surgery cannot cure acromegaly but as it can control hormone hypersecretion it may be indicated in patients who are unlikely to achieve cure following surgery (namely, those with macroadenomas with clinically significant extension) or those who refuse or are poor candidates for surgery. Importantly, even in patients who show favorable biochemical and tumor shrinkage responses with SRL therapy, once the therapy is stopped, the tumor regrows and excess levels of GH and IGF-I return.\textsuperscript{153,170}

The majority of data regarding primary SRL therapy come mainly from nonrandomized studies rather than from prospective randomized trials of surgery versus SRL therapy. In these studies, SRL treatment as a primary therapy is effective in reducing levels of GH and achieving an IGF-I in the normal range in approximately two thirds of patients.\textsuperscript{142,153,158,171-173}

A review has reported that in 14 studies assessing primary medical therapy in patients with acromegaly (n = 424), 36.6% of patients had clinically significant tumor shrinkage >20%.\textsuperscript{8} The wide range in percentages of patients with clinically significant tumor shrinkage in the studies reviewed most probably relates to different definitions of clinically significant shrinkage (range 10–45%) and differences in how this was assessed radiologically.\textsuperscript{8} No difference in tumor shrinkage rates existed between patients treated with subcutaneous or long-acting SRL (43.0% versus 37.8%)\textsuperscript{8}. However, a greater shrinkage rate occurred in patients who received SRL therapy for macroadenomas compared with microadenomas.\textsuperscript{153,168,174}
Pre-operative somatostatin analogue therapy

In a prospective study by Carlsen et al. 175, 30 patients who had primary surgical therapy were compared with 32 patients who had preoperative SRL therapy followed by surgery. No statistically significant increase in biochemical cure was found in the total patient group who received preoperative SRL therapy. However, in the subgroup of patients with macroadenomas there was an improved cure rate with preoperative SRL therapy. The authors concluded that future well-designed studies were required to further assess the role of preoperative SRL therapy. 175 Lucas et al. assessed the efficacy of primary medical therapy with lanreotide-sustained release in 104 patients with acromegaly for 1–3 months prior to transphenoidal surgery. 29% of patients had a >20% reduction in size of tumor (66% had some tumor reduction and 18% had >20% increase in tumor size). 176 Biochemical control was the sole predictor of tumor shrinkage. However, longer studies have shown no relationship between GH response and tumor shrinkage. 153,160,174

Univariate analysis of surgical outcomes revealed that predictors of persistent disease following surgery in patients who had received preoperative SRL therapy were younger age, higher levels of GH and IGF-I at diagnosis, larger preoperative tumor volume and extension into the suprasellar region or cavernous sinus. 176 However, as this study lacked a control group it is difficult to accurately assess the role of preoperative SRL therapy without further randomized, controlled trials. Importantly, in this study some patients did develop cavernous sinus extension during treatment and as this may have a negative impact on surgical outcome. 176
1.7.3.1.7 Adverse effects of SRL therapy

In clinical trials of SRL therapy, the most frequent adverse effects encountered are gastrointestinal in nature, such as nausea, flatulence, cramps and diarrhea, which are mostly mild to moderate in severity and are often transient.\textsuperscript{146} Injection site discomfort, pain and erythema is also often described but is rarely severe enough to lead to drug cessation. The other concern relates to the development of biliary abnormalities (including sediment, sludge, microlithiasis and gallstones); however, these abnormalities are mostly asymptomatic.\textsuperscript{142} One needs to be aware of this possible adverse effect, particularly when patients stop SRL therapy, as gallbladder contraction may occur leading to symptoms. Patients with acromegaly have an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus and SRL therapy has also been reported to increase the risk of hyperglycemia (as these therapies impair insulin secretion).\textsuperscript{177,178} Other adverse effects include rarely reported cases of liver function abnormalities, anaphylaxis and hair loss.

1.7.3.2 Dopamine agonists

Dopamine agonists bind to D2 dopamine receptors in the pituitary gland and suppress prolactin and GH secretion in patients with acromegaly. They have been used in acromegaly as an individual treatment or in combination with SRL therapy. Three main dopamine agonist agents are used in the treatment of hyperprolactinemia and GH excess: bromocriptine, cabergoline and quinagolide.
1.7.3.2.1 Bromocriptine

Bromocriptine was the first dopamine agonist to be widely used in the treatment of acromegaly. The agonist was associated with moderate success, as it normalized IGF-I and GH levels in 10% and 20% of patients, respectively. The utility of dopamine agonists, in particular bromocriptine, has been limited by the disappointing rates of biochemical response reported, and clinically relevant adverse effects that may occur with the high daily doses (40–60 mg), such as nausea, vomiting, diarrhea, fatigue and orthostatic hypotension.

1.7.3.2.2 Cabergoline

The second-generation dopamine agonist cabergoline has been demonstrated to be potentially more effective than bromocriptine in the treatment of acromegaly, as treatment achieved safe GH and IGF-I levels in 46% and 39% of 64 patients, respectively. Moreover, Voyes and colleagues found that on a median weekly dose of cabergoline of 1.75 mg, normalization of both IGF-I and GH levels occurred in 27% of the patients. The greater efficacy of cabergoline than bromocriptine may be due to a number of factors, including greater biological potency, a longer half-life and less adverse effects leading to better compliance. Data relating to cabergoline therapy in acromegaly is limited, and this is most probably related to the fact that it was introduced into clinical practice for patients with acromegaly around the same time as SRL therapy, which is more likely to be used owing to superior efficacy in both hormonal control and tumor reduction. In the largest study assessing the efficacy of cabergoline in patients with acromegaly, Abs et al. treated 64 unselected patients with cabergoline for 3–40 months. The majority of patients received 1.00–1.75 mg of cabergoline per week (although some patients received doses of up to 3.5 mg per week). In the 48
patients who had pure GH-secreting tumors, cabergoline normalized IGF-I levels in 35% and suppressed GH levels to <2 µg/l in 44%. The effect was greater than this result in the subset of patients who co-secreted GH and prolactin, among whom IGF-I levels were normalized in 50% and GH level were suppressed to <2µg/l in 56%.

In this study by Abz et al.\textsuperscript{181}, patients with relatively low baseline levels of GH and IGF-I were more likely to respond to cabergoline therapy. When patients were categorized into those with the highest pre-therapy IGF-I levels (>750 µg/l) compared to others (<750 µg/l) the rate of normalization of IGF-I was 22% and 43%, respectively. Combined data from four smaller studies reveal less impressive response levels: IGF-I levels normalized in 22% of patients treated with cabergoline;\textsuperscript{183-186} however, the rate of response was extremely variable, with response varying from 0–27%.\textsuperscript{183-186} Data on long-term treatment with quinagolide is not as robust as that for bromocriptine or cabergoline, but available data in small numbers report that levels of IGF-I normalize in 28% of patients treated (range 17–43%).\textsuperscript{187,188}

1.7.3.2.3 Predictive value of hyperprolactinemia

The data as to whether the co-secretion of prolactin is predictive of response to dopamine agonist therapy—in other words, patients with elevated prolactin have a greater decrease in GH and IGF-I following dopamine agonist therapy—is conflicting. Some studies conclude that tumors that co-secrete prolactin have a greater response to dopamine agonist therapy\textsuperscript{181,189,190} whereas others show no effect.\textsuperscript{184,191-194} Similarly, no agreement exists concerning the association between a positive GH and PRL immunohistochemistry and a favorable response to dopamine agonist therapy, with some studies reporting this association\textsuperscript{191} and
others not. \cite{184,196} Patients who have a normal prolactin level should, therefore, not necessarily be excluded from receiving dopamine agonist therapy on the assumption that there will be limited GH and IGF-I response.

1.7.3.2.4 Adverse effects of dopamine agonists

The most frequent adverse effects of dopamine agonist therapy are nausea, constipation, headache, mood disturbance, nasal stuffiness and dizziness. \cite{179} Studies in patients treated with dopamine agonists for prolactinomas have shown less frequent adverse effects with cabergoline than bromocriptine. \cite{196,197} Indeed, in the largest study of cabergoline in patients with acromegaly by Abs et al. \cite{181} only 3% of patients had adverse effects that required drug withdrawal (despite relatively high doses).

In the past five years, cabergoline and pergolide have been associated with an increased risk of cardiac valvular dysfunction in patients receiving high-dose therapy for Parkinson disease. \cite{196-200} However, patients receiving dopamine agonist therapy for endocrine indications differ from the Parkinson disease cohorts in a number of key respects, including cumulative dose exposure and age. Since these studies were published a number of studies have assessed the risk of clinically relevant valvular lesions in patients receiving dopamine agonist therapy for hyperprolactinemia, \cite{201-206} the majority of which show reassuring results. One study did, however, report increased levels of tricuspid regurgitation. \cite{202} Another key issue in the assessment of this concern in patients with acromegaly is that they often have clinically relevant cardiac abnormalities (myocardial, valvular and conduction system abnormalities) as a result of acromegaly and its co-morbidities (hypertension, left ventricular hyperplasia and type 2 diabetes mellitus). \cite{207} More data are required regarding the safety of dopamine agonist therapy for patients with
prolactinomas and acromegaly to assess if there is a similar risk in these patients as for those with Parkinson disease.

1.7.3.2.5 Tumor shrinkage on dopamine agonist therapy

Very little data is available regarding tumor shrinkage in patients with acromegaly receiving dopamine agonist therapy. Combined data from a number of studies revealed that 29% of patients had some tumor shrinkage and the majority of patients who had tumor shrinkage were also hyperprolactinemic. In the study by Abs et al., 12 of 48 patients (9 with macroadenomas) had radiographically obvious GH-secreting tumors prior to treatment with cabergoline and 5 of these 9 patients had tumor shrinkage (but it was <50%). In one series involving treatment with quinagolide, two of 16 patients had tumor shrinkage. Whether these findings represent a real effect of dopamine agonist therapy or an effect related to prior radiotherapy exposure is difficult to assess with such small numbers of patients assessed and the heterogeneity of the patients' characteristics.

1.7.3.3 Pegvisomant

1.7.3.3.1 Introduction

Pegvisomant is an injectable, genetically engineered, pegylated analogue of human growth hormone that blocks the action of growth hormone at the site of the growth hormone receptor. Amino acid substitutions in the GH molecule result in structural changes that enable enhanced binding of pegvisomant to the growth hormone receptor, but also prevent the secondary rotational changes at the level of the GH receptor that are needed for GH receptor downstream signaling and function.
The addition of pegylated glycol units to the molecule, or pegylation, extends the half-life of pegvisomant by reducing renal clearance and also decreases immunogenicity.

Unlike other medical therapies for acromegaly, pegvisomant acts at the GH receptor rather than at the level of the pituitary adenoma, which makes it an important additional agent in the treatment of acromegaly, particularly when other agents have failed. In terms of cost, pegvisomant is more expensive than dopamine agonist therapy or SRL therapy and as such it is often used as a second-line agent, or in combination with other agents once other treatments have failed or are poorly tolerated. Pegvisomant therapy results in a reduction in levels of IGF-I and, as a result, the negative feedback loop to the hypothalamus and pituitary gland is altered and GH levels paradoxically rise. For patients with acromegaly treated with pegvisomant, therefore, GH measurements cannot be used to monitor disease activity and IGF-I becomes the key biomarker of disease activity along with clinical signs and symptoms. As IGF-I is the sole marker of disease activity, knowledge of the limitations and performance of local IGF-I assays and reference ranges is essential.

1.7.3.3.2 Efficacy of pegvisomant

The first clinical study to assess the efficacy of pegvisomant in acromegaly showed a rapid and sustained benefit following 12 weeks of treatment. In this randomized, double blind, prospective trial, three different doses of pegvisomant (10, 15 and 20 mg per day) were compared to placebo in 112 participants. Significant dose-dependent reductions in IGF-I levels were observed for the treated group compared with the placebo group; specifically, 38%, 75% and 89% of patients receiving pegvisomant 10, 15 and 20 mg, respectively, achieved IGF-I
levels within the normal reference range. The reduction in IGF-I concentrations occurred rapidly (within the first 2 weeks of treatment, however it should be noted that patients were loaded with 80mg of pegvisomant at the start of the study) in 75% of patients and was sustained for the remaining 12-week study period. In keeping with the biochemical response, the clinical response was also impressive with symptoms of acromegaly being reduced in patients from all three pegvisomant groups compared to control group. Clinically relevant reductions in soft-tissue swelling, excessive perspiration and fatigue in patients receiving the 20 mg per day dose.

Subsequently, Van der Lely et al. performed a study that assessed patients with acromegaly treated with pegvisomant over a longer period (6–18 months). In this study, patients were commenced on 10 mg of pegvisomant daily and the dose was titrated every 2 weeks using normal age-adjusted IGF-I as a target. The maximum dose of pegvisomant used was 40 mg per day. Normal IGF-I levels were achieved in 97% (87 of 90) of patients receiving pegvisomant for 12 months or more. A dose reduction was required in 11 of 90 patients, as IGF-I level fell below their age-matched and sex-matched reference range, thus rendering these patients GH deficient. A caveat to the poor predictive value of IGF-I as a marker for GH deficiency in hypopituitarism is that in patients with hypopituitarism, IGF-I is not a robust marker of GH deficiency. Furthermore, many patients with IGF-I in the normal reference range may be rendered GH deficient on pegvisomant; this concept has been discussed by Mukherjee et al. From a metabolic perspective, pegvisomant therapy also reduced insulin and fasting glucose levels, but no change in HbA1c occurred despite GH levels increasing as IGF-I levels decreased or normalized.
1.7.3.3.3 Use in SRL-treatment resistance

A number of small studies have assessed the use of pegvisomant in patients whose disease is resistant to SRL therapy. Bonert et al. first described six patients who were somatostatin resistant in whom normal IGF-I levels were achieved with pegvisomant treatment. Colao et al. reported on 16 patients with acromegaly who were sub optimally controlled on long-acting SRL. All 16 had undergone surgery and two had also received radiotherapy. The patients had received the maximum monthly dose of octreotide or lanreotide for at least 24 months but did not have adequately suppressed GH or IGF-I levels. Daily pegvisomant was administered and adjusted every 6 weeks to achieve an IGF-I level within the reference range. Four of the patients were withdrawn owing to poor compliance or protocol violation. After 12 months of treatment with pegvisomant, nine of the 12 remaining patients had normal IGF-I levels. In the three patients with elevated IGF-I levels, a >50% decrease from their baseline IGF-I level had occurred.

1.7.3.3.4 Tumor growth while taking pegvisomant

Concern exists that pegvisomant may cause tumor growth because it decreases negative feedback by IGF-I on the pituitary gland and hypothalamus and increases GH levels. Buhk et al. published results of a 24-month prospective trial that assessed tumor volume in 61 patients treated with pegvisomant monotherapy. All patients had received SRL therapy previously, 34% had received radiotherapy and 86.9% had undergone surgery. They were commenced on daily pegvisomant and this agent was adjusted as necessary throughout the trial, with mean dose being about 10 mg and a maximum dose of 30 mg per day. Patients had pituitary MRI scans at 6, 12 and 24 months of therapy. Over the 24-month period, no statistically significant change in tumor volume occurred in 45 of the 61 patients who completed
the study. However, clinically significant tumor growth occurred in 3 patients within 12 months of commencing pegvisomant; it should be noted that none of these patients had received prior radiotherapy.\textsuperscript{215}

Jimenez et al.\textsuperscript{216} reviewed the imaging of 43 patients treated with long-term pegvisomant therapy (>18 months) in various clinical trials and also separately looked at the nine patients from a total of 304 patients within clinical trials in whom tumor growth was noted within 12 months of starting pegvisomant. 29 of the 43 whose imaging was reviewed had received radiotherapy. 24 patients had a significant clinical reduction in tumor volume and of these, 22 had received radiotherapy previously. Importantly, the nine patients who experienced tumor growth within 12 months of starting pegvisomant had not received prior radiotherapy. Six had progressive growth prior to commencing pegvisomant and two of the cases had probable rebound tumor expansion after stopping SRL therapy, as the expansion occurred within a short period of commencing pegvisomant and stopping SRL therapy. In these two cases, the patients have remained on pegvisomant and the tumor has remained stable in size.\textsuperscript{216} In summary, a small risk of clinically significant tumor growth occurs while on pegvisomant therapy and this appears to be particularly true in patients who have not received prior radiotherapy. Whether this potential increased risk of tumor growth is related to pegvisomant per se or the natural history of these pituitary adenomas needs further assessment.

1.7.3.3.5 \hspace{1cm} Adverse effects of pegvisomant

Pegvisomant is generally well tolerated; adverse effects include mild self-limiting skin reactions and lipohypertrophy at drug injection sites. Deranged liver transaminase enzyme levels have also been reported, but it can be difficult to
separate other biliary causes from abnormal liver blood tests and it must be remembered that prior SRL therapy can cause cholestasis. Elevations in transaminase enzyme levels resolve fully on cessation of pegvisomant without any further sequelae and appear to be idiosyncratic. If clinically indicated, a second course of pegvisomant can be considered and some patients have been successfully re-started back onto therapy after normalization of transaminase enzyme levels. Initial and subsequent 6-monthly liver function blood tests are recommended when using pegvisomant. Antibodies to pegvisomant may also be present, although they do not seem to interfere with therapeutic response to pegvisomant or cause adverse effects.

1.7.3.4 Newer agents for the treatment of Acromegaly

1.7.3.4.1 Pasireotide (SOM230)

Pasireotide is a synthetic multi-receptor targeting SRL, which has high affinity for SSR 1, 2, 3 and 5. As somatroph tumors express SSR1, 2, 3 and 5, in particular they have a greater abundance of SSR 2 and 5. The SSR targeting of pasireotide may, therefore, be superior to that of conventional SRLs such as lanreotide and octreotide that primarily target SSR2. A proof of concept trial published in 2004, compared pasireotide (100 µg or 250 µg) with subcutaneous octreotide. All three interventions significantly reduced GH levels and there was a significant dose-dependant reduction in GH levels between the low and higher-dose pasireotide. The authors report three types of response to pasireotide. The first response involved a reduction in GH levels for both octreotide and pasireotide treatment, presumably mediated by SSR2. In the second type of response, pasireotide was more efficacious than octreotide, presumably because of SSR5
overexpression. In the last response, octreotide was better than pasireotide, which was presumed to occur as a consequence of high SSR2 and low SSR5 expression. Pasireotide then underwent a Phase II, multicentre, open label, randomized, crossover trial, in which 60 patients with active acromegaly were initially given octreotide for 28 days to assess response to standard treatment. Thereafter, the patients were randomly assigned to 200, 400 and 600µg pasireotide per day. The primary end point was a binary response based on circulating GH and IGF-I levels and secondary end points included symptoms, signs and MRI findings. After 1 month of treatment, 11 (19%) of 58 patients achieved a full response. The full response rate was as follows for the different doses of pasireotide: 200 µg (14%), 400 µg (12%) and 600 µg (30%). On the 600µg dose, significantly more people achieved GH levels <2.5 µg. After 3 months of treatment, 27% of patients on pasireotide achieved a full biochemical response. 49% had GH levels <2.5 µg and 38% achieved a normal IGF-I level.

No significant increase in tumor size occurred with treatment and 20 patients (39%) experienced clinically significant decreases in pituitary tumor volume. A number of mild to moderate gastrointestinal disturbances were reported, with patients developing nausea (25%), diarrhea (22%), abdominal pain (12%) and flatulence (10%). Other adverse events included increased blood glucose (7%) and increased HbA1c (5%), which lead to diabetes mellitus (5%).

The authors conclude that after 3 months of treatment with 200–600 pasireotide, one third of patients achieved full biochemical control and 39% had reduction in tumor size. Larger phase 3 trials are awaited to further assess efficacy.
1.7.3.4.2 Chimeric molecules

A number of in vitro studies have assessed the efficacy of various compounds, which have affinity for multiple SSR and dopamine receptors.\textsuperscript{221,222} In one study, patients with GH-secreting tumors that partially responded to octreotide therapy were treated in vitro with different chimeric compounds; the result was a greater reduction in GH secretion than reported with octreotide alone\textsuperscript{222}. Future in vitro and clinical studies will determine if these compounds have a role in the management of patients with acromegaly.

1.7.3.5 Conclusions

Medical therapy has an increasingly important role in the management of acromegaly both as a primary and secondary therapy. SRL therapy leads to normalization of GH and IGF-I levels in a 48-52% and 42-68%, respectively in patients and may also lead to clinically significant tumor shrinkage. Dopamine agonist therapy may be useful in patients with mild disease and may also be of benefit in some patients who are not hyperprolactinemic, but further data is needed regarding long-term safety in relation to cardiac valve dysfunction. Pegvisomant normalizes IGF-I levels in the majority of cases but does not lead to tumor shrinkage. In summary, the currently available medical therapies as monotherapy or in combination are effective in a proportion of patients; however, there are still subsets of patients who do not respond to current medical therapy and the ongoing development of newer medical therapies is essential.
1.8 Morbidity associated with Acromegaly

Acromegaly is associated with morbidity due to effects on the cardiovascular and respiratory systems, metabolic control and increased mitotic potential (which will be covered in section 1.9.7). The area of systemic complications in acromegaly has been extensively and expertly reviewed previously by Colao et al.207

1.8.1 Cardiovascular morbidity in acromegaly

Acromegaly leads to well described abnormalities on cardiac and vascular structure and function. The most common cardiac feature of acromegaly is biventricular hypertrophy.207,223-228 Cardiac walls are thickened, however, there is no change in size of cardiac chambers due to the relative increase in cardiac myocyte width.207 This hypertrophy is most common in patients who are older and have been exposed to high GH and IGF-I levels for long periods.207, however, there is evidence that hypertrophy can occur in patients even with short exposure to GH hypersecretion.191,228,230 Indeed, in a recent study by Colao et al patients with acromegaly have 30% higher left ventricular masses than age matched controls and 60% had left ventricular hypertrophy.231 This cardiac hypertrophy occurs independently of hypertension and glucose abnormalities (both of which are common in acromegaly), however if associated with these two abnormalities the hypertrophy is more severe.207

1.8.1.1 Acromegalic Cardiomyopathy

There are three stages described for acromegalic cardiomyopathy. In the early phase there is initial cardiac hypertrophy, elevated heart rate and increased systolic
output which combined lead to a hyperkinetic syndrome. In the middle stage there is increasing hypertrophy and insufficient systolic and diastolic function during exercise. In the final stage there is diastolic and systolic dysfunction at rest and heart failure due to a dilated cardiomyopathy. Despite the prevalence of some of these abnormalities one must remember that patients who are often exposed to the largest cumulative exposure to GH/IGF-I are also the oldest and as such may have higher rates of left ventricular hypertrophy (LVH) and systolic dysfunction due to their age. Left ventricular hypertrophy is found in the majority of patients at diagnosis and interstitial fibrosis is the main abnormality on histology. There is gradual impairment of heart architecture by increased extracellular collagen deposition, myofibrillar derangement, areas of monocyte necrosis and lymphomononuclear infiltration (a similar pattern to that seen in myocarditis). Co-existing hypertension is particularly related to development of acromegalic cardiomyopathy and on multistep linear regression analysis the strongest predictor of cardiac hypertrophy was diastolic blood pressure.

Reduction of GH and IGF-I has been associated with a decrease in left ventricular hypertrophy, heart rate, arrhythmias and blood pressure in some studies. It has been associated with an improvement in diastolic and systolic function in the majority of studies (although some studies showed no improvement, particularly in systolic function).

1.8.1.2. Cardiac valve disease in acromegaly

Not surprisingly, with such degrees of myocardial dysfunction and structural abnormalities there is an increase in valvular heart disease in patients with acromegaly. Lie and Grossman found mitral and aortic valve abnormalities in 19% of patients in their post mortem series of patients with acromegaly. Van der
Klaauw et al reported that 46% of patients with acromegaly had either mitral or aortic valve disease, this increased to 67% after 1.9 years follow up (p=0.008) [237]. However, in one study the cause of increase in valvular disease was solely mitral valve disease (increase from 32 to 60%, p=0.002) with no change in aortic valve disease (27 to 31%, p=NS) [237]. The authors also reported that the increase in valvular disease was correlated with disease activity, patients with active disease had a much higher rate of valvular disease at follow up (56 to 88%, p=0.031), compared to no difference in patients who had controlled disease. The increase in the active group was predominantly due to mitral regurgitation (39 to 78%, p=0.016) [237]. Colao et al have also reported an increased rate of mitral and aortic valve disease assessed by echocardiography in patients with acromegaly (n=42 active acromegaly, n=22 cured acromegaly and n=64 controls) [238]. The prevalence of cardiac valve abnormality was higher in both the active acromegaly (86% vs. 24%, p<0.0001) and cured patients (73% vs. 9%, p<0.0001) compared to control group. Cardiac valve abnormalities perhaps unsurprisingly were associated with LVH [238] and in patients without LVH only patients with acromegaly had aortic or mitral valve abnormalities (nil in control group).

There have also been reports of increased aortic root dimensions in patients with acromegaly (aortic root at sino-tubular junction 30±4mm in acromegaly compared to 26±3mm in control subjects, p=0.0001), although not all measurements of aortic root diameter were increased [239]. Pereira et al [240] also described increased prevalence of regurgitant valve disease in patients with acromegaly (n=40, significant valve disease 22%) compared to 120 controls (significant valve disease 6.7%, p=0.005). This was due to aortic (30% acromegaly compared to 7% controls) and mitral valve disease (5% acromegaly and 0% controls). Logistic regression analysis showed a significant impact of disease duration on valvular disease (OR 1.19, 95% CI 1.028-1.376, p=0.019) [240].
1.8.1.3 Rhythm disturbances in acromegaly

Rhythm disturbances are more common in patients with acromegaly than control patients and are frequently exercise induced\textsuperscript{241,242}. Supraventricular premature complexes are not more common than the general population\textsuperscript{243}. However, ectopic beats, paroxysmal atrial fibrillation, paroxysmal SVT, sick sinus syndrome, ventricular tachycardia and bundle branch blocks are seen more commonly in acromegaly than in healthy controls (particularly at peak exercise)\textsuperscript{241,242}. Up to 40% of patients can suffer from conduction disorders and it is unknown whether recovery from acromegaly improves this. The prevalence and severity of ventricular arrhythmias is greater in patients with acromegaly than in controls and this severity is related to left ventricular mass\textsuperscript{241}. There is also an increase in late potentials (low amplitude, high frequency waves in the terminal tract of QRS) in patients with acromegaly and these are strong predictors of future arrhythmias\textsuperscript{244,245}.

1.8.1.4 Hypertension in Acromegaly

Arterial hypertension is considered to be one of the most adverse prognostic factors for mortality in acromegaly\textsuperscript{207}. There are many postulated mechanisms underpinning hypertension in acromegaly but the true pathogenies remains to be elucidated. Possible mechanisms include increased plasma volume, differences in exchangeable sodium pool (but normal levels of aldosterone and its precursors, ANP and plasma renin activity) and changes in the adrenergic system\textsuperscript{207}. Insulin resistance and diabetes are also likely to play a key role in the development of hypertension in acromegaly and fasting insulin levels have been correlated with diastolic blood pressure in normal controls but not in patients with acromegaly\textsuperscript{207}. Another possible explanation for the development of hypertension in acromegaly is
the increased cardiac output and cardiac index, while systemic vascular resistance is reduced globally but may be increased in certain vascular districts\textsuperscript{207}.

1.8.1.5 Atherosclerosis and endothelial dysfunction

Increased carotid intima medial thickness (CIMT) has been observed in active as well as cured patients with acromegaly but well defined carotid plaques were not more common than in controls\textsuperscript{246}. In this study patients with acromegaly had higher levels of insulin, cholesterol and fibrinogen than controls and this may account for the increased CIMT.

Colao et al have demonstrated that these changes in CIMT most likely relate to risk factors as there was no difference in CIMT in patients with active and cured disease when they were matched for vascular risk factors\textsuperscript{247}.

Studies using Laser Doppler Flowmetry has also reported endothelial dysfunction in the cutaneous circulation of the hand in patients with acromegaly, there was normal vascular smooth muscle vasodilation but abnormal endothelial dependent vasodilation and increased sympathethic mediated vasoconstriction in patients with acromegaly\textsuperscript{248}.

1.8.2 Respiratory Complications of Acromegaly

Increased respiratory mortality in patients with acromegaly has been reported in some\textsuperscript{53,132,134,136,138} but not all studies\textsuperscript{137,249}. There are several abnormalities of both the upper and lower respiratory tracts in patients with acromegaly. Abnormalities in the upper respiratory tract include macroglossia, swelling and collapse of the pharyngeal walls, thickening of the true and false vocal cords, overgrowth of the mandible/ maxilla, prognathism, dorsocaudal rotation of the mandible, thyroid
overgrowth and submandibular gland hyperplasia\textsuperscript{207}. Abnormalities in the lower respiratory tract include small airway narrowing, lung overgrowth, increased lung volume, increased lung compliance, deranged respiratory muscles, alterations in intervertebral disc dimensions and thoracic spine kyphoscoliosis\textsuperscript{207}. The result of these abnormalities is the development of obstructive sleep apnoea and impaired respiratory function. The impaired respiratory function includes subnormal respiratory muscle force, decreased inspiratory cycle duration, accelerated respiratory pattern\textsuperscript{280}. Combined with these changes is an increase in total lung capacity and volume, but also small and large airway narrowing\textsuperscript{251}. The combination of the above changes leads to significant hypoxaemia and in Luboschitzky et al found that 80\% of patients with acromegaly studies had subclinical hypoxaemia\textsuperscript{252}.

GH and IGF-1 have been shown to have direct effects on lung tissue to increase lung and smooth muscle cell proliferation, activate alveolar macrophages and increase type I collagen fibres and mucopolysaccharides\textsuperscript{207}.

Sleep apnoea occurs in between 20-80\% of patients with acromegaly compared to 2-4\% in the normal male population and 1-2\% in the normal female population\textsuperscript{207}. The prevalence of sleep apnoea in acromegaly is important as it may have a role to play in many of the morbidities reported in acromegaly, as sleep apnoea in the general population has been linked with ischaemic heart disease, arrhythmia, hypertension and stroke\textsuperscript{253}. The aetiology of sleep apnoea in acromegaly may be either central (postulated to be related to high somatostatin tone)\textsuperscript{254} or obstructive (due to anatomical and soft tissue changes) or a combination\textsuperscript{207}. The degree of sleep apnoea is associated with the degree of disease activity and several studies have reported some correlation between the degree of sleep apnoea and IGF-1 and GH concentrations\textsuperscript{255-257}. Despite this correlation it should be highlighted that a
number have studies have reported that sleep apnoea does not necessarily improve following cure of acromegaly 258,259.

1.8.3 Metabolic complications of Acromegaly

The prevalence of diabetes mellitus in acromegaly ranges from 19-56% 260, but the majority of patients with acromegaly will have insulin resistance either at the level of the liver or periphery or both 261. Risk factors for the development of diabetes in patients with acromegaly include increasing age 53,262, increased GH concentrations 53, longer duration of disease 53, family history 260 and presence of hypertension 260. The mechanisms underpinning glucose intolerance in acromegaly include GH inducing insulin resistance by impairing the ability of insulin to suppress glucose production and stimulate glucose utilisation 207. Sonksen et al have hypothesised that there are three stages in the development of diabetes in people with acromegaly, the first stage hyperinsulinaemic stage (with normal or borderline glucose tolerance) followed by a stage characterised by a delay in insulin response to glucose (with normal or impaired glucose tolerance) and a final stage which is characterised by maximal insulin secretion in the fasting stage with no further insulin response following glucose loading 263.

Lipid metabolism is also abnormal in patients with acromegaly (particularly those with glucose intolerance) with increases in Lp(a) concentrations (which are positively correlated with GH but not IGF-I concentrations). Other lipid abnormalities include a low HDL cholesterol level which increase following cure of acromegaly and an increase in LDL (particularly small/ dense LDL) 207.
1.9. Mortality in Acromegaly

1.9.1. Studies of mortality in acromegaly

It is now well established that untreated acromegaly is associated with reduced life expectancy. Several retrospective studies have demonstrated a 2- to 3-fold increased mortality in acromegalic patients compared with age- and sex-matched controls. Death is due predominantly to cardio/cerebrovascular disease, respiratory disease and, in some studies, malignancy \(^{53,71,132-134,136-138,249,264,265}\). Results from the more recent studies also demonstrated that the high mortality rates associated with acromegaly can be reversed if treatment is successful in reducing GH levels to less than 2-2.5μg/L \(^{133,134,137,264,266}\) and in some studies the normalisation of IGF-I levels into age specific reference ranges \(^{75,139,267}\).

As far back as the 1920s, patients with acromegaly were thought to have reduced life expectancy. In a series of 100 patients with acromegaly studied and reported on in 1966, 50% had died before the age of 50 years and 89% by the age of 60 years \(^{268}\). The causes of death in these early series included diabetic coma, vascular disease, sepsis and extension of the pituitary tumor.

The excess mortality associated with acromegaly was first accurately qualified and quantified in the series by Wright et al., published in 1970. In this study the cause of death in a cohort of 194 subjects with acromegaly was analyzed and compared with those of the general population of England and Wales \(^{138}\). 54 deaths were observed, compared with 28.5 expected, giving a standardized mortality ratio (SMR) of 1.9. The increased number of deaths was predominantly due to cardiovascular disease in males, cerebrovascular disease in females and respiratory disease in both. There was no increase mortality from malignancies. Factors associated with increased mortality included the presence of hypertension and diabetes mellitus. Even in this early study, it was evident that control or
improvement in GH levels could lead to a decrease in mortality rates [deaths: no
treatment group 27/55 (49.1%), compared to 28/139 (20.1%) in treated group of
which 5/11 surgery, 15/81 radiotherapy and 8/47 multiple treatment modalities].
These findings were confirmed in a number of subsequent series over the following
two decades. The excess deaths were predominantly due to vascular
disease, respiratory disease and, in some studies, malignancy.
In recent years, significant advances have been made in the management of
acromegaly, resulting in a change in overall mortality rates seen in acromegaly. In
epidemiological studies performed over the last decade although mortality in acromegalic patients remains elevated compared to the
general population in several studies, the mortality increase is generally less than 2-
fold, compared with the 2-3 fold mortality rates seen in earlier series, indeed some
studies report no increase in mortality. In a recent meta-analysis pooling 16
studies, SMR ranged from 1.16 to 3.31, with a mean weighted SMR of 1.72 (CI
1.62-1.83). A metaregression pointed towards improved survival in more recent
studies (SMR 1.62 papers published in 1995 onwards compared to SMR 2.11 in
papers published pre 1995), presumably due to modern treatment modalities and
more strictly defined cure criteria. A summary of studies assessing mortality in
patients with acromegaly can be reviewed in Table 1.1a and 1.1b.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Deaths</th>
<th>Total Group SMR</th>
<th>Cause Specific Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al, 1970 (138)</td>
<td>194</td>
<td>55</td>
<td>1.8</td>
<td>Vascular 38.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant 18%</td>
</tr>
<tr>
<td>Alexander et al, 1980 (132)</td>
<td>164</td>
<td>45</td>
<td>3.3 (Male 24/5, SMR=4.8, Female 21/8.1, SMR=2.6)</td>
<td>Vascular 60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory 15.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant 15.5%</td>
</tr>
<tr>
<td>Nabarro 1987 (53)</td>
<td>256</td>
<td>47</td>
<td>1.3 (&lt; 55 years 10/5.3, SMR=1.9, Female 23/13.7, SMR=1.7)</td>
<td>Cardiovascular 47/37.2 SMR = 1.3 N/S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vascular 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant 23%</td>
</tr>
<tr>
<td>Bengtsson et al, 1988 (249)</td>
<td>168</td>
<td>62</td>
<td>3.2</td>
<td>Vascular deaths 32/9 SMR=3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer deaths 15/5.6 SMR=2.7</td>
</tr>
<tr>
<td>Rajasooriya et al, 1994 (137)</td>
<td>151</td>
<td>32</td>
<td>3.0</td>
<td>Cardiovascular SMR 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebrovascular SMR 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignancy SMR 1</td>
</tr>
<tr>
<td>Estabe et al, 1993 (269)</td>
<td>74</td>
<td>10</td>
<td>3.2 (1.55-5.93)</td>
<td>Male SMR 7 (2.81-14.4), Female SMR 1.4 (0.29-4.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vascular 10 (0.25-55.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignancy 7.1 (2.31-18.6)</td>
</tr>
<tr>
<td>Bates et al, 1993 (134)</td>
<td>79</td>
<td>28</td>
<td>2.63 (1.8-3.9)</td>
<td>Vascular 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant 11%</td>
</tr>
<tr>
<td>Orme et al, 1998 (136)</td>
<td>1362</td>
<td>366</td>
<td>1.60 (1.44-1.77)</td>
<td>Vascular SMR 1.76 (1.47-2.07), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebrovascular SMR 2.06 (1.5-2.76), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory SMR 1.85 (0.92-1.44), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant SMR 1.16 (0.92-1.44), p&lt;0.1</td>
</tr>
<tr>
<td>Swearingen et al, 1998 (75)</td>
<td>149</td>
<td>12</td>
<td>1.16 (0.66-2.0)</td>
<td>Vascular 5/12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory 1/12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant 4/12</td>
</tr>
<tr>
<td>Aboch et al, 1998 (270)</td>
<td>254</td>
<td>29</td>
<td>1.28</td>
<td>Cause specific not available in majority of 20 deaths</td>
</tr>
</tbody>
</table>

**Table 1.1a.** Studies assessing disease specific mortality rates in patients with acromegaly (pre year 2000).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Deaths</th>
<th>Total Group SMR</th>
<th>Mortality Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beauregard et al</td>
<td>103</td>
<td>18</td>
<td>2.14</td>
<td>Cause specific: Vascular 5/18, Malignant 9/18</td>
</tr>
<tr>
<td>2003 (71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biermasz et al</td>
<td>164</td>
<td>28</td>
<td>1.33 (0.87, 1.87)</td>
<td>Cause specific: Vascular 7/28, Malignant 13/28</td>
</tr>
<tr>
<td>2004 (139)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holdaway et al</td>
<td>208</td>
<td>72</td>
<td>1.22</td>
<td>Cause specific: Vascular 36/72 (50%), Respiratory 2/76, Malignant 17/72 (24%)</td>
</tr>
<tr>
<td>2004 (264)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayuk et al</td>
<td>419</td>
<td>95</td>
<td>1.26 (1.03-1.54), p=0.045</td>
<td>Cause specific: Cardiovascular SMR 1.37 (0.98-1.9), p=0.111, Cerebrovascular SMR 2.68 (1.73-4.15), p=0.007, Respiratory SMR 1.52 (0.88-2.61), p=0.219, Malignant SMR 0.91 (0.59-1.38), p=0.65</td>
</tr>
<tr>
<td>2004 (133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestron et al</td>
<td>1219</td>
<td>56</td>
<td>Total Group SMR not available</td>
<td>SMR 1.3 (0.52-2.67) for remission group and 1.38 (0.51-3.0) in persistent disease group, Cause specific: Cardiovascular 26.8%, Cerebrovascular 8.9%, Respiratory 5.4%, Malignant 16.1%</td>
</tr>
<tr>
<td>2004 (267)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauppinen-Makelin et al</td>
<td>334</td>
<td>56</td>
<td>1.16 (0.85-1.54)</td>
<td>Cause specific: Cardiovascular 23.2% (coronary artery disease), Other cardiovascular diseases (16.1%), Cerebrovascular 14.3%, Malignant 21.4%</td>
</tr>
<tr>
<td>2005 (266)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trepp et al</td>
<td>94</td>
<td>13</td>
<td>1.34 (0.71-2.29)</td>
<td>Cause specific: Cardiovascular 6/13, Malignant 4/13</td>
</tr>
<tr>
<td>2005 (274)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1b. Studies assessing disease specific mortality rates in patients with acromegaly (post year 2000).

The West Midlands Acromegaly Study reported on outcome in 419 patients with acromegaly, of whom 324 were alive and 95 deceased\textsuperscript{133}. Compared to the general population, all cause mortality was significantly increased with an SMR of 1.26
The excess mortality was due predominantly to cerebrovascular disease with small but non-significant increases due to cardiovascular and respiratory disease. There was no increase in deaths from malignancy. No significant increase in mortality was identified in patients with a post-treatment GH less than 4mU/L (2μg/L), but survival was reduced in the cohort failing to achieve this target, with a RR of 1.55 (CI 0.97-2.5), p=0.068. Insulin-like growth factor (IGF)-I data was available in 360 patients, representing 86% of the cohort. No effect of IGF-I on outcome could be demonstrated, with the rate ratio for those patients achieving serum IGF-I within the normal age-related range similar to those who did not [elevated IGF-I RR 1.2 (0.71-2.020, p=0.5)] 133.

1.9.2 Impact of GH levels on mortality in acromegaly

Results from two studies in the early 1990’s demonstrated that the increased mortality associated with acromegaly can be diminished if treatment is successful in reducing GH hypersecretion to less than 5mU/L (2.5μg/L), whether this is measured as the mean of a growth hormone day profile or as a random growth hormone level 134 137. In the first of these studies by Bates et al, in a cohort of 79 patients with acromegaly, the SMR fell from 2.6 to 2.0 if treatment reduced GH levels to under 10mU/L (5μg/L) 134. Even more significant was the fact that mortality was reduced to normal if post-treatment GH levels of less than 5mU/L (2.5μg/L) were achieved. The second study by Rajasoorya et al in a cohort of 151 patients with acromegaly showed both on univariate and multivariate analysis that higher GH levels were associated with reduced survival 137.

The studies discussed above reached a consensus in showing that post-treatment GH values of less than 2.5μg/L restores SMR to normal, providing an evidence base for targeted reduction of GH concentrations 55,271,272. However, cut off points

62
of 2.5μg/L and <1μg/L to define an adequate response to treatment have been arbitrarily adopted, with little scientific basis for this selection. In the West Midlands Acromegaly Study, comparison of crude death rates per 1000 population suggested that a GH of 2μg/L may be a more appropriate treatment target, with a step-up in the death rate once GH exceeded 2μg/L. Data from Holdaway et al. suggest a further improvement in outcome if GH can be lowered to under 1μg/L as opposed to 2.5μg/L. The Finnish Nationwide Survey of Mortality in Acromegaly reported similar findings. In a cohort of 334 acromegalic patients with 56 deaths, excess mortality was seen in those with post-treatment GH levels greater than 2.5μg/L (SMR 1.63, (1.1-2.35, p<0.001)

In a recent meta-analysis focusing on the relationship between biochemical measurements and mortality during follow-up after treatment for acromegaly, mortality was close to the expected level when last available GH was <2.5μg/L (SMR 1.1, 95% CI 0.9-1.4), but was significantly elevated in those with last available GH >2.5μg/L (SMR 1.9, 95% CI 1.5-2.4). The risk ratio for a serum GH >2.5 μg/L was 1.7 (P<0.05).

Therefore, a fundamental aim of treatment in acromegaly should be reduction of GH values to less than 2.5μg/L and possibly even lower to less than 1μg/L, although care must be taken that this is not at the expense of inducing GH deficiency and hypopituitarism (which in itself is associated with an adverse outcome, see section 1.10). In addition, it must be noted that GH cannot be used to monitor treatment in patients treated with the GH antagonist pegvisomant.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Period</th>
<th>Patients</th>
<th>Deaths</th>
<th>Total Group</th>
<th>SMR if GH above Cut off</th>
<th>SMR if IGF-I above cut off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bates et al</td>
<td>1967-91</td>
<td>79</td>
<td>29</td>
<td>2.63 (1.8-3.9)</td>
<td>GH &lt;2.5ng/ml SMR 1.42 (0.46-3.31)</td>
<td>NA</td>
</tr>
<tr>
<td>Orme et al</td>
<td>1998 (136)</td>
<td>NA</td>
<td>366</td>
<td>1.70 (1.44-1.77)</td>
<td>GH &lt;2.5ng/ml SMR 2.01 (0.9-3.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Swearingen et al</td>
<td>1976-96</td>
<td>149</td>
<td>12</td>
<td>1.16 (0.66-2.0)</td>
<td>NA</td>
<td>Mortality risk if active disease 3.5 fold (1.0-12) (multivariate analysis)</td>
</tr>
<tr>
<td>Aboosh et al</td>
<td>1974-92</td>
<td>254</td>
<td>29</td>
<td>1.28</td>
<td>Remission = GH ≤5 ng/ml</td>
<td>NA</td>
</tr>
<tr>
<td>Beauregard et al</td>
<td>1970-99</td>
<td>103</td>
<td>16</td>
<td>2.14</td>
<td>Persistent SMR = 3.1</td>
<td>NA</td>
</tr>
<tr>
<td>Biemans et al</td>
<td>1977-2002</td>
<td>164</td>
<td>20</td>
<td>1.33 (0.87-1.87)</td>
<td>GH suppressed during OGTT RR 1.77 (0.8-3.94)</td>
<td>Remission SMR = 0.88 (0.57-3.03)</td>
</tr>
<tr>
<td>Holdaway et al</td>
<td>1964-2000</td>
<td>208</td>
<td>72</td>
<td>1.22</td>
<td>GH &lt;1ng/ml 18% deceased</td>
<td>Elevated age related IGF-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH 1-2ng/ml 21% deceased</td>
<td>RR 4.78 (1.01-22.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH 2-5ng/ml 39% deceased</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH &gt;5ng/ml 52% deceased</td>
<td>Multivariate analysis IGF-I not independent variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>But SMR 3.5 (2.8-4.2) when IGF-I SD score &gt;2</td>
</tr>
<tr>
<td>Ayuk et al</td>
<td>Pre 2001</td>
<td>419</td>
<td>95</td>
<td>1.28 (1.03-1.54)</td>
<td>GH &gt;2ng/ml vs. &lt;2ng/ml</td>
<td>IGF-I not predictive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate ratio 1.55 (0.97-2.5)</td>
<td>Internal comparison of normal vs. elevated IGF-I RR =1.2 (0.71-2.02)</td>
<td></td>
</tr>
<tr>
<td>Mestron et al</td>
<td>2004 (267)</td>
<td>NA</td>
<td>56</td>
<td>NA</td>
<td>GH &lt;2ng/ml OGTT (8 deaths) vs.</td>
<td>IGF-I never normal 41 compared with 15 deaths (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH &gt;2ng/ml (46 deaths), p=0.001</td>
<td></td>
</tr>
<tr>
<td>Kauppinen-Makelin et al 2005 (265)</td>
<td>1980-99</td>
<td>334</td>
<td>56</td>
<td>1.16 (0.85-1.54)</td>
<td>GH &lt;2.5ng/ml SMR 0.48 (0.23-0.88)</td>
<td>IGF-I not predictive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH &gt;2.5ng/ml SMR 1.63 (1.1-2.35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multivariate &gt;2.5ng/ml OR 2.1 (1.37-7.52)</td>
<td>OR 0.46 (0.17-1.26)</td>
</tr>
<tr>
<td>Trepp et al</td>
<td>1971-2003</td>
<td>94</td>
<td>13</td>
<td>1.34 (0.71-2.29)</td>
<td>Remission criteria age related IGF-I and either OGTT GH &lt;1ng/ml or random GH &lt;2.5ng/ml</td>
<td>Remission SMR 1.3 (0.52-2.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Persistent SMR 1.38 (0.51-3.0)</td>
<td></td>
</tr>
</tbody>
</table>
1.9.3 Impact of IGF-I levels on mortality in acromegaly

IGF-I is now widely used as a first line investigation for the diagnosis and therapeutic monitoring of patients with acromegaly. Indeed, the introduction of GH-antagonists as medical treatment for acromegaly necessitates the use of IGF-I in the biochemical monitoring of patients treated with these agents. However, the relationship between outcome and latest IGF-I levels is not as clear cut as with latest GH (Table 1.2).

In the first of these studies assessing the relationship between IGF-I and mortality (162 patients, 12 deaths), those patients who were surgically cured, defined by a normal IGF-I, had mortality similar to that of the general population of the United States, while those with active disease as defined by a persistently elevated IGF-I had reduced life expectancy for the period that the IGF-I was elevated. A further study also concluded that IGF-I normalization reduced mortality to expected levels, however serum IGF-I was not an independent predictor of mortality when both GH and IGF-I measurements were included in the multivariate analysis, and was only significant when looking at standard deviation scores (SDS) >2 for IGF-I compared to normal IGF-I levels. Further issues raised included the use of different IGF-I assays over the study period and a relatively small number of deaths.

In the recent meta-analysis by Holdaway et al., those with normal IGF-I had mortality close to the expected values for the general population (SMR 1.1, 95% CI 0.9, 1.4), whereas the SMR for those with elevated IGF-I at last follow-up remained significantly increased (SMR 2.5, 95% CI 1.6, 4.0). The risk ratio for an elevated serum IGF-I was 2.3 (P<0.05). However, it should be noted that two of the largest studies, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between post-treatment IGF-I levels and mortality (RR 1.2, CI 0.71-2.02, p=0.05) and (0.46, CI 0.17-1.26, p=0.13), respectively (Table 2),
suggesting last available serum IGF-I may not be as reliable a marker of mortality in acromegaly as last available GH.

1.9.4 Assay variability in studies of mortality in acromegaly

There are also methodological problems with using the last available GH/IGF-I in the analysis for mortality, as this value is inherently biased and does not take into account prior GH/IGF-I levels. Many studies were also performed using older assays which may not be used in clinical practice today, however it may take many years to get meaningful data on survival using newer more sensitive assays and these older studies have to be interpreted with this in mind. Many studies have used multiple assays during the duration of study or multiple assays in different centers in multicentre studies both for GH and IGF-I. Some studies do not describe the assays used. Both IGF-I and GH assays, even those in use today are prone to large variability which will impact on the result of the studies. Other difficulties include normal age and gender matched reference ranges for IGF-I and different GH standards during time. For example, in the Finnish national acromegaly study during the years 1980 to 1999 GH measurements were performed in 5 laboratories using seven assays (these assays were not all calibrated to the same International Reference Preparation). When the assays changed between 1995 and 2000, 4 laboratories changed to an immunofluorometric assay (measures only 22 kDa form) and one laboratory changed to a chemiluminescent assay (measures 22 and 20kDa forms, leading to a 1.4- to 1.5-fold higher value than the immunofluorometric assay). Serum IGF-I was measured by RIA or IRMA and various centers used different cut-offs.

In recent years the use of higher sensitivity IRMA, immunofluorometric, chemiluminescence, immunoradiometric assays have been associated with
significantly lower nadir GH during OGTT in healthy controls than was previously thought (ranging from 0.029-0.25μg/litre, there was also a gender difference noted in some studies)\textsuperscript{56,57,58,59,275}. Therefore with the use of more sensitive assays the target for GH may decrease over time, as they can detect much lower levels of GH compared to older RIA and have redefined normality during an OGTT. However, it may be some time before we have adequate follow-up data to assess GH cut-offs using these newer assays.

1.9.5 Role of pituitary radiotherapy on mortality in acromegaly

In the West Midlands study, compared with the general population, the use of external radiotherapy was associated with increased mortality, with an SMR of 1.58 (1.22-2.04), p=0.005 and when assessed on internal analysis within the acromegaly cohort resulted in a RR 1.67 (1.1-2.56), p=0.02\textsuperscript{133}. In the Finnish Survey, mortality was also increased in patients who had been treated with radiotherapy (SMR 1.69, (1.05-2.58), p<0.001)\textsuperscript{268}. In the Spanish acromegaly registry, patients who died had a twice-greater probability of having been treated with radiotherapy than those who had survived (hazard ratio of 2.29, CI 1.03-5.08, p=0.026)\textsuperscript{267}, (Table 1.3). The role of radiotherapy is further discussed in section 1.7.2.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>DXT</th>
<th>SMR</th>
<th>RR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biermasz et al,</td>
<td>164</td>
<td>57 CRT</td>
<td>NA</td>
<td>1.73 (0.77-3.88)</td>
<td>Cause of death not known</td>
</tr>
<tr>
<td>2004 (139)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age and sex adjusted 1.169 (0.52-2.55)</td>
</tr>
<tr>
<td>Holdaway et al,</td>
<td>208</td>
<td>143 CRT</td>
<td>NA</td>
<td>NA</td>
<td>No increase stroke mortality</td>
</tr>
<tr>
<td>2004 (264)</td>
<td></td>
<td>35 Yttrium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayuk et al,</td>
<td>419</td>
<td>211 CRT</td>
<td>NA</td>
<td>1.67 (1.1-2.06) (p=0.02)</td>
<td>Cerebrovascular SMR = 4.42</td>
</tr>
<tr>
<td>2004 (133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauppinen-Makelin</td>
<td>334</td>
<td>116 CRT</td>
<td>DXT group 1.69 (1.55-2.05)</td>
<td>2.27 (p=0.08)</td>
<td>5/6 stroke deaths</td>
</tr>
<tr>
<td>et al, 2005 (266)</td>
<td></td>
<td></td>
<td>(p=0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestron et al</td>
<td>1219</td>
<td>104 CRT</td>
<td>DXT group 1.69 (1.55-2.05) vs. 0.94 (0.62-1.37) for non DXT (p=0.01)</td>
<td>N/A</td>
<td>Cerebrovascular mortality data</td>
</tr>
<tr>
<td>2005 (267)</td>
<td></td>
<td>27 stereotactic radiotherapy</td>
<td>9 radiotherapy</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table 1.3.** Studies assessing the role of pituitary radiotherapy in mortality in patients with acromegaly

### 1.9.6 Role of pituitary dysfunction on mortality in acromegaly

Although hypopituitarism is associated with increased mortality (see section 1.10) there is little data on the role of hypopituitarism in patients with acromegaly per se. In the West Midlands study, there was a trend (p=0.07) towards reduced survival in patients with acromegaly who had a greater number of deficient hypothalamo-pituitary axes compared with those without evidence of hypopituitarism.¹³³

### 1.9.7 Cancer mortality in acromegaly

Both IGF-I and GH have well described mitogenic properties in vitro and case controlled studies have found increased serum levels of IGF-I in subjects who had or eventually developed prostate or premenopausal breast cancer,²⁷⁶ therefore one might anticipate excess malignancies in acromegaly. However, epidemiological studies exploring the link between acromegaly, cancer incidence and cancer mortality have given rise to conflicting data. Early studies suggested an increased
incidence of neoplasia overall, particularly of the breast \(^{53}\) and colon \(^{277}\), in patients with acromegaly. More recent studies, however, have failed to confirm these findings, and suggest overall cancer incidence is not increased in acromegaly \(^{136,278}\). Orme et al. retrospectively examined the cancer incidence and mortality in a UK cohort of 1362 patients with acromegaly \(^{136}\); overall cancer mortality rate was not increased (indeed, if anything it was lower SMR 0.76, CI 0.6-0.95), but there was a significant increase in the colon cancer mortality rate (SMR 2.47, CI 1.31-4.22) and a non-significant increase in female breast cancer mortality (SMR 1.60, 0.85-2.74, \(p=0.07\)). An important finding was that the overall mortality rate increased significantly if GH levels were elevated [GH <2.5ng/ml SMR 1.1 (0.89-1.35), GH 2.5-9.9ng/ml SMR 1.41 (1.16-1.68), GH>10ng/ml SMR 2.12 (1.7-2.62), \(p\) for trend <0.0001]. This was also true for cardiovascular death [GH <2.5ng/ml SMR 1.2 (0.83-1.68), GH 2.5-9.9ng/ml SMR 1.59 (1.15-2.15), GH>10ng/ml SMR 2.11 (1.42-3.01), \(p\) for trend 0.02] and cancer death [GH <2.5ng/ml SMR 0.96 (0.63-1.41), GH 2.5-9.9ng/ml SMR 0.81 (0.5-1.24), GH>10ng/ml SMR 1.81(1.13-2.74), \(p\) for trend 0.05]. Most recent studies have found cancer death rates in patients with acromegaly to be similar to those in the general population, suggesting malignancy is not a significant cause of mortality in patients with acromegaly with modern treatment modalities and strict targets \(^{133,264,266,267}\).

The exact magnitude of the risk of colon cancer and the role of screening programs remain the subject of much debate \(^{279-282}\). Full colonoscopy is important as up to two thirds of lesions were right sided in one study \(^{283}\). A significant amount of data in the general population suggests that the majority of colorectal carcinomas arise from adenomas and as such detection and removal of adenomatous polyps should reduce colorectal cancer incidence and mortality \(^{284}\). Ron et al assessed the risk of gastrointestinal cancer in 1041 with acromegaly reviewed between 1969 and 1985 from all VA hospitals in the USA and compared them to over 37,000 veterans
discharged from VA hospitals during the same follow up time. Patients with acromegaly had a SIR for cancer of 1.6 (1.3-1.9), (116 observed cancers compared to 72.8 expected), with an SIR of 2.0 (1.3-2.9) for digestive organ or peritoneal cancers [in particular esophageal (3.1(1.3-6.0) and colonic (3.1 (1.7-5.1) neoplasia]. However other large studies of mortality in patients with acromegaly have not reported raised risk of neoplastic deaths. It is likely that the increased risk of colorectal cancer in acromegaly is modest. Renihan et al have suggested that over a 10 year period 556 colonoscopies would need to be performed to prevent 1 death. Therefore the issue of colonoscopy screening in acromegaly remains a contentious one and further large-scale prospective studies are required.

1.9.8 Other factors influencing mortality in acromegaly

Analysis of the determinants for mortality in acromegaly indicates that approximately 60% of patients die from cardiovascular/ cerebrovascular disease, 25% from respiratory disease, and in 15% of patients, the cause of death is attributed to malignancy. From published retrospective studies, the major negative determinants for survival are high GH levels and the presence of hypertension, cardiac disease and diabetes mellitus. Other variables found to influence outcome included hypertension, duration of the disorder prior to treatment and age. Hypertension and glucose intolerance are important contributory factors to the vascular morbidity associated with acromegaly. However, there are few published reports on their impact on mortality in acromegaly and how this correlates with GH and IGF-I levels. Hypertension occurs in around a third of all patients with acromegaly, ranging in some series up to 60%. The pathogenesis of hypertension in acromegaly is thought to be multifactorial, with an increase in extracellular sodium, a decrease in atrial natriuretic peptide, insulin resistance and
the direct effects of GH/IGF-I on vascular endothelial cells all playing a role\textsuperscript{286}. Hypertension is considered one of the most relevant negative prognostic factors for mortality in acromegaly\textsuperscript{137,138,278,287}.

The presence of diabetes mellitus has been demonstrated to be a significant predictor of mortality in some studies\textsuperscript{137,138}, but not in others\textsuperscript{134,249}. Further studies are required to examine this association and to determine whether diabetes mellitus is primarily responsible for poor outcome or whether glucose intolerance is a surrogate marker for patients with higher GH levels, who are known to have a poor prognosis independent of any other factors.
1.10 Mortality in Hypopituitarism

1.10.1 Introduction

The pituitary gland is the master regulator of the endocrine system controlling adrenal, thyroid and gonadal function, water balance, lactation and the growth hormone/IGF-I axis amongst other processes. Hypopituitarism is defined as a biochemical deficiency of one or more of the hormones of the anterior or posterior pituitary gland.\(^{288}\) The prevalence of hypopituitarism ranges between 290 and 455 cases per million, with a reported incidence of 42.1 cases per million.\(^{289}\) A recent systematic review of the prevalence of pituitary adenomas revealed a prevalence of 14.4% in postmortem studies and 22.5% in radiological studies giving an overall prevalence of 16.7%.\(^{290}\) Thus many patients have pituitary adenomas without any perturbations in endocrine function of the gland. Data from the Swedish Cancer Registry have shown an increasing incidence of pituitary adenomas with 6 cases per million being reported in 1958 rising to 11 cases/million in 1991.\(^{291}\) (Incidence in this study was from cancer registry data, the majority of these patients having pituitary adenomas which required surgery). This increase may simply reflect improvements in medical diagnostics, imaging and clinical surveillance rather than increasing incidence per se.

The underlying pathology leading to hypopituitarism had not changed dramatically with time, until the last decade when a number of other causes of hypopituitarism have been described such as traumatic brain injury,\(^{292}\) subarachnoid haemorrhage,\(^{292}\) and cranial irradiation for non pituitary tumours.\(^{293}\) As a result the incidence of hypopituitarism is likely to increase further as more patients are assessed for pituitary dysfunction with the above disorders. 'Hypopituitarism' remains a heterogeneous group of conditions unified by variable hormonal deficiencies (some patients will have single deficiencies whereas other
will be deficient is several axes). Indeed, in the study by Regal et al, 87% had gonadotropin deficiency, 61% GH deficiency, 62% ACTH deficiency, 64% TSH deficiency and 20% cranial (central) diabetes insipidus with 15%, 23%, 19%, 15% and 7% of patients having 2, 3, 4, 5 and 6 hormone axis deficiencies\textsuperscript{289}. Table 1.4 shows the heterogeneity in incidence of individual hormonal axis deficiencies and replacement levels in studies assessing mortality in hypopituitarism (it must be noted that some of the patients in these studies were postmenopausal women and therefore oestrogen replacement is not always indicated). It should be noted that GH deficiency is the most common deficiency in pituitary disease and these studies did not always assess for GH deficiency systematically nor did they replace all patients who were deficient. Furthermore within anyone particular underlying aetiology, the severity of presentation may differ markedly between patients and this may well impact upon morbidity and mortal

<table>
<thead>
<tr>
<th>Study</th>
<th>% ACTH Deficient</th>
<th>% ACTH Treated</th>
<th>% TSH Deficient</th>
<th>% TSH Treated</th>
<th>% GH Deficient</th>
<th>% GH Treated</th>
<th>% FSH/LH Deficient</th>
<th>% FSH/LH Treated</th>
<th>% CDI Deficient</th>
<th>% CDI Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomlinson et al (119)</td>
<td>75.8</td>
<td>100</td>
<td>66.4</td>
<td>100</td>
<td>9.7</td>
<td>24</td>
<td>65.8</td>
<td>67</td>
<td>18.3</td>
<td>100</td>
</tr>
<tr>
<td>Bates et al (116)</td>
<td>94</td>
<td>NA</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>47</td>
<td>NA</td>
<td>20.7</td>
<td>NA</td>
</tr>
<tr>
<td>Lindholm et al (\Delta) (395)</td>
<td>41</td>
<td>NA</td>
<td>40</td>
<td>NA</td>
<td>95</td>
<td>NA</td>
<td>Male 69</td>
<td>Female 45</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Stockholm et al * (297)</td>
<td>67.6</td>
<td>96.2</td>
<td>70.6</td>
<td>86.2</td>
<td>NA</td>
<td>49.8%</td>
<td>39.2</td>
<td>83.4</td>
<td>17.4</td>
<td>92.9</td>
</tr>
</tbody>
</table>

Table 1.4. Relative prevalence of individual pituitary axis deficiency (and replacement) in studies assessing mortality in hypopituitarism.
\(\diamond\) = Data only available on % patients treated, 56% deficient in all 3 axes and 31% in 2 axes
\(\Delta\) = GH treatment > 75% in childhood onset and <25% in adult onset,
* All patients given adequate substitution if found to be deficient
NA = not available/ not detailed

73
1.10.2 All cause mortality in hypopituitarism

The standardised mortality ratio (SMR) is a measure of observed numbers of death in a study population compared to the expected numbers of deaths if the age-sex specific rates were the same as those of the standard population. In essence it measures how much more (or less) likely a person is to die in the study population compared to someone of the same age and gender in the standard population, with a value of 1 meaning the patients are as equally likely to die as the normal population, a larger value they are more likely to die and a value less than 1 they are less likely to die.

For internal analysis within cohorts (not compared to general population) the risk ratio (RR) is used, which allows a good indication of the strength of association between exposure and disease outcome (RR = risk in exposed group/ risk in unexposed group). Poisson regression analysis allows us to compare rates between two exposures or indeed more than 2 exposure groups and allows us to examine the effect of an ordered or continuous exposure variable. In addition such analysis controls for the confounding effects of one or more variables and the effects of exposures which change over time \(^{294}\).

Analysis of mortality with hypopituitary cohorts is complex and challenging due to the diversity of underlying aetiologies and treatment modalities. The challenge in interpretation is further complicated by the low numbers of deaths reported in the published studies ranging from 41 to 842 patients.
In the cohorts discussed within this section, mortality within the immediate post operative period has been removed as have patients with acromegaly and Cushing's disease as these conditions per se are associated with increased mortality independent of hypopituitarism. In the vast majority of studies presented to date, all cause mortality is increased in patients with hypopituitarism when compared to age and sex-matched controls (Table 1.5). Rosen et al were the first to identify increased mortality in hypopituitary patients. In their retrospective analysis of 333 consecutive patients diagnosed with hypopituitarism, they observed a SMR in the overall group of 1.81 (observed 104/ expected 57.4). When divided by gender the SMR for males was 1.47 (observed 63/ expected 42.9) and in females 2.82 (observed 41/ expected 14.5) \(^{118}\). Subsequently, several other cohort studies have been published (Table 1.5, summarizes all studies to date assessing mortality in patients with hypopituitarism). With one exception\(^{295}\), SMR is increased in men ranging from 1.2 to 3.36 \(^{116-119,291,296-298}\) and in women is elevated, ranging from 1.3 to 4.54. In all cases, values are higher than those seen in men \(^{116-119,291,295-298}\).
<table>
<thead>
<tr>
<th>Study</th>
<th>% RT</th>
<th>SMR All cause</th>
<th>SMR Vascular</th>
<th>SMR Respiratory</th>
<th>SMR Malignancy</th>
<th>SMR All cause</th>
<th>SMR Vascular</th>
<th>SMR Respiratory</th>
<th>SMR Malignancy</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al</td>
<td>47.4</td>
<td>1.47</td>
<td>1.7</td>
<td>NA</td>
<td>0.3</td>
<td>2.82</td>
<td>2.7</td>
<td>NA</td>
<td>0.98</td>
<td>(118)</td>
</tr>
<tr>
<td>Total n = 333</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 104</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates et al</td>
<td>57</td>
<td>1.50</td>
<td>1.32</td>
<td>NA</td>
<td>0.53</td>
<td>2.29</td>
<td>1.46</td>
<td>NA</td>
<td>3.21</td>
<td>(116)</td>
</tr>
<tr>
<td>Total n = 172</td>
<td></td>
<td>(1.02-2.13)</td>
<td>(0.74-2.17)</td>
<td></td>
<td>(0.11-1.54)</td>
<td>(1.37-3.58)</td>
<td>(0.50-3.20)</td>
<td></td>
<td>(1.46-6.11)</td>
<td></td>
</tr>
<tr>
<td>Deceased n = 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulow et al</td>
<td>88.4</td>
<td>1.91</td>
<td>1.54</td>
<td>2.03</td>
<td>1.48</td>
<td>2.93</td>
<td>2.39</td>
<td>2.12</td>
<td>2.28</td>
<td>(117)</td>
</tr>
<tr>
<td>Total n = 344</td>
<td></td>
<td>(1.59-2.28)</td>
<td>(1.16-2.03)</td>
<td>(0.93-3.85)</td>
<td>(0.95-3.85)</td>
<td>(2.28-3.75)</td>
<td>(1.60-3.52)</td>
<td>(0.44-6.21)</td>
<td>(1.25-3.82)</td>
<td></td>
</tr>
<tr>
<td>Deceased n = 122</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates et al</td>
<td>28.5</td>
<td>1.2</td>
<td>0.9</td>
<td>NA</td>
<td>NA</td>
<td>1.3</td>
<td>0.5</td>
<td>NA</td>
<td>NA</td>
<td>(290)</td>
</tr>
<tr>
<td>Total n = 348</td>
<td></td>
<td>(0.5-1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.2-1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomlinson et al</td>
<td>34.8</td>
<td>1.57</td>
<td>1.7</td>
<td>2.1</td>
<td>0.9</td>
<td>2.29</td>
<td>2.34</td>
<td>3.41</td>
<td>1.07</td>
<td>(119)</td>
</tr>
<tr>
<td>Total n = 1014</td>
<td></td>
<td>(1.19-2.06)</td>
<td></td>
<td></td>
<td></td>
<td>(1.75-3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 181</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilsson et al</td>
<td>NA</td>
<td>1.88</td>
<td>1.44</td>
<td>0.98</td>
<td>1.40</td>
<td>2.28</td>
<td>1.79</td>
<td>1.90</td>
<td>1.57</td>
<td>(291)</td>
</tr>
<tr>
<td>Total n = 2279</td>
<td></td>
<td>(1.72-2.05)</td>
<td>(1.26-1.65)</td>
<td>(0.57-1.57)</td>
<td>(1.12-1.72)</td>
<td>(2.04-2.54)</td>
<td>(1.50-2.13)</td>
<td>(1.09-3.09)</td>
<td>(1.19-2.02)</td>
<td></td>
</tr>
<tr>
<td>Deceased n = 842</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Svensson et al</td>
<td>32</td>
<td>3.36</td>
<td>1.20</td>
<td>NA</td>
<td>3.59</td>
<td>4.54</td>
<td>1.87</td>
<td>NA</td>
<td>4.49</td>
<td>(298)</td>
</tr>
<tr>
<td>Total n = 1411</td>
<td></td>
<td>(2.93-3.83)</td>
<td>(0.88-1.60)</td>
<td>(2.74-4.63)</td>
<td>(3.89-5.26)</td>
<td>(1.27-2.65)</td>
<td></td>
<td>(3.26-6.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 399</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindholm et al</td>
<td>18</td>
<td>0.83</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.97</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(395)</td>
</tr>
<tr>
<td>Total n = 161</td>
<td></td>
<td>(0.55-1.26)</td>
<td></td>
<td></td>
<td></td>
<td>(1.2-3.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm et al</td>
<td>19.8-30.8</td>
<td>1.9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(297)</td>
</tr>
<tr>
<td>Total n = 1794</td>
<td></td>
<td>(1.7-2.2)</td>
<td></td>
<td></td>
<td></td>
<td>(2.9-4.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 644</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nielsen et al</td>
<td>22</td>
<td>0.98</td>
<td>1.07</td>
<td>NA</td>
<td>0.69</td>
<td>2.11</td>
<td>1.09</td>
<td>NA</td>
<td>1.70</td>
<td>(299)</td>
</tr>
<tr>
<td>Total n = 192</td>
<td></td>
<td>(0.70-1.37)</td>
<td>(0.59-1.93)</td>
<td>(0.33-1.44)</td>
<td>(1.35-3.31)</td>
<td>(0.27-4.36)</td>
<td></td>
<td>(0.76-3.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased n = 53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15: Standardized mortality ratios (SMR) observed/expected deaths and 95% confidence intervals (where available) for myocardial infarction, excluding fatal events outside hospital. Data relate to hospital survivors at 6 months. Values in parentheses are confidence intervals. Data not available for non-survivors or for myocardial infarction at 6 months. Data not available for specific cause of death.
available). The 95% confidence interval is derived using an error factor (EF = exp(1.96/√d, ci = total observed number). (95% CI = SMR/EF to SMR x EF).

A recent meta-analysis examined all published studies and concluded that the SMR associated with hypopituitarism in men is 2.06 (95% CI 1.94-2.20) and in women 2.80 (95% CI 2.59-3.02)\(^\text{299}\), this increase in SMR in women being statistically significant (p<0.0001). In clinical terms this leads to an age of death in the entire pituitary cohort of ranging between 64.5-72.3 years\(^\text{116,201}\), in men being 56.2 - 65 years\(^\text{116,119,296}\) and 52.0 - 66 years in women\(^\text{116,119,296}\).

The impact of gender upon all cause mortality is clear but the underlying reasons remain obscure. However, these SMR data do not imply that the underlying condition is more severe in men than women or that men respond better to specific treatment. The higher SMR in women may simply reflect that hypopituitarism removes the natural survival advantage that women have over men in the general population. A possible explanation may be under diagnosis of hypopituitarism in women as many of the diagnostic tests are not gender specific. Indeed in the study by Nielsen et al diagnosis of adrenal, thyroid, gonadal deficiency and panhypopituitarism was higher in men (52%, 49%, 73% and 33%, respectively) than women (30%, 30%, 46% and 17%, respectively)\(^\text{295}\).

There is evidence however in healthy post menopausal women that oral oestrogen replacement therapy is associated with increased mortality predominantly due to breast cancer and cardiovascular/thrombo-embolic diseases\(^\text{300}\). In women who take oral oestrogens there is also evidence of GH resistance at the level of the liver to IGF-I generation\(^\text{301}\) and elevations in total circulating cortisol as a result of elevated CBC\(^\text{302}\). GH itself modulates tissue glucocorticoid exposure through modulation of 11 beta-hydroxysteroid dehydrogenase type 1\(^\text{303}\).

The time since diagnosis does not seem to impact upon mortality\(^\text{117,119}\) but age itself is an important factor. SMRs are highest in the youngest patients with
mortality in elderly patients in some cohorts no different from age and sex matched controls. Again this may not reflect differing degrees of severity of the underlying condition with age, but may simply reflect age related mortality rates within the control population. The year of diagnosis is important as judged by historical databases showing higher SMR in patients who were diagnosed in the more distant past, with a negative correlation between 1st year of inclusion in study and SMR ($r=-0.65$, $p=0.017$) 299. However, when data was analysed according to gender the negative correlation was significant for men only ($men \ r = -0.65$, $p=0.03$, women $r = 0.58$, $p=0.18$).

1.10.3 Specific cause mortality

This has been an important step in enhancing our understanding of factors that contribute to increased mortality in patients with hypopituitarism. Furthermore, an appreciation of specific cause mortality can help to target appropriate therapy in an attempt to modify risk. However, several important limitations need to be realized. Firstly, much of the reported data is based on death certification and not on post-mortem findings and therefore complete accuracy of cause mortality cannot be ascertained. Indeed, several studies have reported the potential inaccuracies of death certificate data compared to autopsy data 304,305. This is particularly the case for cardiovascular 306,307, respiratory and gastrointestinal death 304, however recording of cancer death is usually concordant 304. Secondly, in many cases, sub-group analysis is based upon very small numbers of observed deaths and therefore a very small number of excess deaths can seemingly translate to dramatic changes in SMR (Table 1.5).

1.10.3.1. Vascular death

In most studies 117-119,298, but not all 116,295,308 vascular and cardiovascular mortality is increased with SMRs up to 18.4 in the youngest female patients with adult onset hypopituitarism (however, it should be highlighted that this increased
SMR was based on 4 deaths)\textsuperscript{297}. The main cause of mortality in the study by Rosen et al was vascular disease with SMR in the overall group of 1.95 (observed 60, expected 30.8) and in males SMR 1.7 compared to 2.7 in females, however the risk quotient was not significantly higher in women than men\textsuperscript{118}. Similarly, the main causes of the increased mortality in the study of Tomlinson et al were cardiovascular deaths (SMR = 1.62, p<0.0001) but cerebrovascular (SMR = 2.55, p<0.0001) and respiratory (SMR = 2.03, p=0.002) deaths were also increased\textsuperscript{119}.

The findings that in some studies vascular mortality was not increased is interesting. Within 391 patients diagnosed with hypopituitarism (patients with Cushing's disease and acromegaly excluded) who all underwent autopsy (although not formal dissection in all cases), cerebrovascular death was increased in both males [odds ratio (OR), 2.02] and females (OR, 1.73) with a particular increase in cerebral haemorrhage (male OR 4.6, female OR 4.8) but no difference from the general population for cerebral infarction\textsuperscript{308}. Data relating to the exposure to radiotherapy in this group was not reported. However, deaths related to ischemic heart disease were lower (notably in women) than those in age and sex-matched controls (male SMR 0.44, female SMR 0.27)\textsuperscript{308}. In the 2 studies by Bates et al vascular mortality was not increased\textsuperscript{116,296}. In the first unselected hypopituitary cohort, whilst the vascular SMR was increased (1.35, 95% CI, 0.84-2.07), p=0.11), this failed to reach statistical significance, perhaps due to the relatively small size of the cohort (n=172)\textsuperscript{116}. In the subsequent study, mortality was assessed in a cohort of patients who had all undergone pituitary surgery. SMR for vascular mortality was significantly lower than controls at 0.7(0.5-1.1, p=0.03)\textsuperscript{296}. The SMR for cardiovascular death was 0.5 (0.2-1, p<0.01) in women and 0.9 (0.5-1.4, p=0.26) in men\textsuperscript{296}. The discrepancies between studies could perhaps reflect over-reporting of cardiovascular disease related deaths on death certification in
the absence of autopsy, as well as the selection of patients who are suitable for surgical intervention.

The mechanisms that underpin the increase in cardiovascular mortality are not fully understood. The role of growth hormone deficiency has been widely speculated and is dealt with in section 1.10.4.4. Importantly, most of the large cohort studies that have examined mortality in hypopituitary patients have been in patients with either documented or presumed GH deficiency (patients were not on GH replacement in the vast majority of cases). It important to note that to date there is no data reporting normalization of mortality following GH replacement. Indeed the number of patients required to adequately power such a study suggests that such data will never be forthcoming.

Not all studies have had sufficient numbers to allow the analysis specifically of cerebrovascular mortality. However, where data are presented, cerebrovascular disease specific SMRs range between 1.73 and 4.9 \(^{117,119,291,296-298,308}\) (Table 1.5). Furthermore, there is evidence to suggest that those patients diagnosed at a younger age have increase cerebrovascular mortality \(^{117}\). Interpretation of the published data is challenging and in many situations is complicated by the use of radiotherapy and its effects (some studies report radiotherapy rates ranging from 25%-88.4% \(^{117,119,297,298}\) while other do not \(^{291,308}\). Other possible contributing factors to explain the increased vascular mortality are outlined below.

1.10.3.1.1 Insulin sensitivity

The studies of cardiovascular risk in hypopituitarism have either been cross-sectional studies comparing patients on conventional replacement to control subjects or interventional studies primarily examining the impact of GH replacement therapy. Patients on conventional replacement therapy exhibit
abnormalities of protein, fat and carbohydrate metabolism, which contributes to the abnormal body composition observed. Lean mass is reduced and fat mass is increased. There is a propensity to central obesity and intra-abdominal or visceral fat deposition is significantly increased compared to control subjects with similar BMI. In the general population increased visceral adiposity is associated with the metabolic syndrome: insulin resistance or diabetes mellitus, hypercholesterolaemia and hypertension.

Although blood glucose and plasma insulin levels are similar to those seen in controls, patients treated for pituitary disease have been shown to be insulin resistant. Johansson et al used the euglycaemic clamp to assess insulin sensitivity in 15 patients and fifteen controls matched for age, gender and body mass index. The glucose infusion rate required to maintain normal glucose levels was significantly lower in the patients than in controls (3.9 +/- 0.5 v 9.9 +/- 0.7 mg/kg body weight/min, p=0.001). When corrected to account for the differences in body composition the difference was more profound (5.8 +/- 0.8 v 13.9 +/- 0.9 mg/kg lean body mass/min, p<0.001).

1.10.3.1.2 Lipid abnormalities

In some hypopituitary cohorts, patients have adverse fasting lipid profiles including low HDL cholesterol, increased triglycerides and decreased LDL particle size, increased BMI (up to 32% being clinical obese BMI>30kg/m²) and waist circumference. Importantly, in the large cohort studies characterizing metabolic phenotype, interpretation of the data is hampered by lack of age, sex and demographically matched controls. The serum lipid profile is abnormal in patients on conventional pituitary hormone replacement, with elevated total and low-density lipoprotein (LDL) cholesterol and triglyceride levels. Serum levels of high-density lipoprotein (HDL) cholesterol have been reported as either unchanged or decreased in hypopituitarism. In the largest study
to date a centralized laboratory was employed to examine the fasting lipid profile in 2589 patients (48.8% female) aged 44.2±14.6 years, before commencing GH replacement. The mean (±SD) total cholesterol, HDL and LDL were 6.1±1.3 mmol/L, 3.7±1.1 and 1.2±0.4 mmol/L respectively. The total cholesterol was above the target level of 5.2 mmol/L in 71% of patients (66% of males and 75% of females); HDL was below the target level of 1.2 mmol/L in 49% (46% of men, 49% of premenopausal women and 57% of post menopausal women). The ratio of total cholesterol: HDL was increased above 4.5 in 59% of patients (69% of men, 44% premenopausal women and 55% of post menopausal women). Triglycerides were above the target value in 57% of men, 49% of premenopausal women and 60% of postmenopausal women. The frequency of an abnormal lipid profile increased with age in both sexes. Total cholesterol was also increased in the presence of smoking, diabetes mellitus and epilepsy, and in patients taking lipid-lowering drugs. The HDL concentration decreased with increasing BMI, waist: hip ratio and waist circumference, and was also lower in patients who smoke, had diabetes mellitus or took lipid-lowering agents.

1.10.3.1.3 Blood pressure

The data regarding the prevalence of hypertension in patients with hypopituitarism compared to the general population is conflicting. Rosen et al described an increased prevalence of hypertension in patients with hypopituitarism, but a number of other studies have found no difference and some studies have found that patients with hypopituitarism have lower blood pressure than controls. The majority of data would suggest that hypertension is not a major feature of hypopituitarism and is unlikely to play a major role in the associated vascular morbidity.
1.10.3.1.4 Vascular structure and function

The development of atheromatous disease is a gradual process, which has been studied using a variety of structural and functional measures and serological markers. The earliest detectable change is in the intima media thickness (IMT), which increases as lipids are deposited in the intima of large arteries. Carotid IMT can be measured using ultrasound and is a predictor of myocardial infarction and cerebrovascular accident in adults aged over 65 years. The carotid IMT is significantly increased in adults with hypopituitarism compared with age matched controls, however this is not the case in adolescents with untreated GH deficiency. Major blood vessels dilate to accommodate the pulse pressure generated by the heart, to smooth the flow of blood through the arterial system. As vascular disease develops these vessels become stiffer and are less likely to dilate in response to the pressure wave or to stimuli such as acetylcholine. This is dependent upon nitrous oxide generation by nitrous oxide synthase. Impaired vascular reactivity is thought to promote further endothelial damage facilitating the atherogenic process. Patients with hypopituitarism on conventional replacement therapy have impaired large vessel reactivity and evidence of impaired nitrous oxide generation.

Impaired endothelial function promotes adhesion of leukocytes to the endothelium which migrate through it and produce an inflammatory response. This is mediated via adhesion molecules, which are expressed on the luminal surface of the endothelium. Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are increased in patients with hypopituitarism. Adhesion molecules such as ICAM-1, E-selectin and P-selectin are reported to be elevated in patients with panhypopituitarism, although these findings appear to be variable. Furthermore in vitro studies demonstrate that monocytes collected from these patients show increased adhesion to bovine endothelial cells.
Fibrinolytic activity is an important contributor to cardiovascular risk; reduced activity is associated with venous thromboembolic disease, stroke and ischaemic heart disease. One of the major regulators of the fibrinolytic system is plasminogen activator inhibitor-1 (PAI-1) which regulates, through inhibition, tissue plasminogen activator (tPA) \(^{341}\). PAI-1 levels are elevated in patients with hypopituitarism \(^{342-345}\). Devin et al demonstrated that the 24-hour fibrinolytic profile was abnormal in hypopituitarism reporting a 62% increase in PAI-1 antigen levels \((p<0.05)\) and a 24% reduction in tPA levels \((p=0.003)\). In addition the normal circadian rhythm of PAI-1 was lost \(^{342}\). Thus hypopituitarism treated with conventional replacement therapy (but not GH) is a pro-thrombotic state which may contribute to the increased cardiovascular mortality observed in patients, and this has been shown to be improved by GH replacement in some studies \(^{343,345}\). Circulating AMDA (assymetrical dimethylarginine) levels, an endogenous NO synthase antagonist, are elevated in hypopituitary patients independent of GHD \(^{346}\). In addition, in hypopituitary women, inflammatory cytokines that have been implicated in the pathogenesis of cardiovascular disease including IL-6 and CRP and remain elevated in women after correcting for BMI \(^{347}\).

### 1.10.3.2 Malignancy

Where data have been reported, malignant causes of death have included tumors within the gastro-intestinal tract, pancreas, liver, bone, CNS, lungs, skin, breast, urogenital tract and lymphohemopoetic system \(^{291,308}\). The data have been somewhat conflicting as to whether mortality secondary to malignancy is different in patients with hypopituitarism compared to the general population. In the earliest reports \(^{116,118}\), deaths related to malignancy were lower than expected, notably in men, although the actual number of deaths was very small (3 male deaths in each of those studies with 10.1 \(^{118}\) and 5.7 \(^{116}\) expected,
respectively). Larger studies have either reported no increase in malignant deaths\textsuperscript{117,119,299,308} or a significant increase\textsuperscript{116,291,297,298} with SMRs up to 12.2 in the youngest patients, reflecting the rarity of malignant diagnoses in the control cohort\textsuperscript{297}. Differences in control populations may be important bearing in mind the prevalence of specific cancer types within certain populations. Also, patients with a pituitary adenoma may have an inherent increased risk of malignancy. Overall, the lack of consensus within the literature may reflect differences in the specific populations (and control cohorts) that have been studied as well as differences in treatment modalities and power of studies to assess this outcome.

1.10.3.3 \textit{Respiratory and Respiratory tract infections}

Respiratory mortality remains a poorly defined area in most studies. Only three studies have quoted specific respiratory mortality and the data is contradictory. Mortality was increased in both males and females in one study (overall SMR 2.55, p<0.0001)\textsuperscript{119} increased in males but not females in another (SMR 1.48, 95% CI 1.02-2.14 vs. SMR 0.818, 95% CI 0.53-1.3)\textsuperscript{300} and increased in females but not males in another (SMR 1.9, 0.57-1.57 vs. SMR 0.98, 0.57-1.57)\textsuperscript{291}. Whilst there are theoretical reasons as to why hypopituitary patients may be more vulnerable to respiratory tract infections including the role of glucocorticoid replacement and potential defects in immune function, there is still little evidence to suggest that this translates to increased respiratory mortality. There is some evidence within the literature to suggest that hypopituitary patients may be more susceptible to life-threatening infection\textsuperscript{346}. In a retrospective case note series, severe infections including those affecting the respiratory tract were more common in neurosurgically treated hypopituitary patients compared to control treated patients without pituitary hormone deficiencies. This was a small retrospective study and the control group may not be entirely appropriate, but the results do provide an indication of increased susceptibility to infection\textsuperscript{348}. 

85
Mukherjee et al found that the immune response to pneumococcal vaccine and other markers of humoral immunity were abnormal, particularly in patients with low prolactin and IGF-I\textsuperscript{349}. This impaired immune function may contribute to the mortality attributed to respiratory disease, particularly in patients with craniopharyngioma who are likely to have severe hypopituitarism including prolactin deficiency. Dehydroepiandrosterone (DHEA) replacement, which is frequently deficient in patients with hypopituitarism, may have a positive effect on immune function in patients with Addison’s disease\textsuperscript{350} and there is much in vitro work which suggests that DHEA may have an immunomodulatory role\textsuperscript{351} (it must be noted that many of these studies have used supraphysiological DHEA levels) but to date the evidence for this effect in patients with hypopituitarism is lacking.

1.10.4 Role of ACTH deficiency and glucocorticoid replacement

1.10.4.1 Dosage of glucocorticoid replacement

Patients with primary adrenal failure in addition to those with hypopituitarism have an increased risk of premature mortality compared to the general population\textsuperscript{352,353}. This increased mortality is predominantly due to cardiovascular, respiratory and cancer mortality\textsuperscript{352,353}.

Traditionally the daily dose of hydrocortisone was 30mg per day split into two doses (two thirds in the morning and one third in the evening). In recent years it has been reported that the cortisol production rate in normal subjects is less than was previously thought. Esteban et al (using stable isotope dilution chemospray liquid chromatography/ mass spectrometry) showed that the normal cortisol production rate in young adults can be estimated to be 27.3mmol/day
(equivalent to 5.7mg/m²/day or approximately 9.9mg/day) \(^{354}\). This was supported by deconvolution analysis data from young males who on average had a total daily cortisol production rate of 5.7 \pm 0.3\text{mg/m²/day} \(^{355}\). In recent years endocrinologists have tried to decrease glucocorticoid replacement doses in patients to levels, which remain safe but do not lead to over treatment. Nevertheless it is possible that subtle increased glucocorticoid exposure over time might contribute to morbidity and increased mortality as observed in patients with Cushing’s syndrome.

Cortisol day curves reveal that median doses of hydrocortisone of 29.5 \pm 1.2\text{mg} lead to peak cortisol and mean daily cortisol concentrations above the normal range, which in one study lead to a change in therapy in 88\% of patients (75\% of patients received a dose reduction) \(^{356}\). Agha et al have shown that patients with ‘partial ACTH deficiency’ (basal 9.00 cortisol >200nmol/l but a peak cortisol on insulin tolerance test of <500nmol/l) have similar day curves to healthy controls suggesting that these patients may be overtreated by conventional steroid replacement therapy \(^{357}\). Fillipson et al \(^{358}\) have described an adverse metabolic profile in a cohort of GH deficient hypopituitary patients on higher doses of glucocorticoid replacement. They found that patients on hydrocortisone replacement had increased total cholesterol, triglycerides, waist circumference and HbA1c compared to the ACTH sufficient patients. Importantly, subjects who had hydrocortisone equivalent doses of less than 20\text{mg/day} did not differ in metabolic endpoints compared to the ACTH sufficient patients. However, when a hydrocortisone equivalent doses of more than 20\text{mg/day} was administered patients had an adverse metabolic profile \(^{358}\). However, Dunne et al reported no changes in weight, glucose or HbA1c in patients after decreasing their hydrocortisone dose from 30\text{mg per day} to 15\text{mg per day} for 3 months \(^{328}\).
1.10.4.2  

Mode of glucocorticoid delivery

Twice or thrice daily doses of glucocorticoids are recommended to mimic the normal circadian rhythm and changes to circulating cortisol but this is rarely achieved. The bioavailability of orally administered hydrocortisone is $\sim$95\% \cite{359,360} and its half-life is 60-90 minutes. A single morning dose of 15mg hydrocortisone leads to supraphysiological serum cortisol concentrations one to two hours post oral administration and a return to subphysiological or undetectable levels 6-8 hours later \cite{359,361,362}. There is evidence that continuous, prolonged compared to intermittent short exposure to glucocorticoids may have different effects on a number of steroid responsive enzymes \cite{363}. Pulsatility is also important as it has significant effects on the occupancy of the glucocorticoid receptor \cite{363}. Circadian intravenous infusions of hydrocortisone can mimic the normal cortisol rhythm via a programmable pump resulting in beneficial effects in patients with Addison’s disease and congenital adrenal hyperplasia (CAH) \cite{364}; using these infusions it was also possible to reduce the daily dose of hydrocortisone \cite{365}. These infusions are obviously cumbersome and not practical, however, over the last few years there has been a push to design orally active delayed or sustained release formulations of hydrocortisone to reproduce ‘physiological replacement’ \cite{366}. Johannsson et al recently showed that a novel modified release once daily oral hydrocortisone preparation (Duocort) produced a diurnal plasma cortisol profile which mimicked the physiological serum cortisol profile \cite{367}. Similar results are reported with a preparation originating from Sheffield, UK (Chronocort) \cite{368,369}.

The metabolic fuel profile of 10 patients who were treated with conventional doses of glucocorticoid therapy (median 22mg, range 10-30mg per 24 hours) were assessed compared to 13 age, gender and BMI matched controls. In the patient group there was decreased glucose, NEFA and 3-OHB overnight, this was associated with decreased integrated levels of total and free plasma cortisol and 24 hour urine cortisol excretion. Indeed the decreased glucose and NEFA
continued throughout the 24 hour period of testing\textsuperscript{370}. In a further study morning replacement doses of GC resulted in higher glucose insulin levels, which were correlated with the maximal plasma cortisol levels\textsuperscript{371}.

In a further study, Howlett et al assessed the GC replacement in 130 patients requiring hydrocortisone replacement therapy for ACTH deficiency (in total 174 day curves were performed (65 on twice daily and 109 on thrice daily GC replacement)\textsuperscript{362}. Optimum replacement was defined as achieving a 09:00h cortisol within the reference range (after taking am hydrocortisone on awakening), 1230h and 1730hr cortisol above 50nmol/l and ideally above 100nmol/l. Patients on twice daily hydrocortisone replacement regimens achieved optimal replacement in 15% compared to 60% on thrice daily regimens. When regimens were compared the patients who received 10/5/5mgs achieved optimal replacement in 66% (mean quality score of 3.62), 10/10/5mgs 50% (mean quality score of 3.32) and 20/10mgs 10% (mean quality score of 2.48)\textsuperscript{362}. Dunne et al assessed if lowering the dose of hydrocortisone replacement from 30mg to 15mg per day in a hypopituitary cohort was associated with improvements in blood pressure and other markers of cardiovascular function. After three months on the lower dose of hydrocortisone there was no change in blood pressure, glucose or HbA1c, however there was a significant improvement in forearm blood flow\textsuperscript{328}.

\textbf{1.10.4.3 Tissue metabolism of glucocorticoids}

At the tissue level glucocorticoid action is modulated by isozymes of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD), type 1 and 2. 11 beta-HSD 2 is a NAD dependent enzyme predominantly located in tissues, which express the mineralocorticoid receptor (MR), it acts as a dehydrogenase (i.e. converting active (cortisol) to inactive (cortisone) glucocorticoids). This action protects the MR from illicit binding of cortisol which has similar affinity for the MR as for the glucocorticoid receptor\textsuperscript{372}. 11 beta-HSD 1 is a bidirectional enzyme, however in
vivo it acts predominantly as an oxoreductase enzyme (due to NADPH cofactor supply from the endoplasmic reticulum located enzyme hexose-6-phosphate dehydrogenase) \(^{373}\). Thus it converts inactive (cortisone) to active (cortisol) glucocorticoids within tissues. \(^{11}\) beta-HSD 1 is modulated by many factors, including GH/IGF-I, thyroid hormone, insulin, glucocorticoids and sex steroids \(^{374}\). Thus in patients with hypopituitarism there may be alterations in tissue specific exposure to glucocorticoids independent of circulating values. This is particularly relevant in patients with GH deficiency.

### 1.10.4.4 Role of GH deficiency and replacement

The majority of studies to evaluate a role for GH have been performed in patients with hypopituitarism who are also receiving replacement with sex steroids, glucocorticoids, thyroxine and desmopressin where appropriate. However, abnormal findings of these studies have been attributed in many cases to untreated GH deficiency leading to the supposition that patients should receive GH replacement therapy to correct these abnormalities and potentially reduce cardiovascular mortality to normal.

There is now a substantial body of evidence that indicates that GH replacement therapy has a beneficial effect upon many of the parameters outlined above. Body composition improves consistently with growth hormone replacement. Lean mass increases and fat mass decreases significantly. Studies utilizing computed tomography \(^{310}\), waist: hip ratio \(^{315,375,376}\) or simply waist circumference \(^{315}\) have demonstrated a significant reduction in central adiposity. The fasting lipid profile improves with reductions in total and LDL cholesterol and an improvement in the total: HDL cholesterol ratio \(^{315,320,321,377,378}\). A study of 1206 patients who received GH treatment for two years demonstrated an average reduction in total and LDL cholesterol levels of 0.4mmol/L (95% CI -0.4 to -0.3, \(p<0.0001\)) and 0.4mmol/L (95% CI -0.4 to -0.3, \(p<0.0301\)) respectively, with a
further reduction reported after two years of treatment. Although there was a small but significant reduction in HDL cholesterol the ratio of total: HDL cholesterol improved by 0.3 (95%CI -0.2 to -0.0, p<0.0001). Serum triglyceride levels were not affected by GH treatment. Growth hormone treatment in hypopituitary adults also impacts upon endothelial function, the inflammatory process and fibrinolytic profile. GH replacement results in increased excretion of nitrous oxide metabolites in the urine, however it is not clear whether this reflects greater production or decreased inactivation of nitrous oxide. The markers of inflammation, CRP, IL-6 and TNF-α also fall during GH replacement therapy. Perhaps as a consequence of the reduction in inflammation and improvement in nitrous oxide metabolism the reactivity of the blood vessels also improves. Measurement of the carotid IMT also demonstrates a significant improvement during therapy. Although these studies have been of relatively short duration one study compared the outcome of patients after ten years of treatment and demonstrated that the beneficial changes in lipid profile, body composition and carotid IMT were sustained over that period. These changes all reflect beneficial effects on recognized markers of cardiovascular risk. However GH replacement procuces changes in some parameters, which may have an adverse effect upon cardiovascular outcome. Although GH replacement therapy results in a reduction of central fat mass, insulin resistance is increased. In one study of 9C patients there was an increase in glycosylated haemoglobin levels from 4.9% ± 0.05 to 5.07% ± 0.06 (p<0.001). Plasma glucose levels rose from 4.72mmol/L ± 0.06 to 5.15mmol/L ± 0.07 (p<0.001). These changes were evident after six months of treatment and were sustained for two years. Lipoprotein (a) is an independent marker of cardiovascular risk which increases significantly during GH replacement. Despite these changes, which in isolation would suggest a negative effect on cardiovascular risk, the balance of the effect of GH on overall cardiovascular risk
appears to be positive as evident from the beneficial effects upon vascular structure and function.

The beneficial effects upon the cardiovascular risk profile provided by GH replacement therapy in GH deficient adults would imply a reduction in expected cardiovascular mortality in that population, but there are currently no data that directly demonstrate GH replacement therapy reduces cardiovascular mortality in hypopituitary adults. Long term, post marketing surveillance studies supported by the pharmaceutical industry are in place, which, in the future may answer this important question.

There is evidence that GH increases the clearance of cortisol by inhibition of 11 beta-HSD1 (thus preventing conversion of inactive cortisone to active cortisol) \(^{387}\). There is in-vitro data to indicate that this is through the direct action of IGF-I not GH \(^ {388}\). Clinically patients starting on GH may need a slight increase in glucocorticoid replacement dose or patients who are ACTH replete prior to GH replacement may need retesting once on GH treatment \(^ {389}\). However, in GH deficient patients, cortisol bioavailability is increased in key tissue such as liver, fat and muscle. This might explain some of the reported deleterious effects of GH deficiency (abnormal lipid profile, increased fat mass, low muscle mass and increased BMI/ waist hip ratio).

### 1.10.5 Role of TSH deficiency and replacement

Adequacy of thyroid hormone replacement in patients with hypopituitarism is difficult to assess, because the normal negative feedback mechanisms are disrupted and serum thyrotropin (TSH) levels cannot be used as a marker to determine the correct dose of thyroxine (T\(_4\)). Instead, one has to rely upon measures of the serum T\(_4\) level. There is no true consensus at which level of T\(_4\) a patient with pituitary disease should be diagnosed with secondary hypothyroidism. Lower limits of reference ranges are used suggesting that many patients may have secondary hypothyroidism and not be adequately
replaced. In the normal population, a suppressed TSH level (a marker of thyroid hormone excess) is associated with an increased risk of atrial fibrillation \(^{390}\), placing the individual at increased risk of embolic events, such as stroke. Furthermore, in a population study, deaths from cardiovascular disease were significantly increased in subjects who had a suppressed TSH level but a normal free T\(_4\) concentration \(^{391}\). Thus, mild over-treatment with T\(_4\) in patients with hypopituitarism may contribute to the increased cardiovascular mortality observed. This risk may be augmented by the prothrombotic state of patients with hypopituitarism \(^{344}\). It should be highlighted that in the general population there is still debate regarding increased mortality in patients with thyroid dysfunction \(^{392}\).

1.10.6 Role of sex steroid deficiency and replacement

For many years the use of sex-steroid replacement in normal, post-menopausal women was advocated for the amelioration of menopausal symptoms and the prevention of cardiovascular disease. This practice was thrown into doubt by two large, randomized, placebo-controlled studies that reported increased cerebrovascular and cardiovascular events and an increased risk of developing breast cancer after prolonged HRT in post-menopausal women \(^{393,394}\). These findings raised concern in young women of premenopausal age who require sex steroid replacement to manage hypopituitarism or other conditions that result in ovarian failure. However, Tomlinson et al demonstrated that mortality was increased in subjects with gonadotrophin deficiency that were not receiving sex steroid replacement while mortality in those on sex steroid replacement was similar to patients with an intact axis \(^{119}\). Further reassurance is provided by the low frequency of malignant disease reported in patients with hypopituitarism; one study reported a 50% reduction in deaths from this cause \(^{118}\). More detailed studies of sex-steroid replacement strategies and their long-term effect on
cardiovascular risk factors and outcome in women with hypopituitarism are required to ensure that current practice is not placing patients at risk.

1.10.7 Role of underlying aetiology in mortality in hypopituitarism

Hypopituitarism encompasses a number of diverse conditions. In the majority of cases, studies have not been able to analyse data with respect to specific etiology due to insufficient patient numbers and power. However, in 2 studies, non-functioning pituitary adenomas have been analyzed in separate cohort analyses \(^{119,396}\). In the study by Lindholm et al., all patients had undergone surgical intervention and overall mortality was not significantly different from that of the control population \(^{395}\). However, 30% had normal pituitary function post operatively and even once they had been excluded from the analysis, mortality was not different from control subjects (SMR 1.21, 95% CI 0.86-1.70). Importantly however, this study only included a total of 109 patients. In the study by Tomlinson et al., 573 patients were identified with an underlying diagnosis of non-functioning pituitary adenoma \(^{119}\). SMR remained significantly elevated compared to an age and sex matched population (SMR 1.70, 95% CI 1.34-2.15) and deaths were increased in women and were predominantly due to vascular and respiratory causes. When compared against other causes of hypopituitarism (which included craniopharyngiomas in this study) mortality outcome was improved when non-functioning adenoma was the underlying diagnosis (SMR 1.70 vs. 2.34). Whilst non-functioning pituitary adenomas appear to be associated with improved mortality outcome, it is very hard to generalize. Not all non-functioning pituitary adenomas behave in the same way and as described above, tumor characteristics may have an impact upon mortality outcome \(^{396}\).
1.10.8 Other factors contributing to mortality in hypopituitarism

Tumor characteristics may influence mortality. In a series of 281 patients who underwent operative procedures (transcranial surgery in 96% of cases) and radiotherapy in (98% of cases within 6 months of operation) all cause mortality was increased significantly in those patients that had tumor regrowth compared to those with no tumour regrowth (SMR 3.74 vs. 1.71). However, hypopituitarism was only diagnosed in 89% of patients within 5 years of diagnosis and mortality was increased in the cohort with and without tumor regrowth. Cerebrovascular deaths were increased in both the re-growth and non-regrowth groups although this only reached statistical significance in the non-regrowth group compared to age and sex-matched controls, principally due to the total numbers of observed deaths.³⁶⁶
1.11 Aims

Given the above information the aims of this thesis were to interrogate the West Midlands Acromegaly Study database for a number of areas in which there is debate or a paucity of data in patients with acromegaly, including:

a. With regard to optimum follow-up of patients with acromegaly

- Does a basal fasting GH reliably predict the nadir GH during an OGGT or mean GH during a GHDC in the assessment of disease activity during follow up in patients with acromegaly?
- What is the degree of discordance between disease activity measured by GH and IGF-I values?
- Does exposure to radiotherapy have any effect on the above relationships?

b. With regard to medical therapy

Data about potential factors that could have a predictive role in the response to medical therapy (particularly for DA) is scarce. The aims of our study were to evaluate:

- The role of baseline prolactin concentrations (and tumour immunohistochemical staining), prior surgery or radiotherapy and pituitary hormonal deficiencies in the response of GH and IGF-I to DA and SSA therapies in patients with acromegaly.
- The relative efficacy of dopamine agonist therapy compared to somatostatin analogue therapy in patients with acromegaly.
- The efficacy of SSA in clinical practice compared to that observed in clinical trials (and the relative efficacy of subcutaneous versus long acting preparations of SSA).
c. With regard to hypopituitarism and endocrine replacement

Given the above observations the aims of our study were to assess the role of hypopituitarism (in particular the effect of individual pituitary axis deficiency) and the effect of different doses of hydrocortisone replacement therapy on mortality in a large cohort of patients with acromegaly.

d. With regard to radiotherapy

Given the above observations the aims of our study were to assess the role of radiotherapy on mortality in a large cohort of patients with acromegaly.

e. With regard to the impact of GH and IGF-I on mortality

Our hypothesis was that the current method of assessing mortality risk in acromegaly based on the last available GH/IGF-I results in a biased risk associated with levels of GH/IGF-I. Having acquired follow up data over a long period of time in a large cohort of patients with acromegaly we aimed to assess mortality risk using a number of methods of analysis including the previously used last available GH/IGF-I, assessments of cumulative GH exposure and a novel ‘instantaneous GH/IGF-I’ method.
Chapter 2

Study Design, Methods and Participants
2.1 Participants

The West Midlands Acromegaly database was established in 1990 as collaboration between 16 West Midland Endocrine centres and is centred at the Queen Elizabeth Hospital in Birmingham. The data was collected initially retrospectively (from patients prior to 1990), but following the initiation of the study in 1990 the data was recorded prospectively until study completion.

The majority of patients attended the endocrine departments either at the Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham, NHS Foundation Trust) or the University Hospital of North Staffordshire. These 2 hospitals were the 2 main endocrine (particularly pituitary endocrinology), neurosurgical and radiotherapy centres for the West Midlands region. Some patients after their initial diagnosis and therapy were followed up in other referral centres. Patients were treated according to consensus guidelines at the time of treatment and there was frequent correspondence between centres regarding patients. The data was collected centrally in the Queen Elizabeth Hospital on a computerised Microsoft access database. When the data attainment was near completion, a full review of available data was undertaken and any missing data were filled wherever possible by direct correspondence with the physicians who were following up individual patients (at the Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham, NHS Foundation Trust) or the University Hospital of North Staffordshire).

To ensure optimum patient ascertainment, all patients with a diagnosis of acromegaly in each of the referral centres were flagged. Also, all patients with an elevated GH or IGF-I measurement in the Regional Endocrine laboratory at Selly Oak Hospital Birmingham were also flagged and their clinical notes assessed for a diagnosis of acromegaly (this is the regional centre for these assays therefore all patients samples from the region are analysed here). The West Midlands region has an overall population of 5.7 million.
Data collected included initial visit demographic data, medical history, medications, presentation symptoms, biochemical results and radiological results. All treatment information was recorded including dates of surgery, radiotherapy and medication changes during follow up. Results of histological assessment of surgical specimens were recorded. At each follow up visit GH, IGF-I and other endocrine tests were recorded. At each visit a full medications history was recorded including dose of medication and dates of any changes of medications or doses.

The database was closed for analysis on the 31st of December 2006, at this point demographic and clinical details, at time of diagnosis and follow up, of 501 patients (275 female) with acromegaly were analysed. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1μg/litre after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (n=34) had died prior to the introduction of IGF-I to routine clinical practice in the early 1990s.

The study was approved by the local research ethics committee of each site, the Office of National Statistics and the Patient Information Advisory Group (PIAG). Three hundred and thirty nine patients were alive on the exit date of the study and 162 patients were deceased (data relating to radiotherapy and GH/IGF-I and mortality have been reviewed in 419 of these patients previously)\textsuperscript{133}. The study and all patients were registered with the Office of National Statistics (ONS) and death certification data from the ONS were reviewed to obtain information relating to cause of death according to ICD-10 criteria.
Figure 2.1. Centres referring patients to the West Midlands Acromegaly Database: Queen Elizabeth and Selly Oak Hospitals, Birmingham; County Hospital, Hereford; Birmingham Heartlands Hospital; Staffordshire District General Hospital; City Hospital, Birmingham; Coventry and Warwick Hospital; North Staffordshire Hospital; Worcester Royal Infirmary; New Cross Hospital, Wolverhampton; Alexandra Hospital, Redditch; Burton District Hospital; Sandwell Hospital; Telford District General Hospital; Manor Hospital, Walsall and Wordsley Hospital.

2.2 GH assays

2.2.1 GH assay used in this study

Prior to December 2000, serum GH was measured using an in-house RIA calibrated against IS 80/505 at the Regional Endocrine Laboratory at the University Hospital Birmingham, Selly Oak. From December 18th 2000, this changed to the DPC Immulite 1000 immunometric assay calibrated against IS 80/505. This standard (IS 80/505) was assigned a value in International Units, and therefore GH was reported in mIU/L with a conversion factor of 2 for μg/litre. For results < 20 mIU/L the DPC assay gave similar results to the RIA. For results >20 mIU/L the DPC assay gave results between 10-20% lower. The
assay was transferred to the Immunlite 2500 when DPC was bought by Siemens. This did not result in any significant change in GH values. Serum GH levels were measured by an in house RIA in a central laboratory as previously described (the value in mlU/litre was divided by a conversion factor of 2 to obtain µg/litre). The limit of detection of the assay is 0.5 µg/litre and the interassay CV is 5.7% at 2 µg/litre, 4.3% at 3 µg/litre, 5.5% at 7.3 µg/litre and 4.47% at 14.7 µg/litre.

A new international standard was produced in 2001 (WHO IS 98/574). This is comprised of recombinant material consisting of a 22kDa growth hormone of >95% purity. Unlike the previous standard, IS 98/574 has been assigned values in both mass and International Units, allowing conversion between mass units and International Units such that 1 µg corresponds to 3 milli-International Units. Although our GH assay has remained the same (Siemens Immunlite 2500), it has now been calibrated against the new IS 98/574 and since May 12th 2008, results have been reported in µg/L. This was after the closing date of the study and therefore no results using this system are included in the study.

2.2.2 GH Assays – General Description

The measurement of GH has evolved from polyclonal radioimmunoassay (RIA) to modern two-site monoclonal antibodies, which are now non-isotopic and have enhanced sensitivity. The old assays were limited by sensitivity, being unable to tell unmeasurable levels from measurable low concentrations.

The development of GH assays was closely linked to the invention of the classic immunoassay. When enzyme immunoassays and other non-radioactive immunoassays became available they were also applied to GH measurement. As the production of monoclonal antibodies became possible the specificity of GH assays increased as these monoclonal antibodies are directed against a very distinct three dimensional structure on the surface of the antigen and
therefore are less likely to recognise isoforms and fragments of the molecule\textsuperscript{400}. The most frequently used assays today are the classical sandwich-type immunometric assays with secondary antibody labelled by something which can be quantified by labelling with radioactivity (IRMA), enzyme mediated colorimetry (ELISA), time resolved fluorescence (IFMA) or chemiluminescence (ILMA/ICMA). These sandwich type assays have sensitivities of around 0.2µg/litre and some of them can have sensitivities as low as 0.002µg/litre\textsuperscript{400}. This is in contrast to older competitive assays, which frequently use polyclonal antibodies (which are the basis of many of our recommendations for diagnosis and long term follow up in acromegaly). Compared to the more recent assays they are less sensitive with lower detection limits between 0.5 and 1 µg/litre for GH\textsuperscript{400}.

2.2.3 Comparability of GH assay results
The method dependent variability exceeds 100% in many cases making it difficult to compare results from one study to the next or indeed different laboratories measuring the same sample in national studies. Studies directly comparing results from different assays in the same clinical samples in one laboratory confirmed disagreement between methods\textsuperscript{401-403}. Over the last 15 years variability in GH measurements have been reported by different laboratories in many countries participating in national external quality assessments\textsuperscript{404-407}.

2.2.4 Factors contributing to GH assay heterogeneity
GH in the circulation consists of a wide variety of molecular isoforms and therefore is not a homogenous substance\textsuperscript{406}. Dimers of GH occur both as hetero and homo dimmers as well as multimers\textsuperscript{409}. Depending on the antibody used in the assay one could only pick up a selected spectrum of isoforms (narrow in monoclonal antibodies but broad in polyclonal antibodies). Therefore
GH assays using polyclonal antibodies will give higher values than monoclonal antibodies for the same serum sample (however interestingly the between method agreement is often better for polyclonal antibodies). This is a problem with new monoclonal antibodies in that they are particularly sensitive to the isoform composition of each sample and this is important as different isoforms have different biological activities. The first international reference preparations of GH were of pituitary origin (66/217 1969, 80/505 in 1982) contained a variety of GH isoforms (but some purification was performed in order to increase 22kD isoform. These preparations were arbitrarily assigned concentrations of 2.0 and 2.6U/mg. The IRP 88/674 was predominantly 22kD and this preparation should be the reference material of choice for current GH assays.

High affinity of GH binding protein in human serum. GHBP responds to the extracellular domain of the GH receptor and its concentration varies with nutritional and metabolic conditions. In the circulation up to 50% of GH is bound to GHBP, this is important as if this GHBP interferes with the epitope for GH on the GH assay the levels of GH would be underestimated.
2.3 IGF-I Assays

2.3.1 IGF-I assays used in this study

Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described. The limit of detection of the assay is 2.0 nmol/litre. The interassay CV is 5.4-8.4% between 16-104 nmol/litre. Reference ranges were derived from adults with no known or suspected endocrine disorders. Reference range values were 14-48 nmol/litre at 21-30 years (n=71), 13-37 nmol/litre at age 31-45 years (n=123) and 8.9-32 nmol/litre (n=75) above 45 years. IGF-I data were available on 409/501 patients (81.6%). IGF-I data were available on 409/501 patients (81.6%).

2.3.2 IGF-I assays – General description

Several factors of IGF-I physiology are important to remember when utilising information from IGF-I assays and in assessing IGF-I assay performance including: circadian rhythms, nutrition, age, IGF-BPs, insulin, oestrogen, androgens, thyroxine and cortisol. IGF-I levels increase from birth until puberty (5-fold increase) then decrease with age (3.5 fold decrease from puberty to old age). For these reasons it is important when assessing IGF-I that once compares to age adjusted reference ranges. After the age of 30 it is reasonable to have age related reference ranges according to decades due to the steady rate of decline.

Diabetes and renal disease can lead to significant increases in IGF-BP, therefore if assays are used in which there is IGFBP assay interference the IGF-I value may be artificially high. There is significant day to day sample variability in IGF-I levels, Milani et al reported that serial samples (intervals of 6-12 weeks) from the same patient may show large variability in IGF-I (3-36%).
All of the initial IGF-I assays were conventional radioimmunoassays (RIAs) that used competitive binding between radiolabelled and unlabeled IGF-I in serum and were therefore open to binding protein interference \(^{413}\). The degree of interference in these original RIA was related to the affinity of the antibody, in higher affinity antibodies the sample could be diluted to overcome effect of binding proteins \(^{416}\). Because of these problems with binding protein interference a large number of techniques were developed to remove or nullify their effect. These included acid gel filtration chromatography (which is the gold standard as it has high reproducibility but is difficult to perform) and acid/ethanol precipitation (which is easy to use and highly reproducibility but does not remove all binding proteins). The West Midlands Regional Endocrine Laboratory uses the acid ethanol technique which removes the vast majority of IGF-BP3 and 5 which are bound to acid labile subunit but does not remove smaller binding proteins that do not bind to ALS such as IGF-BP1 and 4 \(^{417,418}\). Another potential limitation of this method is that some of the IGF-I is also precipitated by this method and laboratories need to account for this if possible otherwise the IGF-I concentration will be an underestimation. Some units add IGF-II to the elute from acid ethanol extraction to increase the removal of IGF-BP1 and 4, which completely eliminates IGFBP assay interference \(^{419}\) but this needed an antibody with low affinity for IGF-II but high affinity for IGF-I. Newer techniques have tried to avoid the problem of binding protein interference by using a two antibody capture technique \(^{420}\) which does not need radiolabelled tracers and successfully eliminates binding protein interference.

### 2.4 Diagnosis of ACTH deficiency

The hypothalamic pituitary adrenal axis was deficient if the peak cortisol response to short synacthen testing was <550nmol/litre \(^{421}\) or less than 500nmol/litre following insulin induced hypoglycaemia during an insulin stress
test. Samples were assayed for cortisol using a chemiluminescence immunoassay (Advia Centaur; Bayer Diagnostics, Newbury, UK) with an interassay imprecision of less than 10% for serum cortisol concentrations between 68 and 970 nmol/liter (with interassay coefficients of variation of 10.2% at 76 nmol/liter, 7.7% at 528 nmol/liter, and 7.4% at 882 nmol/liter)\textsuperscript{422}. This assay is equivalent to the previously described Bayer ACS 180\textsuperscript{421} using the same reagents on a larger automated platform\textsuperscript{423}.

2.5 Diagnosis of TSH deficiency

The thyroid axis was deficient if the free T4 concentration was below the local reference range, with an inappropriately low/normal TSH. Serum free T\textsubscript{4}, free triiodothyronine (T\textsubscript{3}), and TSH were measured by chemiluminescent immunoassay (Advia Centaur; Bayer Diagnostics, Newbury, England). The laboratory reference range for free T\textsubscript{4} was 0.70 to 1.55 ng/dL (9.0-20.0 pmol/L), with an interassay coefficient of variation of 8.2% to 9.8% over the range of 0.64 to 4.27 ng/dL (8.2-54.9 pmol/L). Serum TSH concentration had a reference range of 0.4-5.5 mU/L, with an interassay coefficient of variation of 4.4% to 10.9% over the range of 0.41 to 24.5 mU/L. The lower limit of reporting for the TSH assay was 0.1 mU/L, with a mean functional sensitivity 0.02 mU/L. Free T\textsubscript{4} and TSH concentrations were determined in all; in those with serum TSH concentrations below the reference range, serum free T\textsubscript{3} (reference range, 227.3-422.1 pg/dL [3.5-6.5 pmol/L], interassay coefficient of variation of 4.2%-6.9% over the range of 259.7-1039.0 pg/dL [4.0-16.0 pmol/L]) was additionally measured. The reference ranges used for free T\textsubscript{4}, TSH, and free T\textsubscript{3} were those recommended by the manufacturer and used in other studies of this cohort and studies from our unit\textsuperscript{424,425}.
2.6 Diagnosis of hyperprolactinaemia

Hyperprolactinaemia was diagnosed if the prolactin level was above the gender related reference range. The assays used for prolactin (PRL) measurement were: competitive radioimmunoassay up until 1992; Immunometric assay, Abbott IMX between 1992-1995, Immunometric assay, Corning ACS between 1995-2000, Immunometric assay, Bayer Advia Centaur, now owned by Siemens Healthcare Diagnostics between 2000-2005 and Immunometric assay, E170 Roche Diagnostics from 2005 to date.

2.7 Diagnosis of FSH and LH deficiency

Hypothalamic-pituitary gonadal dysfunction in males was diagnosed in the setting of a low serum testosterone and inappropriately low/normal gonadotropins. In females hypothalamic-pituitary gonadal dysfunction was diagnosed in premenopausal females if the patient was amenorrheic (with normal prolactin levels) and in post-menopausal females if the FSH was inappropriately low (<35IU/litre).
2.8 Statistical Methods

2.8.1 Standardised Mortality Ratios (SMRs)

Standardised Mortality Ratios (SMRs) for overall mortality, cardiovascular, cancer, respiratory, and cerebrovascular deaths were calculated by using Stata statistical software. The expected number was estimated by multiplying age, sex and calendar period specific death rates in the general population of England and Wales by the person-years at risk accumulated within the age, sex and calendar-period specific strata corresponding to the patient cohort. SMRs for overall and cause specific mortality were also evaluated by whether patients were treated with radiotherapy, whether patients were ACTH, TSH or gonadotropin deficient, and whether patients were treated with hydrocortisone. Most of the statistical modeling was internal since such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders.

2.8.2 Poisson regression

Poisson regression is a method of modelling disease rates as a function of covariate levels that is often applied in the analysis of data from occupational cohort studies. Analyses are typically conducted using grouped input data in the form of a tabulation of person-time and events in which all predictor variables are categorised.

In an internal analysis a multivariable Poisson regression model was used to calculate Relative Risks (RR) of mortality based on tumour size, treatment with radiotherapy, ACTH, TSH, or gonadotropin deficiency, and dose of hydrocortisone received, if applicable. Unless otherwise stated, relative risks were adjusted for GH level, attained age, sex, calendar period, and period of follow-up. To assess the role of GH/IGF-I level on 11 beta-hydroxysteroid
dehydrogenase type 1 and mortality in patients on hydrocortisone therapy an interaction term was added to the above model.

2.8.3 Other Statistical Methods

In each chapter of results the statistical methods will be repeated that are pertinent to that part of the study. For example in Chapter 3 positive and negative predictive values were calculated for basal GH with respect to GH nadir during OGTT and mean during GHDC. GH nadir during OGTT and mean during GHDC <1μg/litre and <2.5μg/litre were considered as true positive with relation to disease remission and levels known to normalize mortality, respectively. Differences in predictive values and changes in discordance levels dependant on radiotherapy were assessed by the c² test. Correlation coefficients comparing basal GH and GH nadir during OGTT/ mean during GHDC are reported as Spearman correlation coefficients. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism (CA, USA). We performed an Altman-Bland analysis to quantify agreements between basal GH and nadir/mean GH during OGTT/ GHDC. This involves plotting a difference of measured values vs. an average of the same values (these calculations were performed on log transformed data).

2.9 Descriptive Statistics

The median age at diagnosis in the patient group was 46.6 years (IQR 11.6-84.2) in the entire cohort, 44.2 (IQR 34.6-53.7) in those who were still alive and 53.8 (IQR 44.6-61.8) in those who had died. Median duration of follow up was 14.0 years (IQR 7.9-21) in the entire cohort with a total of 7567 patient years.
and there was no difference in duration of follow up between those who are still alive and those who had died, 14.2 years and 13.8 years, respectively.

2.9.1 Therapy received

128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone and 104 received all 3 treatment modalities. 143 received surgery and radiotherapy (of these 104/143 patients also received medical therapy), 68 surgery and medical therapy, 162 radiotherapy and medical therapy (of these 102/162 also received surgery). In total, 237 received radiotherapy, 220 received conventional three-field radiotherapy with a median dose of 45Gy [interquartile range (IQR) 45-47Gy] administered over a median of 25 fractions (IQR 25-30). 10 patients received stereotactic radiosurgery and 7 received Yttrium implants.

2.9.2 Endocrinology at baseline

2.9.2.1 IGF-I at baseline

IGF-I assessments were available on 205 patients at first visit [but 409/501 (31.6%) during follow up]. The median IGF-I at baseline was 102nmol/litre (IQR 75.3-123.8) and the distribution of IGF-I at diagnosis is shown in Figure 2.1.
Figure 2.2. Distribution of IGF-I at diagnosis in patients with acromegaly (n=205).

2.9.2.2 GH at baseline

GH values were available in 425/501 patients at first visit [but 470/501 (93.8%) during follow up]. The median GH at baseline during OGTT was 15.5 μg/litre (IQR 8.45-39.23). 177 patients had a basal GH <10 μg/litre, 97 patients 10-20 μg/litre, 79 patients 20-50 μg/litre, 47 patients 50-100 μg/litre and 25 patients >100 μg/litre (see Figure 2.2).

Figure 2.3. Distribution of GH at diagnosis in patients with acromegaly (n=425).
2.9.2.3  Relationship between GH and IGF-I at baseline

The relationship between baseline GH and IGF-I was curvilinear with a plateau in IGF-I generation occurring after a GH concentration >10µg/litre. Figure 2.3

![Graph showing relationship between GH and IGF-I](image)

**Figure 2.4.** Relationship between GH and IGF-I at baseline in patients with acromegaly

2.9.2.4  Pituitary function at diagnosis

In total 344 patients had some documented assessment of pituitary function at baseline available in the medical records or endocrine laboratory archives, of these 221 patients (64.2%) had no degree of hypopituitarism, 99 patients (28.8) had one axis deficiency, 18 patients (5.2%) had 2 axes deficient and 3 patients had 3 or more axes deficient. ACTH status was recorded at presentation in 289 patients [230 (79.6%) had normal ACTH reserve and 59 (21.4%) were ACTH deficient]. Secondary hypothyroidism assessment was available at presentation in 287 patients [276 (96.2%) had normal TSH function and 11(3.8%) had evidence of TSH deficiency]. Gonadotropin status was recorded at presentation in 267 patients [188 (70.5%) had normal gonadotropin function and 79 (29.5%) had evidence of gonadotropin deficiency].

Prolactin concentration was available in 276 patients at diagnosis. The median Prolactin at baseline was 307.5 (IQR 170-772 IU/L). The distribution of prolactin
results at baseline are shown in Figure 2.3, 179 patients had a prolactin <500IU/L, 50 patients had a prolactin between 501-1000IU/L, 29 patients had a prolactin between 1000-2000IU/L, 4 patients had a prolactin between 2001-3000IU/L and 14 patients had a prolactin >3000IU/L.

Figure 2.5. Distribution of prolactin concentrations at diagnosis in patients with acromegaly.

Further descriptive statistics will be reported in each results chapter as required.
Chapter 3

Monitoring disease Activity using GH and IGF-I in the follow up of 501 patients with Acromegaly
3.1 Abstract

Context. The aims of treatment in patients with acromegaly are to achieve serum GH/IGF-I concentrations associated with cure or normalisation of mortality and alleviation of symptoms.

Objective and Methods. Using the West Midlands Acromegaly database (n=501) we investigated the reliability of basal fasting GH in predicting nadir or mean GH during oral glucose tolerance test (OGTT) or growth hormone day curve (GHDC), respectively, the degree of discordance between disease activity measured by GH and IGF-I values and the effect of radiotherapy on the above relationships. In total 773 OGTT and 507 GHDC were performed.

Results. Basal fasting GH was strongly correlated with nadir/mean GH on OGTT/GHDC (r=+0.87, p<0.0001, r=+0.93, p<0.0001, respectively). A basal GH<2.5μg/litre was associated with a nadir/mean GH during OGTT/GHDC<2.5μg/litre in 98.6% and 88.2% of cases, respectively.

Elevated IGF-I was seen in 32.4% and 46.4% of patients with GH nadir values during OGTT<1 and <2.5μg/litre, respectively, and in 21.2% and 45.9% of GHDC with mean GH<1 and <2.5μg/litre, respectively. Radiotherapy increased the discordance in GH and IGF-I as markers of disease activity at GH<2.5μg/litre (elevated IGF-I values when OGTT nadir GH<2.5μg/litre: radiotherapy 55.5% vs. no radiotherapy 36.9%, p=0.002).

Conclusions. There is a close relationship between a basal fasting GH<2.5μg/litre and nadir/mean GH<2.5μg/litre during OGTT/GHDC. There is a large discordance between disease activity when assessed by GH and IGF-I which is further increased by radiotherapy. These observations illustrate the challenge of defining appropriate biochemical endpoints to achieve control of disease and normalization of mortality in acromegaly.
3.2 Introduction

Acromegaly is a disabling disease characterised by excess growth hormone (GH) secretion and circulating insulin like growth factor-I (IGF-I) concentrations. In addition to significant morbidity, acromegaly is associated with increased mortality, which has been demonstrated in a number of retrospective studies with standardised mortality ratios (SMR) between 1.3 and 3 (comprising over 5,000 patients and 1,000 deaths). \(^{53,71,75,132-134,136-138}\)

This increase in mortality can be normalised if GH levels are decreased \(^{75,133,134,136,137}\), we and others have previously described normalisation of mortality if GH can be reduced to <2.5μg/ litre \(^{133,134,136,137}\). The evidence for using IGF-I as a predictor of outcome is not as robust. To date only two studies have provided support for the use of IGF-I as a predictor of long term outcome, and the observed number of deaths in both these studies was small \(^{71,75}\). The most recent consensus statement for cure of acromegaly has defined the criteria for remission as a normal age related IGF-I and a GH < 1μg/ litre during an oral glucose tolerance test (OGTT) \(^{55}\). Many endocrinologists have adopted a target GH for normalisation of mortality as <2.5μg/ litre \(^{75,134,136,137}\) and a recent meta-analysis of the effect of lowering GH values has shown that GH values <2.5μg/ litre are associated with a normalisation of mortality (SMR 1.1, 95% CI 0.9-1.4) \(^{273}\).

The method of assessing GH during follow up in patients with acromegaly varies widely across the endocrine community. Many have adopted the suppression of GH following a glucose load (OGTT) as the gold standard for follow up \(^{140}\). Other investigators use a 5-point GH day curve (GHDC) or a single random/ basal GH measurement. IGF-I should be measured at the same time as GH secretion is assessed \(^{430}\). The OGTT and GHDC require time and resources, both in terms of personnel and multiple assays; whereas a single random fasting GH level can
be performed easily at a clinic visit or in the phlebotomy department and only requires one sample, similar to IGF-I which measures integrated GH secretion.

Radiotherapy is widely used in the treatment of acromegaly and has been shown to be effective in decreasing GH and IGF-I levels. Using data from the West Midlands Acromegaly database (n=501) we examined a number of issues surrounding the biochemical follow up of patients with acromegaly. Firstly, did a basal fasting GH reliably predict the nadir GH during an OGTT or mean GH during a GHDC in the assessment of disease activity during follow up in patients with acromegaly? Secondly, what was the degree of discordance between disease activity measured by GH and IGF-I values and finally does exposure to radiotherapy have any effect on the above relationships?

3.3 Patients and methods

3.3.1 Patients

The West Midlands Acromegaly database was established in 1990 and on the 31st of December 2006, contained demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centres across the West Midlands region of the United Kingdom. The region has an overall population of 5.7 million. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1μg/litre after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (34) had died prior to the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site.

128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone, 143 surgery and radiotherapy, 68 surgery and medical therapy,
162 had radiotherapy and medical therapy and 104 received all 3. Median duration of follow up was 13.9 years (inter-quartile range 7.9 -21.0 years).

3.3.2 Endocrine Evaluation

Serum GH levels were measured by an in house RIA in a central laboratory as previously described \(^{398}\) (the value in mlU/litre was divided by a conversion factor of 2 to obtain µg/litre). The limit of detection of the assay is 0.5µg/litre and the interassay CV is 5.7% at 2 µg/litre, 4.3% at 3µg/litre, 5.5% at 7.3 µg/litre and 4.47% at 14.7 µg/litre. Assessment of GH secretion after treatment differed between units within centres in the West Midlands. GH levels were recorded as a nadir of five GH assessments over two hours following administration of 75g oral glucose (2-h 75g-OGTT), the mean of a GH day profile (the average of five GH measurements taken at 2-h intervals) or a random/ basal GH measurement performed in an outpatient setting. Data on GH levels during follow up were available in 470/ 501 (93.8%) patients. Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described \(^{412}\). The limit of detection of the assay is 2.0nmol/litre. The interassay CV is 5.4-8.4% between 16-104 nmol/litre. Reference ranges were derived from adults with no known or suspected endocrine disorders. Reference range values were 14-48nmol/litre at 21-30 years (n=71), 13-37 nmol/litre at age 31-45 years (n=123) and 8.9-32nmol/litre (n=75) above 45 years. IGF-I data were available on 409/ 501 patients (81.6%).

3.3.3. Statistical Analysis

Positive and negative predictive values were calculated for basal GH with respect to GH nadir during OGGT and mean during GHDC. GH nadir during OGGT and mean during GHDC <1µg/litre and <2.5µg/litre were considered as
true positive with relation to disease remission and levels known to normalize mortality, respectively. Differences in predictive values and changes in discordance levels dependant on radiotherapy were assessed by the chi² test. Correlation coefficients comparing basal GH and GH nadir during OGTT/mean during GHDC are reported as Spearman correlation coefficients. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism (CA, USA). We performed an Altman-Bland analysis to quantify agreements between basal GH and nadir/mean GH during OGTT/GHDC. This involves plotting a difference of measured values vs. an average of the same values (these calculations were performed on log transformed data)⁴²⁹.
3.4 Results

3.4.1 The association between basal fasting GH and nadir GH during OGTT /mean GH during GHDC

In total there were 773 OGTT performed on 282 patients and 507 GHDC performed on 109 patients during follow up. This included 480 (62.1%) OGTT and 436 (86%) GHDC performed in patients who had received radiotherapy and 293 (37.9%) OGTT and 71 (14%) GHDC in patients who were radiotherapy naïve. In the analysis of OGTT data if the basal GH was also the nadir reading then the next lowest reading was taken to avoid bias. In analysis of all tests performed the basal GH was strongly correlated with mean GH during GHDC (r= +0.93, p<0.0001) and with nadir GH during OGTT (r= +0.87, p<0.0001) (Figure 3.1).

The concordance between basal GH and nadir/ mean GH during OGTT/ GHDC are represented by Altman-Bland plots (Figure 3.2). In the Altman-Bland analysis of log basal GH vs. log GH nadir during OGTT the bias was -0.18 and the 95% limit of agreement -0.68 to 0.31. In the Altman-Bland analysis of log basal GH vs. log GH mean during GHDC the bias was 0.004 and the 95% limit of agreement -0.31 to 0.32.
Figure 3.1 Correlation between basal GH and GH nadir/mean during oral glucose tolerance test (OGTT) and growth hormone day curve (GHDC) in all patients.
Figure 3.2 Altman-Bland analysis of comparison between basal GH and GH nadir during oral glucose tolerance test (OGTT) (2a) and basal GH and mean GH during growth hormone day curve (GHDC) (2b). Dotted lines represent 95% limits of agreement.

The predictive value of a basal fasting GH indicating degrees of disease activity with respect to GH nadir/mean during OGTT/GHDC are represented in Table 3.1. In the 208 patients who recorded a nadir GH during OGTT <1 µg/litre 112 (53.8%) had a basal GH <1µg/litre and 96 (46.2%) had a basal GH >1µg/litre. 68 of these 96 patients had a basal GH <2.5µg/litre, leaving 28/208 (13.5%) patients with a nadir GH on OGTT <1µg/litre having a basal >2.5µg/litre, of these 28 subjects 12 had a raised IGF-I.
<table>
<thead>
<tr>
<th>GH μg/litre</th>
<th>GH Nadir OGTT &lt;2.5</th>
<th>GH Nadir OGTT &gt;2.5</th>
<th>GH Mean GHDC &lt;2.5</th>
<th>GH Mean GHDC &gt;2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal GH &lt;2.5</td>
<td>287/281 (98.8%)</td>
<td>4/281 (1.4%)</td>
<td>149/169 (88.2%)</td>
<td>20/169 (11.8%)</td>
</tr>
<tr>
<td>Basal GH 2.5-5</td>
<td>85/167 (50.9%)</td>
<td>82/167 (49.1%)</td>
<td>23/130 (17.7%)</td>
<td>107/130 (82.3%)</td>
</tr>
<tr>
<td>Basal GH &gt;5</td>
<td>35/312 (11.2%)</td>
<td>277/312 (88.8%)</td>
<td>1/208 (0.5%)</td>
<td>207/208 (99.5%)</td>
</tr>
</tbody>
</table>

Table 3.1 The predictive value of basal GH indicating degrees of disease activity with respect to GH nadir on OGTT and mean GH on GHDC

3.4.2 Discordance between disease activity as assessed by GH values and IGF-I status

The discordance between disease activities as assessed by IGF-I values and nadir/ mean GH during OGTT/ GHDC were examined. IGF-I values were categorized into being within, above or below the age specific local reference range. For this purpose only OGTT and GHDC results within the database which had IGF-I data recorded on the same day were included. 421 OGTT in 173 patients (83 subjects following radiotherapy, 90 no radiotherapy) and 223 GHDC in 75 patients (54 subjects following radiotherapy, 21 no radiotherapy) had corresponding IGF-I assessments. 32.4% of patients with GH nadir values on OGTT <1μg/litre and 46.4% of patients with a GH nadir on OGTT <2.5μg/litre had an elevated IGF-I. 21.2% of GHDC with mean GH <1μg/litre and 45.9% of GHDC with mean GH <2.5 μg/litre had an elevated IGF-I. In patients who had an OGTT, 27.0% with a basal GH >2.5μg/litre and 18.6% with a nadir GH >2.5μg/litre during OGTT had a normal IGF-I. In patients who had a
GHDC, 13.5% with a mean GH >2.5µg/litre and 15.4% with a basal GH of >2.5µg/litre had a normal IGF-I (Table 3.2). The degree of discordance between GH and IGF-I was similar whether the GH used was basal or mean/ nadir GH at all levels during a GHDC. During an OGGT the discordance between GH and IGF-I was similar if basal GH or nadir GH was <2.5µg/litre. However, this was not true for basal or nadir GH >2.5µg/litre during an OGGT (Table 3.2).

<table>
<thead>
<tr>
<th>GH µg/ litre</th>
<th>ELEVATED IGF-I</th>
<th>NORMAL IGF-I</th>
<th>LOW IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GHDC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASAL &lt;1</td>
<td>9/40 (22.5%)</td>
<td>27/40 (67.5%)</td>
<td>4/40 (10%)</td>
</tr>
<tr>
<td>MEAN &lt;1</td>
<td>73/33 (21.2%)</td>
<td>22/33 (65.7%)</td>
<td>4/33 (12.1%)</td>
</tr>
<tr>
<td>BASAL &lt;2.5</td>
<td>46/93 (49.5%)</td>
<td>43/93 (48.2%)</td>
<td>4/89 (4.3%)</td>
</tr>
<tr>
<td>MEAN &lt;2.5</td>
<td>45/98 (45.9%)</td>
<td>49/98 (50.0%)</td>
<td>4/88 (4.1%)</td>
</tr>
<tr>
<td>BASAL 2.5 - 5</td>
<td>45/55 (81.8%)</td>
<td>10/55 (18.2%)</td>
<td>0/55</td>
</tr>
<tr>
<td>MEAN 2.5 - 5</td>
<td>41/51 (80.4%)</td>
<td>10/51 (19.6%)</td>
<td>0/51</td>
</tr>
<tr>
<td>BASAL &gt;5</td>
<td>65/75 (86.7%)</td>
<td>10/75 (13.3%)</td>
<td>0/75</td>
</tr>
<tr>
<td>MEAN &gt;5</td>
<td>68/75 (90.7%)</td>
<td>7/75 (9.3%)</td>
<td>0/75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GH µg/ litre</th>
<th>ELEVATED IGF-I</th>
<th>NORMAL IGF-I</th>
<th>LOW IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OGTT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASAL &lt;1</td>
<td>18/73 (24.7%)</td>
<td>49/73 (67.1%)</td>
<td>6/73 (8.2%)</td>
</tr>
<tr>
<td>NADIR &lt;1</td>
<td>47/145 (32.4%)</td>
<td>92/145 (63.4%)</td>
<td>6/145 (4.2%)</td>
</tr>
<tr>
<td>BASAL &lt;2.5</td>
<td>76/190 (41.1%)</td>
<td>106/190 (55.8%)</td>
<td>6/190 (3.1%)</td>
</tr>
<tr>
<td>NADIR &lt;2.5</td>
<td>129/278 (46.4%)</td>
<td>142/278 (51.1%)</td>
<td>7/278 (2.5%)</td>
</tr>
<tr>
<td>BASAL 2.5 - 5</td>
<td>67/109 (61.5%)</td>
<td>41/109 (37.8%)</td>
<td>1/109 (0.9%)</td>
</tr>
<tr>
<td>NADIR 2.5 - 5</td>
<td>61/84 (72.6%)</td>
<td>23/84 (27.4%)</td>
<td>0/84</td>
</tr>
<tr>
<td>BASAL &gt;5</td>
<td>102/124 (82.3%)</td>
<td>22/124 (17.7%)</td>
<td>0/124</td>
</tr>
<tr>
<td>NADIR &gt;5</td>
<td>57/81 (93.4%)</td>
<td>4/81 (6.6%)</td>
<td>0/81</td>
</tr>
</tbody>
</table>

Table 3.2 Discordance between disease activity as assessed by GH (basal or nadir/mean GH during OGTT/GHDC) and IGF-I values. (Chi Square Pearson * p <0.05, ** p=<0.002).
3.4.3 Changes in relationship between basal GH and nadir/mean GH on OGTT/GHDC and IGF-I in patients receiving radiotherapy

Radiotherapy had no effect on the association between a basal GH <5μg/litre and a nadir/mean GH during OGTT/GHDC (Table 3.3) or on correlation values between basal and nadir/mean GH during OGTT/GHDC (Table 3.3 and Figure 3.3). However, if the basal GH was >5μg/litre patients who were radiotherapy naïve were more likely to have a GH nadir <2.5μg/litre (Table 3.3). Radiotherapy increased the discordance between disease activity as assessed by GH nadir during OGTT compared with IGF-I at GH levels <2.5μg/litre with 55.5% of patients who had radiotherapy having an elevated IGF-I compared to 36.9% in the radiotherapy naïve group, p<0.004 (Table 3.4 and Figure 3.4).

<table>
<thead>
<tr>
<th>GH μg/litre</th>
<th>Radiotherapy</th>
<th>No Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal &lt;2.5 with Mean GHDC &lt;2.5</td>
<td>114/133 (85.7%)</td>
<td>36/36 (100%)</td>
</tr>
<tr>
<td>Basal &lt;1 with Nadir OGTT &lt;1</td>
<td>45/46 (97.8%)</td>
<td>73/73 (100%)</td>
</tr>
<tr>
<td>Basal &lt;2.5 with Nadir OGTT &lt;2.5</td>
<td>142/146 (97.3%)</td>
<td>145/145 (100%)</td>
</tr>
<tr>
<td>Basal 2.5-5 with Nadir OGTT &gt;2.5</td>
<td>52/111 (46.8%)</td>
<td>32/57 (56.1%)</td>
</tr>
<tr>
<td>Basal &gt;5 with Nadir OGTT &gt;2.5</td>
<td>226/233 (95.3%)*</td>
<td>72/93 (77.4%)</td>
</tr>
</tbody>
</table>

Table 3.3 Effect of radiotherapy on predictive value of basal GH compared to nadir/mean GH during oral glucose tolerance test and growth hormone day curve. (Chi Square, Pearson *p=0.02, **p<0.0001)
Figure 3.3 Correlation between mean and basal GH during GHDC in radiotherapy naïve patients (3.3a) and patients following radiotherapy (3.3b) and nadir and basal GH during OGTT in radiotherapy naïve patients (3.3c) and patients following radiotherapy (3.3d). (GHDC = growth hormone day curve, OGTT = oral glucose tolerance test).
<table>
<thead>
<tr>
<th>GH µg/litre</th>
<th>IGF-I Level</th>
<th>Radiotherapy IGF-I</th>
<th>No Radiotherapy IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GHDC&lt;2.5</td>
<td>Normal</td>
<td>33/66 (50.0%)</td>
<td>15/31 (48.4%)</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>31/66 (47.0%)</td>
<td>14/31 (45.2%)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>2/66 (3.0%)</td>
<td>2/31 (6.4%)</td>
</tr>
<tr>
<td>Nadir OGTT&lt;1</td>
<td>Normal</td>
<td>25/53 (47.2%) *</td>
<td>67/92 (72.8%)</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>28/53 (52.8%) *</td>
<td>19/92 (20.7%)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>6/92 (6.5%)</td>
<td>6/92 (6.5%)</td>
</tr>
<tr>
<td>Nadir OGTT&lt;2.5</td>
<td>Normal</td>
<td>61/137 (44.5%) *</td>
<td>82/141 (58.2%)</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>76/137 (55.5%) *</td>
<td>52/141 (36.9%)</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>7/141 (4.9%)</td>
<td>7/141 (4.9%)</td>
</tr>
<tr>
<td>Nadir OGTT&gt;2.5</td>
<td>Normal</td>
<td>17/103 (16.5%)</td>
<td>10/42 (23.8%)</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>86/103 (83.5%)</td>
<td>32/42 (76.2%)</td>
</tr>
</tbody>
</table>

Table 3.4 Effect of radiotherapy on the discordance between disease activity assessed by GH and IGF-I concentrations (* p< 0.005)

![Graph showing effect of radiotherapy on discordance between GH and IGF-I concentrations](image)

Figure 3.4 Effect of radiotherapy on discordance between GH and IGF-I during oral glucose tolerance test (GH = µg/litre).
3.5 Discussion

These results demonstrate that a basal fasting GH correlates strongly with both nadir/ mean GH on OGTT/ GHDC in the follow up of a large cohort of patients with acromegaly. We have demonstrated that a basal fasting GH <2.5 μg/litre is strongly predictive of achieving a nadir GH during OGTT and mean GH during GHDC <2.5 μg/litre. Conversely, a basal fasting GH >5μg/litre is predictive of a failure to achieve a nadir/ mean GH during OGTT/ GHDC <2.5 μg/litre (i.e. GH levels previously shown to normalise mortality). We have also shown a significant discordance between GH values during OGTT and GHDC indicating remission or associated with normalisation of mortality and disease activity assessed by IGF-I. Radiotherapy leads to increased discordance between disease activity defined by GH and IGF-I (when GH <2.5μg/litre) (Tables 3.3 and 3.4, and Figure 3.4).

The validity of a single basal or random GH compared to an OGTT or GHDC has been criticized because of the pulsatile nature of GH secretion in normal individuals and the risk of under or over estimating disease activity in acromegaly. Our study, similar to a recent study from Jayasena et al\textsuperscript{432} reveals that a basal fasting GH is strongly predictive of a GH nadir on OGTT and other studies have shown a similarly strong correlation between a basal GH and a mean GH during a GHDC\textsuperscript{77,433}. Bajuk Studen et al\textsuperscript{434} have recently reported a strong correlation (r=0.93, p<0.0001) between an 8am single GH sample and mean GH from 24 hour sampling (samples taken every 10-20minutes) in patients with active acromegaly. However, they suggested caution be exercised due to the low positive predictive value (0.67) that a basal GH <2.5μg/ litre will predict a mean GH<2.5μg/ litre on 24-hour sampling. Our correlation is similar (r=+0.93), however, we took GH levels from patients with both active and cured acromegaly and also sampled 5 times over a 10 hour period (the use of 10-20 minute sampling is rarely used in clinical practice)\textsuperscript{434}. In our study, there is a
strong predictive value of a basal fasting GH <2.5 µg/litre at predicting a nadir / mean GH during OGTT/ GHDC of <2.5 µg/litre. A basal GH sample between 2.5-5 µg/litre is however less likely to predict GH levels during OGTT or GHDC and is thus more difficult to interpret disease activity from basal GH values between these levels, and more formal testing may be required. Previous concerns regarding the validity of a single basal fasting GH measure do not seem to be born out in clinical practice, providing caution is exercised in interpreting basal GH values between 2.5-5 µg/litre. Based on this data, a basal fasting GH is a useful initial test of disease activity and is less time consuming than either an OGTT or GHDC for both patient and staff, however, if a basal GH is between 2.5-5µg/litre or if there is clinical evidence of disease activity then the patient should go on to have a formal OGTT/ GHDC. One limitation of our study is that OGTT and GHDC performed on the same patients are never truly independent, even if they have been performed after long intervals. However, this is the largest series over a long timeframe of OGTT/ GHDC in patients with acromegaly reported, and as such provides important observations for clinical practice.

When IGF-I levels are stratified into low, normal or high according to age related reference ranges we have shown a significant discordance between disease activity assessed by IGF-I and the nadir/ mean GH during OGTT/ GHDC. 32.4% of subjects who had a GH nadir <1µg/litre during an OGTT and 46.4% of patients with a GH nadir <2.5µg/litre during an OGTT had an elevated IGF-I (similar values were seen for GHDC). Conversely, in patients with a basal/ nadir GH >2.5 µg/litre during OGTT, 27% and 18.6% had a normal IGF-I, respectively. The high degrees of discordance between disease activity as assessed by GH and IGF-I concentrations has major clinical implications, as the current criteria for the assessment of disease activity are based on both GH and IGF-I measurements.⁵⁵,⁴³⁰.
Discordance between GH and IGF-I have been reported in earlier studies. Gullu et al. showed that 15 of 21 patients with normal basal GH had an elevated IGF-I, and 14 of 21 patients with a GH <1μg/litre on OGTT still had an elevated IGF-I. However, all patients with GH suppression <0.3μg/litre on OGTT had a normal IGF-I. In other studies when mean GH was <2.5μg/litre, IGF-I has been reported to be elevated in 13-37.5% of subjects and when GH was >2.5μg/litre IGF-I was normal in 5-18%. Freda et al have reported that 50% of patients who suppress GH to <1μg/litre have an elevated IGF-I. All patients with a normal IGF-I had a GH during OGTT <1μg/litre, however suppression to <1μg/litre may be too crude as a cut off of normality, as the normal population all suppressed to <0.14μg/litre. As a result of these studies and the development of more sensitive GH assays the degree of suppression required to confidently predict remission has recently been challenged. In the study by Freda et al. 50/76 patients with a normal IGF-I had a GH <0.14μg/litre, whereas 26/76 had a nadir GH above this and separate from the normal population, these patients had a higher GH despite similar IGF-I levels. It has been suggested that this discordance may be due to recovery of GH sensitivity leading to a fluctuation in IGF-I until a new equilibrium is set between GH secretion and responsiveness. However, in our cohort this explanation is unlikely as the discordance persisted for many years following normalisation of GH.

Given the degree of discordance between GH and IGF-I the issue of how one integrates measures of GH and IGF-I to assess disease activity is a matter of much debate. The control of IGF-I synthesis is not only dependant on GH but is also regulated by exercise, oestrogen, nutrition, body mass index and insulin, any of which may account for the observed. The main body of epidemiological evidence supports the use of GH as a predictor of excess mortality and the discordance between IGF-I and GH may explain
to some degree the less robust evidence supporting IGF-I as a predictor of excess mortality.

We also demonstrated a significant increase in discordance between GH and IGF-I in patients treated with radiotherapy. GH and IGF-I dynamics following radiotherapy for acromegaly have been studied in detail by Peacey et al.\textsuperscript{94,442} In a study of 21 treated acromegalic patients with GH <2μg/litre on OGTT or GHDC a number of important differences occurred in patients who had received radiotherapy, compared to those treated surgically. In the radiotherapy group correlations were found between IGF-I and mean GH valley nadir GH, peak height of GH pulses, mean 24 hour GH, basal GH secretion, GH pulse amplitude and GH production rate\textsuperscript{94}. Patients in the radiotherapy group also had a greater mean valley GH nadir on cluster analysis and despite similar mean 24 hour GH concentrations patients with prior radiotherapy had higher IGF-I levels. It was hypothesized that this elevation in IGF-I levels were due to the altered characteristics of GH release, as the mean valley GH nadir and GH burst amplitude correlate positively with IGF-I. The authors suggested that sustained elevated basal GH release was responsible for determining the elevated IGF-I levels in these patients, despite otherwise safe GH levels\textsuperscript{94}. Altered GH dynamics might arise from hypothalamic damage due to radiotherapy, the increased GH trough activity in the radiotherapy group may be secondary to decreased somatostatin tone or growth hormone releasing hormone, leading to a decrease in generation of large pulses and reduced amplitude of GH release. Disruption of somatostatin tone has been shown to lead to a more rapid fall in GH than IGF-I which may explain the increase in discordance between disease activity assessed by GH and IGF-I following radiotherapy\textsuperscript{442,443}.

The use of a basal fasting GH to measure disease activity does mean that additional tests are required to assess glucose tolerance. However, if a basal
GH and IGF-I were to be the initial tests of choice, a fasting glucose and HbA1c could be performed at the same time as a primary screening tool for diabetes.

3.6 Conclusion

On the basis of this data, in patients who have a basal fasting GH <2.5 µg/litre, there is no added diagnostic benefit in performing an OGTT or GHDC given the close association between basal fasting GH and nadir/ mean during OGTT/ GHDC. Similarly, in those patients with a fasting basal GH is >5 µg/litre there is no added benefit in performing an OGTT or GHDC as the likelihood of nadir/ mean GH being suppressed to <2.5 µg/litre is low. However, if the basal GH is between 2.5-5 µg/litre then an OGTT or GHDC should be performed as a basal fasting GH has a poor correlation with GH nadir/ mean in this range (Table 3.1, Figure 3.5). There is a large discordance between disease activity assessed by GH and IGF-I and this discordance is exaggerated by radiotherapy. With the weight of evidence supporting GH versus IGF-I as a mortality outcome measure, the pitfalls of measuring only IGF-I to monitor disease activity in acromegaly are self evident.
Figure 3.5. Algorithm for assessment of GH in the follow-up of patients with acromegaly. Patients should also as routine have an IGF-I assessment as per consensus guidelines. Cut off of 2.5μg/ litre chosen according to level associated with normalisation of mortality. In patients who have a basal GH <2.5μg/litre, but there is strong clinical evidence of disease activity, should go on to have more formal testing with an OGTT or GHDC.
Chapter 4
Medical therapy in patients with Acromegaly; predictors of response and comparison of efficacy of dopamine agonists and somatostatin analogues.
4.1 Abstract

Context: Acromegaly is associated with increased morbidity and mortality. Treatment options include surgery, radiotherapy and medical therapy (including somatostatin analogues, dopamine agonists and pegvisomant).

Aims: To examine the role of prolactin status, prior surgery and radiotherapy on the response to medical therapy in patients with acromegaly. To assess the relative efficacy of dopamine agonist therapy compared to somatostatin analogue therapy.

Materials and Methods: 276 patients with acromegaly received either dopamine agonists (DA) and/or somatostatin analogues (SSA). 172 patients had received surgery and 73 radiotherapy prior to receiving medical therapy. 198/276 received DA, 143/276 received SSA. GH and IGF-I values at baseline and after 12 months on therapy were analysed.

Results: In the DA group basal prolactin concentration did not predict response to therapy, GH % reduction: hyperprolactinaemia 26.7% (-10.4-48) vs. normoprolactinaemia 34.8% (0.2-53.2), p=0.58, IGF-I % reduction: hyperprolactinaemia 30.0% (9.2-43.1) vs. normoprolactinaemia 16.8% (4-37), p=0.45. Prior surgery was not associated with any difference in response to DA: GH % reduction (p=0.1) and IGF-I % reduction (p=0.08). By contrast, prior radiotherapy was associated with an enhanced efficacy of GH response to DA, p=0.02. In the SSA group there was no effect of prior surgery or radiotherapy on response of GH but radiotherapy was associated with less marked IGF-I % reduction (p=0.05). SSA were more potent than DA at decreasing both GH [62.8% (20.7-85%) vs. 42.4% (-6.5-68.6), p<0.008] and IGF-I [SSA 40.4% (0-64.3) vs. 8% [0-40.8], p=0.05].

Conclusions: The effects of DA are irrespective of baseline prolactin concentrations. Prior surgery and radiotherapy are associated with differences in GH and IGF-I response to DA and SSA therapy.
4.2 Introduction

Acromegaly is a disabling disease characterised by excess growth hormone (GH) secretion and increased circulating insulin like growth factor-I (IGF-I) concentrations. It is associated with increased morbidity and premature mortality, which has been demonstrated in a number of retrospective studies (comprising over 5,000 patients and 1,000 deaths)\textsuperscript{53,71,75,132-138} reporting standardised mortality ratios between 1.3 and 3. This increase in mortality can probably be normalised if GH levels can be decreased to <2.5 µg/litre\textsuperscript{133,134,136,137}.

Therapy for acromegaly is targeted at reducing excess morbidity and mortality by decreasing GH and IGF-I levels, ameliorating patient’s symptoms and decreasing any local compressive effects of the pituitary adenoma. Currently the therapeutic options for acromegaly include surgery, radiotherapy and medical therapies such as dopamine agonists (DA), somatostatin analogues (SSA) and the GH receptor antagonist pegvisomant.

DA and SSA are used to inhibit GH secretion by pituitary tumours, whereas the GH receptor antagonist, pegvisomant, has no direct effect on GH secretion by the tumour but blocks GH activity at peripheral GH receptors\textsuperscript{210}. Medical therapy is currently most widely used as secondary treatment for persistent or recurrent acromegaly following unsuccessful surgery, although it can be used as primary therapy for patients in whom surgery is not an option or as short-term therapy preoperatively\textsuperscript{180}. SSA have become the first choice medical therapy for the majority of patients with acromegaly due to their efficacy on GH/IGF-I reduction (a recent meta-analysis reported that SSA reduced GH levels and normalised IGF-I levels in at 48 and 42% of acromegalic patients, respectively)\textsuperscript{155} and antitumoural effect\textsuperscript{153,164,174}. Dopamine agonists are not used as frequently as SSA; this is due to a number of factors including lower reported GH/IGF-I control rates, higher rates of side effects and decreased effect on
tumour shrinkage\textsuperscript{179}. However, it must be remembered that the majority of the studies regarding the efficacy of DA in acromegaly were performed using the DA bromocriptine (BC), and more recent studies suggest that cabergoline (CBG) may be more efficacious\textsuperscript{181}. The question whether prolactin levels prior to DA therapy are predictive of response (i.e. patients with elevated prolactin having a greater decrease in GH and IGF-I following DA therapy) is controversial and there are conflicting data from small studies, with some concluding that tumours which co-secrete prolactin have a greater response to DA\textsuperscript{181,189,190,445} and others showing no effect\textsuperscript{184,191-194}. Similarly, there is no agreement about the association between a positive GH and PRL immunostaining and a favourable response to DA, with some studies showing this association\textsuperscript{191} and others not\textsuperscript{184,193,195}.

4.3 Aims of Study

Data about potential factors that could have a predictive role in the response to medical therapy (particularly for DA) is scarce\textsuperscript{397}. The aims of our study were to evaluate the role of baseline prolactin concentrations (and tumour immunohistochemical staining), prior surgery or radiotherapy and pituitary hormonal deficiencies in the response of GH and IGF-I to DA and SSA therapies in patients with acromegaly. We also wanted to assess the relative efficacy of dopamine agonist therapy compared to somatostatin analogue therapy in patients with acromegaly. Finally we wanted to determine the efficacy of SSA in clinical practice compared to that observed in clinical trials (and the relative efficacy of subcutaneous versus long acting preparations of SSA).
4.4 Patients and Methods

4.4.1 Patients

The West Midlands Acromegaly database was established in 1990 and on the 31st of December 2006 contained demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centres across the West Midlands region of the United Kingdom. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1μg/litre after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (n=34) had died prior to measurement of IGF-I being part of routine clinical practice within the region in the early 1990s. The study was approved by the local research ethics committee of each site.

276 (151 female) of 501 patients with acromegaly received medical treatment at some stage during follow up and the remaining 225 patients were treated solely with surgery and/or radiotherapy. 198 patients received DA (71.7%) and 143 patients were treated with SSA (51.9%). 65 patients received both drugs at the same time (17.4%). In 17 of these 65 patients, one of the drugs was added to the other during the first year of treatment follow up; these 65 patients were excluded from the analysis. Choice of medical therapy was at the discretion of the treating endocrinologist as per consensus guidelines available at the time.

Surgery had been performed in 172 (62.4%) patients and 73 (26.4%) patients had received radiotherapy before starting medical therapy. Patients had received radiotherapy a median of 15 months before the initiation of medical treatment (IQR 6.75-44.5 months). Median duration of follow up was 14.9 years (IQR 8.5-21.3).
4.4.2 Endocrine Evaluation

Serum GH levels were measured by an in house RIA in a central laboratory as previously described. The limit of detection of the assay was 0.5μg/litre, the intra-assay coefficient of variation (CV) 4.1% and the interassay CV 5.7% at 2μg/litre. Assessment of GH secretion after treatment differed between units within centres in the West Midlands. GH levels were recorded as a nadir of five GH assessments over two hours following administration of 75g oral glucose (2-h 75g OGTT), the mean of a GH day profile (the average of five GH measurements taken at 2-h intervals) or a random/ basal GH measurement performed in an outpatient setting. Whenever possible either the nadir GH during an OGTT or mean GH during 5 point GH day curve were used. If these were not available a random GH sample was used. A random or fasting GH has been previously shown to correlate well with the GH nadir during an oral glucose tolerance test and a mean GH during a GH day curve. The GH value in mIU/litre was divided by a conversion factor of 2 to obtain μg/litre. Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described. The limit of detection of the assay is 2.0nmol/litre. The interassay CV is 5.4-8.4% between 16-104 nmol/litre. Reference ranges were derived from adults with no known or suspected endocrine disorders. Reference range values were 14-48nmol/litre at 21-30 years (n=71), 13-37 nmol/litre at age 31-45 years (n=123) and 8.9-32nmol/litre (n=75) above 45 years. Paired data for basal and 1 year follow up were available for GH in 227/276 (82.2%) patients and IGF-I in 146/276 patients (52.9%), however, 52/276 (18.8%) had received medical therapy prior to the availability of IGF-I assessment.
4.4.3 Statistical Analysis

GH and IGF-I levels before commencing and 1 year after medical therapy were recorded and the percentage decrease in GH/IGF-I calculated, as well as the number and percentage of those achieving GH <2.5μg/litre and a normal age adjusted IGF-I. Only patients with pre and post treatment GH and IGF-I were included in the analysis. Patients were divided into groups according to type of medical therapy prescribed (DA and SSA). To assess the relative role of radiotherapy and surgery and to avoid confounding factors, the response to medical therapy was only assessed in those patients who had prior surgery before commencing medical therapy and were radiotherapy naïve and vice versa. Prolactin levels at baseline and tumour immunohistochemistry were also noted and assessed for a role in the response to medical therapy. As all data was nonparametric, the Wilcoxon Rank Sum test was used to compare the groups. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism (CA, USA).

4.5 Results

There were no differences in baseline prolactin or IGF-I levels between DA and SSA (p=0.47 and 0.15, respectively) (Table 4.1). However, baseline GH was higher in the DA group (p=0.03) (Table 4.1). There were no differences between baseline prolactin, GH and IGF-I levels in patients who had prior surgery compared to those who were surgically naïve (no prior radiotherapy), (p= 0.5, 0.34 and 0.5 respectively) (Table 4.1). In patients who had received prior radiotherapy (but no prior surgery) there was no difference in baseline prolactin or IGF-I levels (p=0.53 and 0.85), however, basal GH levels were higher in the radiotherapy group (p=0.02) than in the radiotherapy naïve cohort (Table 4.1). There was no effect of gender on the GH or IGF-I response to DA
Median prolactin in the normoprolactinaemic group was 240mIU/litre (IQR 163-381) and in the hyperprolactinaemic group 1116mIU/litre (IQR 857-1652) (p<0.001).

<table>
<thead>
<tr>
<th>Medical Therapy</th>
<th>Baseline Prolactin (mIU/litre)</th>
<th>Baseline GH (μg/litre)</th>
<th>Baseline IGF-I (nmol/litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA</td>
<td>Median (IQR)</td>
<td>p</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>371 (185-860)</td>
<td>0.47</td>
<td>11.2 (6.5-31.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>SSA</td>
<td>294 (183-706)</td>
<td>8.0 (4.2-15.5)</td>
<td>97 (63.5-118.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>337 (168-745)</td>
<td>0.5</td>
<td>11 (5.4-27.0)</td>
</tr>
<tr>
<td>No</td>
<td>363 (183-687.5)</td>
<td>9.5 (6.2-18.8)</td>
<td>60 (53.5-114.9)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>298 (168-800)</td>
<td>0.63</td>
<td>12.2 (7-40.6)</td>
</tr>
<tr>
<td>No</td>
<td>366 (185-770)</td>
<td>8.1 (4.7-16.8)</td>
<td>60 (58.5-118.8)</td>
</tr>
</tbody>
</table>

**Table 4.1. Comparison between baseline prolactin, GH and IGF-I levels depending on medical therapy, surgery and radiotherapy (SSA = somatostatin analogue, DA = Dopamine agonist, IQ = interquartile range)**

### 4.5.1 Dopamine agonist group

In the patients receiving DA alone in the first year of medical therapy, BC was used in 159 patients (88.3%), CBG in 20 (11.1%) and pergolide in 1 (0.6%). The median dose of DA was 7.5mg per day (IQR 2.5-10) for BC and 0.5mg per week (IQR 0.5-1.25) for CBG. In the DA group the median baseline GH was 10 μg/ litre (6-24.5) with a median GH of 7 μg/ litre (3.3-15.8) at 12 months, giving a median decrease of 3.4 μg/litre (-0.4-10.1) or 42.4% (-0.5-68.6). The median decrease of GH at 12 months in the patients taking BC was 42.4% (-1.6-68.6%) and in those taking CBG was 36.0% (-3.9-83.0), (p=0.85). The median IGF-I at baseline in the DA group was 69.0 nmol/litre (52.3-101.7) and at 12 months was 63 nmol/ litre (39.8-84.5), giving a median decrease of 15.8nmol/ litre (2.7-41) or 22.9% (5.3-54.3). The median decrease of IGF-I at 12 months was 23.6% (5.9-47.9) in the BC group and 21.7% (1.6-54.7) in the CBG group (p=0.95). After 12 months of DA therapy, 28% of patients achieved a GH <2.5μg/ litre [18/118
(15.3%) and 6/16 (37.5%) of those treated with BC and CBG, respectively (p=0.04)]. IGF-I was in the normal age related reference range in 17/ 53 (32.1%) [10/39 (25.6%) of patients on bromocriptine and 7/14 (50%) of patients on cabergoline, (p=0.1)].

We evaluated the influence of previous radiotherapy on the decrease in GH and IGF-I levels in patients who received DA therapy. Radiotherapy prior to starting DA (without prior surgery) was associated with a greater increase in % GH reduction radiotherapy group 53% (28.8-70.9) compared to 3.1% (-66.8-66.1), (p=0.02), however there was insufficient data to analyse the difference in IGF-I reduction. (Figure 4.1)

![Figure 4.1. Effect of prior radiotherapy on percentage reduction of GH to dopamine agonist therapy.](image)

Patients treated surgically (without prior exposure to radiotherapy) before starting DA had no change in their sensitivity to DA for GH or IGF-I response (p=0.1 and 0.08, respectively). (Figure 4.2)
Figure 4.2. Effect of prior surgery on percentage reduction of GH and IGF-I to dopamine agonist therapy.

We found no difference in responsiveness to DA in patients who had an elevated or normal baseline prolactin [hyperprolactinaemia group decrease in GH 26.7% (-10.4-48) vs. normal prolactin 34.8% (0.2-53.2), p= 0.58, and IGF-I 30% (9.2-43.1) vs. 16.8% (4-37), p= 0.45], (Figure 4.3).

Figure 4.3. Effect of elevated prolactin on percentage reduction of GH and IGF-I to dopamine agonist therapy.

Data from immunohistochemical staining was obtained in 48 patients in the DA group (n=34 GH immunostaining, n=14 GH and prolactin immunostaining).
There was no difference in response of GH (p=0.19) or IGF-I (p=0.27) to DA in patients whose histology showed GH only compared to tumours which co-
stained with GH and prolactin.

4.5.2 Somatostatin analogue group

In the patients receiving SSA alone (n=116), 73 patients were treated with subcutaneous octreotide during the first year of therapy at a median dose of 150μg/day (IQR 100-300). The remaining 43 patients were treated with long acting depot SSA (lanreotide 26 and octreotide LAR 17). In those treated with octreotide LAR the median dose was 20mg monthly (IQR 20-30) and those treated with lanreotide LAR the median dose was 60mg monthly (IQR 60-90). In the entire SSA group the median baseline GH was 8.0 μg/ litre (3.9-14.6) with a median GH at 12 months of 2.8 μg/ litre (1.6-6.6), giving a median decrease of 3.9 μg/ litre (1.8-10.1) or 62.8% (20.7-85). The median IGF-I was 96.5nmol/ litre (59.9-119.7) at baseline and 46.8 nmol/ litre (30.7-71.9) at 12 months, giving a median decrease of 35.5 nmol/ litre (11.8-71.9) or 50% (16.4-68.4). 48.8% of patients achieved a GH <2.5μg/ litre and 45.7% achieved an IGF-I in the normal age related reference range. SSA were more potent than DA at decreasing both GH [62.8% (IQR 20.7-85%) vs. 42.4% (IQR -0.5-68.6), p<0.008] and IGF-I [SSA 50.0% (IQR 16.4-68.4) vs. 22.9% (IQR 5.3-54.3), p=0.05]. (Figure 4.4) There was no difference in either GH or IGF-I percentage reduction between subcutaneous (s/c) and long acting (LA) SSA [s/c octreotide 63.5% (21.1-84.5) vs. LA 62.9% (27.5-86.1), p=0.77] and IGF-I % [s/c octreotide 39.6% (9.8-60.9) vs. LA 53.4% (4.4-72.7), p=0.25].
Figure 4.4. Effect of Dopamine agonist and somatostatin analogue therapy on the percentage reduction in GH and IGF-I.

When % decrease in GH to SSA analogues was divided into those who had received prior radiotherapy (with no previous surgery) or not, no differences were found [radiotherapy 44.2% (11.4-70.6) vs. no radiotherapy 59.0% (21-84.5), p=0.64] (Figure 4.5). However, the response in IGF-I levels to SSA was lower in patients treated with radiotherapy before starting the SSA [radiotherapy 15.4% (5.5-72.1) vs. no radiotherapy 49.1% (0-78), (p=0.05)]. This led to a discordance between disease activity as assessed by GH and IGF-I as 10 of 29 patients (34.5%) who had a GH <2.5µg/litre had a raised age related IGF-I.

Figure 4.5. Effect of prior radiotherapy on percentage reduction of GH and IGF-I to somatostatin analogue therapy.
No difference was found in GH response to SSA depending on prior surgery (with no prior radiotherapy), [decrease in GH: surgery group 70.5% (42.5-90.1) vs. no surgery group 59.0% (21-84.5), (p=0.39)] or IGF-I: surgery group 50.3% (16-65.1) vs. no surgery group 49.1% (0-78.1), (p=0.62) (Figure 4.6).

Figure 4.6. Effect of prior surgery on percentage reduction of GH and IGF-I to somatostatin analogue therapy.

Prolactin levels did not influence the response of GH levels to SSA [normal prolactin 62.0% (9-85.2) vs. hyperprolactinaemia 65.9% (42.8-75.4), p=0.46] or IGF-I [normal prolactin 31.2% (0-62.4) vs. hyperprolactinaemia 60.2% (32.1-71.6), p=0.15].

4.5.3 Effect of Pituitary Hormone deficiency on response to medical therapy

The prevalence of anterior pituitary abnormality at time of starting medical therapy was 44/148 (29.7%) for LH/FSH deficiency, 30/153 (19.6%) for ACTH deficiency and 6/164 (3.7%) for TSH deficiency.

In patients treated with DA, there were no statistically significant differences in the decrease of GH levels if the patients had ACTH, TSH or gonadotrophin
deficiency (p= 0.28, 0.53 and 0.11 respectively). However, we found a lower IGF-I reduction in DA therapy if gonadotrophin deficiency was present, 4.5% (-0.36-11.52) vs. 25% (9.4-40.4), (p<0.05) but no differences in IGF-I response in patients with ACTH and TSH deficiency (p= 0.86 and 0.35 respectively).

Similarly, there were no significant differences in patients with ACTH, TSH and FSH/LH deficiency with respect to GH % reduction (p= 0.59, 0.10 and 0.94 respectively) or IGF-I % reduction in the SSA group (p= 0.79, 0.69 and 0.86 respectively).
4.6 Discussion

These results demonstrate that neither basal prolactin concentrations nor co-immunostaining of GH and prolactin predicts a more favourable response in GH/IGF-I to DA. Prior therapy with radiotherapy may have an effect on the subsequent response of GH /IGF-I to DA and SSA. We have shown that efficacy of SSA in clinical practice is similar to that described in clinical trials and that there is no difference in efficacy between subcutaneous and long acting somatostatin analogues. DA therapy is associated with moderate decreases in GH and IGF-I and therefore may be beneficial in patients with mildly active disease.

Transsphenoidal surgery is still considered the first choice of treatment for the majority of patients with acromegaly. Surgical outcomes depend on several factors including the size and local invasiveness of the tumour and surgical skill. As the majority of GH secreting pituitary tumours are macroadenomas, patients often do not attain GH or IGF-I levels associated with remission or normalisation of mortality after surgery, so adjuvant therapy is often required.

Radiotherapy is widely used in patients with acromegaly and is effective in reducing GH and IGF-I to levels associated with cure or normalisation of GH, however, there is often a period of several years before this effect is achieved. Despite its beneficial effect on GH/IGF-I levels and tumour growth the use of conventional radiotherapy in patients with acromegaly has been associated with increased cerebrovascular mortality and increased risk of hypopituitarism. As a result of these factors and others (access to surgical/radiotherapy expertise and medical therapy) in this historic cohort we are aware that there may be a selection or allocation bias, however patients were treated according to best practice at the particular timepoint. There is also the possible bias that patients who received one year of medical therapy may have been
selected based on a favourable initial biochemical response to SSA or DA therapy based on a formal biochemical challenge test. These tests are not routinely used and as such most patients will not have been assessed in this manner. For DA patients are given an initial low dose of bromocriptine or cabergoline and then this is usually titrated accordingly. Patients who receive SSA are generally given a short trial of subcutaneous octreotide to assess for side effects but biochemistry is not checked in a formal octreotide challenge test to assess for response of GH during this trial. If there are no side effects from subcutaneous octreotide then patients are given long acting SSA and effect is assessed between 3-6 months followed by appropriate titration of dose as required. Patients would frequently be given up to a year to respond to medical therapy, which has been up titrated.

Medical therapy can be used as an adjunct to surgery or radiotherapy or as primary therapy for acromegaly.

4.6.1 Dopamine agonists

Dopamine agonists bind to D2 receptors in the pituitary and suppress GH secretion in patients with acromegaly. They have been used in acromegaly as an individual treatment or combined with SSA. Bromocriptine was the first DA widely used, normalizing IGF-I and GH levels in 10% and 20% of patients, respectively \(^{179}\). The utility of DA, in particular BC, has been limited by the disappointing rates of biochemical response reported, and significant side effects that may occur with the high doses (40–60 mg daily, which have been previously reported) such as nausea, vomiting, diarrhoea, fatigue, and orthostatic hypotension \(^{180}\). In our patients taking BC, lower doses (median 7.5mg/day) were used, however, even these relatively low doses achieved GH/IGF-I reductions of 42.4% and 23.6%, respectively. These changes, although
not as significant as those with SSA therapy, reduced GH and IGF-I levels in patients receiving DA into the range associated with normalisation of mortality in 28% and 32.1% of patients respectively and therefore may be of use in mildly active disease.

The second generation dopamine agonist, CBG has been demonstrated to be potentially more effective in the treatment of acromegaly, achieving safe GH and IGF-I levels in 46% and 39% of patients respectively \(^{181}\). In a recent study, Moyes and colleagues found that, on a median weekly dose of CBG of 1.75 mg, normalization of both IGF-I and GH occurred in 27% of the patients \(^{182}\). The greater efficacy of cabergoline may be due to a number of factors including greater biological potency, longer half-life and less side effects leading to improved compliance when compared with BC. In our patient cohort CBG was used less frequently than BC and in lower doses than those reported in some studies to be effective in reducing GH/IGF-I \(^{182,184}\). The lower rate of prescribing of CBG than BC is probably due to the historic nature of the cohort and also the fact that cabergoline was introduced into clinical practice for patients with acromegaly around the same time as long acting SSA (which may be more likely to be used due to their greater efficacy). In contrast to SSA there are limited studies that specifically evaluated the effect of previous surgery or radiotherapy on response of GH/IGF-I to DA therapy \(^{184}\). We found that prior radiotherapy lead to a greater reduction of GH in patients receiving DA therapy. However, there was insufficient data due to the historical nature of this cohort to assess the effect on IGF-I. There was no difference in GH or IGF-I response to DA in patients who had received prior surgery.

The predictive value of prolactin regarding GH/IGF-I response to DA therapy is controversial and there are conflicting data from small studies, with some studies concluding that tumours which co-secrete prolactin have a greater response to DA \(^{181,169,190,445}\) and other showing no increase \(^{184,191,192}\). In our
study of a large group of patients receiving DA therapy for acromegaly we could not find an association between pretreatment prolactin and GH/IGF-I response to DA therapy. Therefore patients who have a normal prolactin should not be excluded from receiving DA on the assumption that there will be limited GH/IGF-I response. Similarly, our study did not show a correlation between positive GH and prolactin immunostaining and a favourable response to DA. In the literature there is again conflicting data in smaller studies regarding the existence of this association, with some studies showing it and others not.

Recently cabergoline and pergolide have been associated with valvular regurgitation in patients on high dose DA for Parkinson’s disease and further studies are required to assess if there is a similar risk in patients taking DA for acromegaly and hyperprolactinaemia. Over the last year a number of studies have been reported looking at the effect of lower dose DA in patients with prolactinoma with conflicting results. More data is required regarding the safety of doses of DA that are used in prolactinomas and acromegaly.

4.6.2 Somatostatin Analogue Therapy

A recent meta-analysis of prospective studies reported that SSA reduced GH-levels to <2.5μg/litre and normalised IGF-I levels in 48-52% and 42-68% of acromegalic patients, respectively. Despite our study being retrospective we found similar responses to SSA (48.8% of patients achieved a GH <2.5μg/litre and 45.7% achieved an IGF-I in the normal age related reference range). This is important as it shows that GH and IGF-I reductions seen in clinical trials are possible to achieve in routine clinical practice. We found no difference in efficacy between subcutaneous and long acting SSA, as it has previously been reported in smaller single centre studies and one large multicentre study. Our study shows that this is also the case in clinical practice.
However, the convenience of the long acting SSA still makes them a more appealing option from the patient perspective.

The added advantage of SSA is their ability to reduce tumour volume \(^{153,161,164,174}\). However, results vary depending on several factors, such as baseline GH levels and the presence of functioning receptors for somatostatin \(^{447}\).

We have not found any effect of prior surgery or radiotherapy in the response of GH to SSA, we did however find that previous radiotherapy led to a decreased response of IGF-I to SSA therapy. The dynamics of GH and IGF-I secretion following radiotherapy have been studied in detail by Peacey et al \(^{94,442}\). Patients treated with radiotherapy had a greater mean valley GH nadir on cluster analysis and despite similar mean 24 hour GH concentrations patients with prior radiotherapy had a higher IGF-I value. It was felt that this elevation in IGF-I may be due to the altered characteristics of GH release, as the mean valley GH nadir and GH burst amplitude correlate positively with IGF-I the authors suggest that sustained elevated basal GH release determines the elevated IGF-I levels in these patients with otherwise safe GH levels \(^{94,442}\). This hypothesis is strengthened by studies in GH deficient adults whereby regimens leading to greater interpulse GH levels via multiple daily injections or continuous infusion of GH leads to greater IGF-I production rates than the equivalent amount of GH given as two doses \(^{446}\). Animal studies also showed that there was an increased hepatic stimulation of IGF-I after continuous GH infusion compared to that seen during pulsatile infusion (however, there was not a greater release in muscle derived IGF-I) \(^{65}\).

The effect of prior surgery on GH/IGF-I response to SSA is also controversial with some studies reporting that prior surgery leads to a greater decrease in GH and IGF-I than in surgery naïve patients \(^{449,450}\), and others similar to ours reporting no such association \(^{451}\).
4.6.3 Pituitary Hormone Deficiency

We also assessed the role of pituitary hormone deficiencies in predicting response to medical therapy. It has been shown that glucocorticoids downregulate somatostatin receptors on pituitary cells in culture\(^{452}\); however we did not find any effect of ACTH or any other anterior pituitary deficiencies on efficacy of SSA (or DA) therapies, apart from a lower IGF-I reductions in the patients receiving DA with gonadotrophin deficiency. This may possibly be due to the effect of circulating oestrogen levels and different modes of oestrogen replacement on the hepatic generation of IGF-I\(^{453}\). However, as this was a retrospective study we were unable to assess this. Little can be gleaned from the TSH results due to the low frequency of TSH deficiency in the cohort.

4.7 Conclusion

In conclusion, in a large cohort of patients with acromegaly we have demonstrated that neither basal prolactin concentrations nor co-immunostaining with GH and prolactin predict a more favourable response in GH/IGF-I to DA. Prior therapy with surgery or radiotherapy do not have a significant effect on the subsequent response of GH/IGF-I to DA. Similarly previous radiotherapy or surgery does not have an impact on GH response to SSA, however, prior radiotherapy is associated with a lower IGF-I response to SSA. Although results of reviews of clinical practice are never truly as robust as randomised control trials they are also important as the can give an idea of what happens outside the tightly monitored clinical trial environment (often difficult to attain in clinical practice). The efficacy of SSA in our clinical practice is similar to that described in rigorously designed and executed clinical trails. DA therapy is associated with moderate decreases in GH and IGF-I and therefore may be beneficial in patients with mildly active disease.
Chapter 5

ACTH deficiency, higher doses of hydrocortisone replacement and radiotherapy, are independent predictors of mortality in patients with acromegaly.
5.1 Abstract

Context: A number of retrospective studies report that patients with acromegaly have increased morbidity and premature mortality with standardised mortality ratios (SMR) of 1.3-3. Many patients with acromegaly develop hypopituitarism as a result of the pituitary adenoma itself or therapies such as surgery and radiotherapy. Pituitary radiotherapy and hypopituitarism have also been associated with an increased SMR.

Methods: West Midlands Acromegaly database (n=501, 275 female). We assessed the influence of prior radiotherapy and hypopituitarism (and replacement therapy) on mortality in patients with acromegaly. Median duration of follow up was 14.0 years (IQR 7.9-21 years).

Results: All cause mortality was elevated [SMR 1.7(1.4, 2.0), p<0.001]. On external analysis, prior radiotherapy, ACTH and gonadotropin deficiency were associated with an elevated SMR [Radiotherapy SMR 2.1(1.7-2.6), p=0.006, ACTH deficiency SMR 2.5(1.9-3.2), p<0.0005 and gonadotropin deficiency SMR 2.1(1.6-2.7), p=0.037].

On internal analysis, the relative risk of mortality was increased in the radiotherapy [RR 1.8(1.2-2.8, p=0.008)] and ACTH deficiency groups [RR 1.7(1.2-2.5), p=0.004], but not in the gonadotropin or TSH deficiency groups. In the ACTH deficient group, increased replacement doses of hydrocortisone > 25mg/ day was associated with increased mortality compared to lower doses.

Conclusions: Radiotherapy and ACTH deficiency are significantly associated with increased mortality in patients with acromegaly. In ACTH deficient patients a daily dose of > 25mg hydrocortisone is associated with increased mortality compared to lower doses. These results have important implications for the treatment of patients with acromegaly and also raise issues as to the optimum hydrocortisone treatment regimens for ACTH deficient patients.
5.2 Introduction

Acromegaly is characterised by excess GH secretion and IGF-I concentrations, most commonly due to a pituitary adenoma. Several studies have reported an increased mortality in patients with acromegaly with standardised mortality ratios (SMR) ranging between 1.3 and 3 \(^{71,133-136,138,264}\). Several factors have been associated with this increased mortality including elevated GH and IGF-I concentrations and radiotherapy. GH has been linked with excess mortality in a number of studies; decreasing GH levels reverses this increased mortality \(^{133,134,264,266}\). Some studies have also reported an improvement in mortality if IGF-I is normalised \(^{75,139}\), while others have not \(^{133,266}\). External beam conventional radiotherapy for acromegaly decreases GH to <2.5μg/litre in 60% of patients after 10 years and ~75-80% after 20 years \(^{93}\). However, in recent years external beam conventional pituitary radiotherapy has been associated with increased mortality in patients with both acromegaly \(^{133}\) and other pituitary disorders \(^{119}\). Hypopituitarism has also been associated with increased mortality, predominantly due to cardiovascular deaths \(^{118,119}\).

The dose of hydrocortisone replacement in patients with pituitary disease, which traditionally was 30mg per day in divided doses, has been shown recently to be an over replacement compared to cortisol production rates in healthy subjects \(^{354,355}\). In a recent study, Filipsson et al assessed the effect of ACTH deficiency and hydrocortisone dose in a large cohort of GH deficient adults. Patients with ACTH deficiency receiving doses of hydrocortisone greater than or equal to 25mg per day had an adverse metabolic profile compared to GH deficient patients on no hydrocortisone replacement and those with ACTH deficiency on lower doses of hydrocortisone \(^{358}\). Despite these changes in cardiovascular risk profile there have, to date, been no studies reporting an increase in mortality associated with higher doses of hydrocortisone replacement in patients with ACTH deficiency. Given the above observations the aims of our study were to
assess the role of radiotherapy, hypopituitarism (in particular the effect of individual pituitary axis deficiency) and the effect of different doses of hydrocortisone replacement therapy on mortality in a large cohort of patients with acromegaly.

5.3 Patients and methods

5.3.1 Patients

The West Midlands Acromegaly database was established in 1990 and on the 31st of December 2006, contained demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centres across the West Midlands region of the United Kingdom. The region has an overall population of 5.7 million. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1μg/litre after oral glucose loading and in most cases an elevated IGF-I). All patients with samples showing elevated GH or IGF-I in the West Midlands Regional Endocrine Laboratory were flagged as potentially having acromegaly and appropriately assessed; therefore there we feel patient capture is good and there are no grounds to assume that selection bias is substantial. However, a small number of patients (n=34) had died prior to the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site and the Office of National Statistics. 128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone and 104 received all 3 treatment modalities. 143 received surgery and radiotherapy (of these 104/143 patients also received medical therapy), 68 surgery and medical therapy, 162 radiotherapy and medical therapy (of these 102/162 also received surgery). In total, 237 received radiotherapy, 220 received conventional three field radiotherapy with a median dose of 45Gy [interquartile range (IQR) 45-47Gy] administered over a median of 25 fractions.
10 patients received stereotactic radiosurgery and 7 received Yttrium implants.

All patients were registered with the Office of National Statistics (ONS) and death certification data from the ONS were reviewed to obtain information relating to cause of death according to ICD-9 criteria. Three hundred and thirty nine patients were alive on the exit date of the study and 162 patients were deceased (data relating to radiotherapy and GH/IGF-I and mortality have been reviewed in 419 of these patients previously) \(^{133}\).

Median age at diagnosis was 46.6 years (IQR 11.6-84.2) in the entire cohort, 44.2 (IQR 34.6-53.7) in those who were still alive and 53.8 (IQR 44.6-61.8) in those who had died. Median duration of follow up was 14.0 years (IQR 7.9-21) in the entire cohort with a total of 7567 patient years and there was no difference in duration of follow up between those who are still alive and those who had died, 14.2 years and 13.8 years, respectively.

In total, 178 patients had ACTH deficiency and received hydrocortisone therapy. The daily dose of hydrocortisone (HC) was 15mg in 15 patients (taken as HC 10mg/ 5mg), 20mg in 29 patients (5 taken as HC 10mg/5mg/5mg, 11 as HC 15mg/5mg and 13 as HC 10mg/10mg), 25 mg in 14 patients (13 taken as HC 15mg/10mg and 1 as HC 15mg/5mg/5mg), 30mg in 115 patients (4 taken as HC 10mg/10mg/10mg and 111 taken as HC 20mg/10mg) and 5 patients received HC >30mgs/day.

### 5.3.2 Endocrine evaluation

Serum GH levels were measured by an in house RIA in a central laboratory as previously described \(^{398}\) (the value in mIU/litre was divided by a conversion factor of 2 to obtain µg/litre). The limit of detection of the assay is 0.5µg/litre and the interassay CV is 5.7% at 2µg/litre, 4.3% at 3µg/litre, 5.5% at 7.3µg/litre and
4.47% at 14.7μg/litre. Data on GH levels during follow up were available in 470/501 (93.8%) patients. Serum IGF-I was measured using an in house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described \(^{412}\). The limit of detection of the assay is 2.0nmol/litre. The interassay CV is 5.4-8.4% between 16-104 nmol/litre. IGF-I data were available on 409/501 patients (81.6%).

The presence or absence of hypopituitarism was defined by proven biochemical deficiency of at least one endocrine axis. The hypothalamic pituitary adrenal axis was deficient if the peak cortisol response to short synacthen testing was <550nmol/litre \(^{421}\) or less than 500nmol/litre following insulin induced hypoglycaemia during an insulin stress test. The thyroid axis was deficient if the free T4 concentration was below the local reference range, with an inappropriately low/normal TSH. Hypothalamic-pituitary gonadal dysfunction in males was diagnosed in the setting of a low serum testosterone and inappropriately low/normal gonadotropins. In females hypothalamic-pituitary gonadal dysfunction was diagnosed in premenopausal females if the patient was amenorrheic (with normal prolactin levels) and in post-menopausal females if the FSH was inappropriately low (<35IU/litre). The dose and duration of hydrocortisone, thyroxine, testosterone and oestrogen replacement were documented.

5.3.3 Statistical Analysis

5.3.3.1 Standardised Mortality Ratios

Standardised Mortality Ratios (SMRs) for overall mortality, cardiovascular, respiratory, and cerebrovascular deaths were calculated by using Stata statistical software \(^{426}\). The expected number was estimated by multiplying age, sex and calendar period specific death rates in the general population of
England and Wales by the person-years at risk accumulated within the age, sex and calendar-period specific strata corresponding to the patient cohort. SMRs for overall and cause specific mortality were also evaluated by whether patients were treated with radiotherapy, whether patients were ACTH, TSH or gonadotropin deficient, and whether patients were treated with hydrocortisone. The dose of hydrocortisone was treated as a time dependent variable i.e. if a patient was on a higher dose of hydrocortisone for any given period then person years at that level were contributed; however if the dosage was reduced, person years were added to the analysis for the lower dose category. Similarly radiotherapy was assessed in a time dependent fashion such that patients only entered the radiotherapy group for assessment of risk on the date they started radiotherapy. Most of the statistical modeling was internal since such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders.

5.3.3.2 Poisson regression

In an internal analysis a multivariable Poisson regression model was used to calculate Relative Risks (RR) of mortality based on tumour size, treatment with radiotherapy, ACTH, TSH, or gonadotropin deficiency, and dose of hydrocortisone received, if applicable. Unless otherwise stated, relative risks were adjusted for GH level, attained age, sex, calendar period, and period of follow-up. To assess the role of GH/IGF-I level or 11 beta-hydroxysteroid dehydrogenase type 1 and mortality in patients on hydrocortisone therapy an interaction term was added to the above model.
5.4 Results

5.4.1 Overall group

All cause mortality was increased significantly in the overall group of patients compared to the general population [SMR 1.7 (1.4, 2.0), p<0.001]. There was a significant increase in cardiovascular [SMR 1.9 (1.6, 2.4), p<0.001], respiratory [SMR 1.8 (1.1, 2.8), p=0.01] and cerebrovascular death [SMR 2.7 (1.9, 4.1), p<0.001], but no increase in death due to cancer [SMR 1.2 (0.9, 1.7), p=0.26], (Table 5.1). In the respiratory death category, 16 patients died from pneumonia and 4 from exacerbations of asthma/ COPD. There was a significant difference in mortality in patients with macroadenoma [SMR 1.9 (1.6, 2.3)] compared to microadenoma [SMR 1.0 (0.6, 1.7), p=0.021]. On internal analysis having adjusted for GH level, sex, attained age, calendar period, period of follow up and pre-treatment level of GH there was also an increase in mortality associated with increased tumour size [microadenoma RR 1 and macroadenoma RR 1.5 (0.9, 2.6), p=0.11], although this was not significant.
<table>
<thead>
<tr>
<th>Cause of death</th>
<th>O</th>
<th>E</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>162</td>
<td>95.9</td>
<td>1.7</td>
<td>1.4, 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>36</td>
<td>29.8</td>
<td>1.2</td>
<td>0.9, 1.7</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>77</td>
<td>39.5</td>
<td>1.9</td>
<td>1.6, 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>20</td>
<td>11.2</td>
<td>1.8</td>
<td>1.1, 2.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>25</td>
<td>9.1</td>
<td>2.7</td>
<td>1.9, 4.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 5.1. Cause of death in all patients (n=501, deaths 162) compared to the general population. (O = Observed, E = Expected, SMR = Standardised Mortality Ratio, CI = Confidence Interval).

5.4.2 The effect of pituitary irradiation on mortality

All cause mortality was higher in patients who had received radiotherapy compared to the general population; no radiotherapy [SMR 1.4 (1.1, 1.7)] compared to radiotherapy [SMR 2.1 (1.7, 2.6), p=0.006]. (Table 5.2). On internal analysis, correcting for GH level, sex, hypopituitarism, attained age, calendar period, period of follow up and pre treatment level of GH, radiotherapy was associated with a significantly increased relative risk of mortality [RR 1.8 (1.2-2.8), p=0.008], (Table 5.2). Among those exposed to radiotherapy there was a significantly increased risk of cerebrovascular death [SMR 4.1 (2.3, 6.6), p=0.034], (Table 5.3); there was no significant increase in any other specific cause of death. Of the 90 deaths in the 237 patients exposed to radiotherapy, there were 7 deaths (in 17 patients, 41.1%) in radiosurgery/ yttrium implant groups compared to 83 deaths (in 220 patients, 37.7%) in the conventional radiotherapy group.
<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>SMR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.4</td>
<td>1.1, 1.7</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.1</td>
<td>1.7, 2.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.8</td>
<td>1.2, 2.8</td>
</tr>
</tbody>
</table>

Table 5.2. Effect of radiotherapy on mortality in patients with acromegaly. External analysis compared to the general population, (SMR = Standardised Mortality Ratio, standardized for sex, attained age and calendar period). Internal analysis adjusted for GH level, sex, attained age, calendar period, hypopituitarism, period of follow up and pre treatment level of GH (RR = relative risk). CI = Confidence Interval.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Radiotherapy</th>
<th>O</th>
<th>E</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>No</td>
<td>72</td>
<td>52.9</td>
<td>1.4</td>
<td>1.1, 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>90</td>
<td>42.9</td>
<td>2.1</td>
<td>1.7, 2.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Cancer</td>
<td>No</td>
<td>17</td>
<td>16.0</td>
<td>1.1</td>
<td>0.6, 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19</td>
<td>13.8</td>
<td>1.4</td>
<td>0.8, 2.2</td>
<td>0.442</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>No</td>
<td>38</td>
<td>22.1</td>
<td>1.7</td>
<td>1.1, 2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>39</td>
<td>17.4</td>
<td>2.2</td>
<td>1.6, 3.1</td>
<td>0.247</td>
</tr>
<tr>
<td>Respiratory</td>
<td>No</td>
<td>9</td>
<td>6.2</td>
<td>1.4</td>
<td>0.7, 2.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11</td>
<td>5.0</td>
<td>2.2</td>
<td>1.1, 3.9</td>
<td>0.342</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>No</td>
<td>9</td>
<td>5.2</td>
<td>1.7</td>
<td>0.8, 3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>3.9</td>
<td>4.1</td>
<td>2.3, 6.6</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Table 5.3. Cause of death in acromegaly cohort divided according to radiotherapy exposure, standardized for sex, attained age and calendar period. P value reflects test of homogeneity in SMRs. (O = Observed, E = Expected, SMR = Standardised Mortality Ratio, CI = Confidence Interval).
5.4.3 The effect of pituitary hormone deficiency on mortality

Patients with ACTH deficiency and gonadotropin deficiency had a significantly increased SMR but patients with TSH deficiency did not (Table 5.4). However, on internal analysis, having adjusted for sex, attained age, calendar period, period of follow up and radiotherapy, only ACTH deficiency was associated with significantly increased mortality [RR 1.7, (1.2, 2.5), p=0.004], (table 5). There was no significant linear trend (p trend=0.515) in RR of mortality with increasing number of pituitary hormone axis deficiency.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Observed</th>
<th>Expected</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69</td>
<td>53.8</td>
<td>1.3</td>
<td>1.0, 1.6</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62</td>
<td>25.1</td>
<td>2.5</td>
<td>1.9, 3.2</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>93</td>
<td>57.1</td>
<td>1.6</td>
<td>1.3, 2.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42</td>
<td>19.7</td>
<td>2.1</td>
<td>1.5, 2.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40</td>
<td>28.8</td>
<td>1.4</td>
<td>0.99, 1.9</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>31.4</td>
<td>2.1</td>
<td>1.6, 2.7</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 5.4. Effect of pituitary axis deficiency of mortality compared to the general population, standardized for sex, attained age and calendar period. ACTH = adrenocorticotropic hormone, TSH = thyrotropin stimulating hormone. (O = Observed, E = Expected, SMR = Standardised Mortality Ratio, CI = Confidence Interval).
<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.7</td>
<td>1.2, 2.5</td>
<td>0.004</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.0</td>
<td>0.7, 1.4</td>
<td>0.829</td>
</tr>
<tr>
<td>Gonadotrophins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.2</td>
<td>0.8, 1.8</td>
<td>0.433</td>
</tr>
</tbody>
</table>

Table 5.5. Internal analysis of the effect of pituitary axis deficiency of mortality, adjusted for radiotherapy, follow-up time, sex, attained age, and calendar year. ACTH = adrenocorticotropic hormone, TSH = thyrotropin stimulating hormone. (RR = Relative Risk, CI = Confidence Interval).

5.4.4 The effect of hydrocortisone replacement dose on mortality

Increasing doses of hydrocortisone were associated with an increasing SMR (p for linear trend <0.001), Table 6. On internal analysis, having adjusted for age, sex, calendar period, period of follow up and radiotherapy, there was a significant increase in RR of mortality in patients receiving hydrocortisone daily doses between 25 and 30mg [RR 1.6, (1.1, 2.4), p=0.014] and hydrocortisone daily doses >30mg [RR 2.9, (1.4, 5.9), p=0.003], (Table 5.6). On internal analysis, there was a significant association between an increasing dose of hydrocortisone and mortality as assessed by the likelihood ratio test for linear trend in relative risks (p=0.002). The main cause of death in the higher dose hydrocortisone group was cardiovascular disease. In the group of patients who were ACTH replete, 26.2% of deaths were due to cardiovascular causes. In the overall group of ACTH deficient patients 31.6% of patients died from cardiovascular causes and there was an increase in cardiovascular death with
increasing hydrocortisone dose (HC dose >0 & ≤20 mg per day, 10% CVS mortality; HC dose >20 & ≤25 mg per day, 33.3% CVS mortality; HC dose >25 & ≤30 mg per day 38.5%, CVS mortality and HC >30 mg per day, 44.4% CVS mortality).

When GH levels were included in the above model as an interaction term with hydrocortisone exposure to account for the possible effect of GH on glucocorticoid metabolism of 11 beta-hydroxysteroid dehydrogenase type 1, this interaction was not statistically significant (p=0.44). This was repeated with IGF-I instead of GH but the model did not converge due to lack of power.

<table>
<thead>
<tr>
<th>Hydrocortisone daily dose</th>
<th>SMR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.35</td>
<td>1.1, 1.7</td>
<td>0.006</td>
</tr>
<tr>
<td>&lt;25mg</td>
<td>2.26</td>
<td>1.4, 3.7</td>
<td>0.0011</td>
</tr>
<tr>
<td>≥25mg</td>
<td>2.82</td>
<td>2.2, 3.7</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hydrocortisone daily dose</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 &lt; HC ≤ 20</td>
<td>1.3</td>
<td>0.7, 2.6</td>
<td>0.439</td>
</tr>
<tr>
<td>20 &lt; HC ≤ 25</td>
<td>1.4</td>
<td>0.6, 3.3</td>
<td>0.429</td>
</tr>
<tr>
<td>25 &lt; HC ≤ 30</td>
<td>1.6</td>
<td>1.1, 2.4</td>
<td>0.014</td>
</tr>
<tr>
<td>HC &gt; 30</td>
<td>2.9</td>
<td>1.4, 5.9</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 5.6. Effect of increasing dose of hydrocortisone replacement of mortality in patients with acromegaly compared to the general population standardized for sex, attained age and calendar period. Linear trend in SMR of mortality with increasing dose of HC therapy, p value for linear trend <0.001. Internal analysis of the effect of increasing daily hydrocortisone replacement doses on mortality in patients with acromegaly adjusted for sex, attained age, calendar period, period of follow up and radiotherapy. Likelihood Ratio Test for Linear Trend in relative risks p=0.002. (HC = hydrocortisone, SMR = Standardised Mortality Ratio, RR = Relative Risk, CI = Confidence Interval).
5.5 Discussion

In a large cohort of patients with acromegaly we have shown that ACTH deficiency, higher doses of hydrocortisone replacement therapy and radiotherapy are independently associated with increased mortality. Conventional external beam radiotherapy in acromegaly decreases GH to <2.5μg/litre in 60% of cases after 10 years and 75-80% after 20 years. However, it has been reported that pituitary radiotherapy is associated with a number of adverse events such as risk of secondary intracranial neoplasms, cognitive impairment, damage to the optic nerves, hypopituitarism, increased risk of cerebrovascular disease and in some previous studies increased mortality.

Increased cerebrovascular disease and death have been reported in a number of studies following pituitary irradiation. In a series of 156 patients with non-functioning pituitary adenoma, increased cerebral infarction rates were found in patients administered higher doses of radiotherapy. In a study assessing the role of pituitary radiotherapy in the development of cerebrovascular accidents (CVA) in 331 patients who received pituitary radiotherapy, it was reported that patients who received radiotherapy had a relative risk of CVA of 4.1 (CI 3.6-4.7) compared to the general population. On multivariate analysis the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared to biopsy or no operation, higher doses of radiotherapy and an underlying diagnosis of acromegaly.

In a further study, Brada et al. reported that cerebrovascular mortality was increased in patients who had received pituitary irradiation [accounting for 26% of all death, (RR 4.11, CI 2.84 – 5.75)], with an even further increase in female compared to male patients [RR 6.9 and 2.4, respectively, p=0.002]. Surgery may also play a role in the increased cerebrovascular mortality reported in this study as patients with prior surgery had an increase RR compared to those with
no surgery or biopsy alone [radiotherapy RR 5.19, surgery alone RR 1.33, p=0.02] 113.

We have previously shown an increased mortality in 419 patients 211 of which were treated with radiotherapy for acromegaly in the West Midlands Cohort 133. In patients treated with radiotherapy, overall SMR was 1.58 with an SMR of 4.42 for cerebrovascular death. Similarly, the Finnish national acromegaly database study reported an increased mortality in patients who had received radiotherapy compared to the general population. In 116/334 patients treated with radiotherapy mortality was increased (SMR1.69) compared to patients who did not receive radiotherapy (SMR of 0.94) 266.

Radiation leads to damage of both large and small vessels, but has a predilection to smaller vessels 121. The vasculature is vulnerable as endothelial cells are radiosensitive which leads to several ultrastructural changes 121 with resultant increased capillary permeability and intracellular oedema which may be followed by platelet and fibrin thrombosis. Larger lesions in arterioles can also occur, leading to myointimal proliferation, foamy macrophage plaques, fibrinoid necrosis of the media or hyalinisation of the media leading to narrowing of the vessel lumen 121. There is evidence that these changes may be clinically significant, as in a large study of patients with Hodgkin’s disease (n=4,665) who received irradiation to the heart, the relative risk of myocardial infarction was 2.56 times higher than patients who had just received chemotherapy 125.

Over 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiency within the following decade 106,108,114. A number of studies have described increased mortality in patients with hypopituitarism compared to age and sex matched controls 116-119. In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. In total, nearly 1900 patients have been included in these studies and approximately 50% had radiotherapy: in 2 studies
radiotherapy was not associated with increased mortality\textsuperscript{116,118} and in the 3\textsuperscript{rd} study it was not possible to investigate the link between radiotherapy and mortality as nearly all patients had radiotherapy\textsuperscript{117}. In the largest series in the literature, Tomlinson et al\textsuperscript{119} reported that radiotherapy was associated with significantly increased mortality [SMR 2.32 (1.7-3.14, p=0.004)] compared to the general cohort of patients with hypopituitarism [SMR 1.87 (1.62-2.16)]. In particular, patients who had received radiotherapy had an elevated cerebrovascular risk [SMR 4.36, (2.48-7.68), p=0.001]. There is no clear answer to date regarding the causal relationship between hypopituitarism and mortality. In the study by Tomlinson et al, only gonadotropin deficiency was associated with increased mortality (sex steroid replacement decreased mortality)\textsuperscript{119}. Erfurth et al\textsuperscript{120} compared radiation regimens and duration of symptoms of hypopituitarism in 342 patients treated with surgery and radiotherapy. They found no significant difference between patients who had died from cerebrovascular disease and a matched cohort who had not died for a number of irradiation parameters such as maximum absorbed dose, maximum biological equivalent dose, field size and number of fractions. The only difference found was a longer duration of symptoms of hypopituitarism in the patients who had died from cerebrovascular causes. This lead to the conclusion that untreated hormone deficiency may be more directly implicated in cerebrovascular mortality than radiotherapy per se. The findings of our study do not support this but rather suggest that both radiotherapy and ACTH deficiency were risk factors for mortality independent of each other.

Recent studies have suggested that patients with primary adrenal failure have an increased risk of mortality compared to the general population\textsuperscript{352,353}. Increased cardiovascular event rate (RR 2.56, CI 2.18-2.99) has also been described in patients receiving high dose glucocorticoids (prednisolone
>7.5mg/day) \(^{458}\). However, the association between mortality and secondary adrenal insufficiency from ACTH deficiency is not well described.

In recent years it has been reported that the cortisol production rate in normal subjects is less than was previously thought [Esteban et al, normal cortisol production rate in young adults 27.3mmol/day (equivalent to 5.7mg/m\(^2\)/day or approximately 9.9mg/day) \(^{354}\) and Kerrigan et al., total daily cortisol production rate of 5.7 ± 0.3mg/m\(^2\)/day] \(^{355}\). Traditionally the daily dose of hydrocortisone was 30mg per day split into two doses (frequently, two thirds in the morning and one third in the evening); given the recent discovery of lower levels of cortisol production rates this would lead to levels which were supraphysiological. Indeed, in the study by Esteban et al, patients with Cushing’s syndrome had daily cortisol production rates of 30.7± 9.3mg/day \(^{354}\). The bioavailability of orally administered hydrocortisone is ~95% \(^{359,360}\) therefore 30mgs of hydrocortisone per day could achieve levels similar to those seen in patients with Cushing’s syndrome albeit with greater peaks and troughs as the half life of orally administered cortisol is only 90 minutes \(^{459}\). A single morning dose of 15mg hydrocortisone leads to supraphysiological serum cortisol concentrations one to two hours post oral administration and a return to subphysiological or undetectable levels 6-8 hours later \(^{361,362}\). Glucocorticoid replacement dose has effects on a number of clinical parameters including bone metabolism, glucose metabolism, cardiovascular function and quality of life \(^{363}\).

Current glucocorticoid replacement regimens cannot mimic the physiological circadian and ultradian rhythm of endogenous cortisol. There is evidence that continuous, prolonged compared to intermittent: short exposure to glucocorticoids may have different effects on a number of steroid responsive enzymes and occupancy of the glucocorticoid receptor \(^{363}\).

Circadian infusions of hydrocortisone can mimic the normal cortisol rhythm resulting in beneficial effects in patients with Addison’s disease and congenital
adrenal hyperplasia (CAH) \textsuperscript{364}; using these infusions it was also possible to reduce the daily dose of hydrocortisone \textsuperscript{365}. These infusions are obviously cumbersome and not practical, however, over the last few years there has been a push to design orally active delayed or sustained release formulations of hydrocortisone to aid the physiological replacement of hydrocortisone and ultimately improve quality of life and side effect profiles in patients requiring long glucocorticoid replacement \textsuperscript{366}.

Fillipson et al \textsuperscript{358} have described an adverse metabolic profile in a cohort of GH deficient patients on higher doses of glucocorticoid replacement. They found that patients on hydrocortisone replacement had increased total cholesterol, triglycerides, waist circumference and HbA1c compared to the ACTH sufficient patients, all these factors are associated with increased cardiovascular morbidity. Importantly, subjects who had hydrocortisone equivalent doses of less than 20mg/day did not differ in metabolic endpoints compared to the ACTH sufficient patients. However, when a hydrocortisone equivalent doses of more than 20mg/day was administered patients had an adverse metabolic profile \textsuperscript{358}.

Acromegaly is associated with increased rates of hypertension and biventricular hypertrophy as well as metabolic complications such as impairment of glucose tolerance and lipid abnormalities \textsuperscript{236}. These abnormalities are also seen in patients with glucocorticoid excess in Cushing’s syndrome \textsuperscript{460} and one could speculate that in this study the increased mortality seen in patients receiving higher doses of hydrocortisone replacement therapy may be contributed to by the development of subclinical iatrogenic Cushing’s syndrome in these patients. Indeed, patients with Cushing’s disease have been reported to have a cardiovascular SMR of 5 \textsuperscript{461} which is due to a combination of abnormalities in blood pressure, glucose and lipid metabolism and coagulation system \textsuperscript{460}. Importantly, in a recent study the length of disease was the only predictor of increased cardiovascular risk after multivariate analysis \textsuperscript{460}. Patients on higher
doses of hydrocortisone replacement therapy are often exposed to elevated circulating cortisol levels (although not as severe as many patients with Cushing's syndrome) for many decades which may explain the increased cardiovascular mortality we have reported in our patients on higher doses of hydrocortisone.

At a tissue level, active glucocorticoid availability to the glucocorticoid/mineralocorticoid receptor is determined by the interconversion of hormonally active cortisol and inactive cortisone by isozymes of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD) \(^{374}\). Many authors have reported an interaction between the GH/IGF-I system and 11 beta-HSD1 both in vivo and in vitro \(^{387}\). This interaction may be clinically important, as it suggests the appropriate dose of hydrocortisone for patients with controlled acromegaly may be lower than that for patients with active disease, although what the exact dose adjustment should be is unknown. However, in this study GH levels had no impact on the effect of mortality in patients on hydrocortison therapy but it must be remembered that this was not a physiological study to assess this, but rather an assessment to ensure that this phenomenon did not bias our results.

Regarding the predictive vale of size of tumour and future mortality, although, the increase in mortality in patients with macroadenomas was not statistically significant (\(p=0.11\)) on internal analysis the RR was 1.5 (95% CI 0.9-2.6), this should be interpreted cautiously as the non significance may be related to sample size and the fact that adjusting for a number of variables may have decreased the power.

### 5.6 Conclusion

In conclusion, ACTH deficiency, higher doses of hydrocortisone and radiotherapy are independently associated with increased mortality. Further
work is needed to assess the relative roles of these risk factors in the premature mortality seen in patients with acromegaly and also to assess the relative importance of these risk factors compared to excess exposure to GH and IGF-I. This is the first study to show an increase in mortality in patients with ACTH deficiency on higher doses of hydrocortisone therapy. Further larger studies are required in patients with ACTH deficiency to assess the optimum therapy. These results add to the evidence regarding the deleterious effects of higher doses of hydrocortisone replacement therapy in patients with ACTH deficiency.
Chapter 6
A Paradigm Shift in the monitoring of patients with Acromegaly: Last available growth hormone overestimates risk
6.1 Abstract

Context: Acromegaly is associated with increased standardised mortality ratios (SMR) ranging between 1.3 and 3. The current consensus guidelines for normalisation of mortality suggest a target GH of <2.5μg/litre and an IGF-I in the age related reference range. There is a large body of evidence showing a decrease in GH improves mortality in acromegaly, however there is recent evidence that suggests a target GH of <2.5μg/ litre may be too high. There is less robust evidence that normalisation of IGF-I improves mortality.

Methods: Using the West Midlands Acromegaly database (n=501, 275 female) we assessed the effect of GH and IGF-I on mortality using a number of statistical methods including last available values, cumulative values and instantaneous methods. We compared the SMR in patients with acromegaly to the general population and used Poisson regression analysis to assess relative risk (RR) within the acromegaly cohort depending on GH and IGF-I levels. GH and IGF-I data during follow up were available in 470/ 501 (93.8%) and 409/ 501 patients (81.6%), respectively.

Results: The overall SMR in the acromegaly cohort was 1.7 (1.4, 2.0), p<0.001. Elevated levels of GH were significantly associated with an increased SMR, however at all levels of GH the effect on mortality was more significant using the last available GH compared to the instantaneous GH measurement (which is more statistically robust method). With increasing GH cumulative exposure there was a trend to increased mortality (p=0.06). Normalisation of IGF-I levels was not associated with a reduction in mortality [RR normal 1 vs. RR elevated 0.93 (95%CI: 0.52-1.64), p=0.81], nor was there a trend with increasing quartiles of IGF-I, p=0.73.

Conclusion: This data adds to the body of evidence for using GH in the follow up of patients with acromegaly. This study emphasizes the potential statistical
bias of using the latest available GH and IGF-I levels to predict mortality and highlights the limitations of IGF-I in predicting outcome. Therapy for each patient should be individualized and future detrimental outcomes depending on treatment modalities be assessed on a risk benefit basis.

6.2 Introduction

Acromegaly is associated with reduced life expectancy. Several retrospective studies have demonstrated a 2- to 3-fold increased mortality in patients with acromegaly compared with age- and sex-matched controls. Death is due predominantly to cardio/ cerebrovascular disease, respiratory disease and, in some studies, malignancy. Results from more recent studies also demonstrate that the high mortality rates associated with acromegaly can be normalized towards that of the general population if treatment is successful in reducing GH levels to less than 2-2.5μg/L. Normalization of IGF-I levels into age specific reference ranges has also been associated with normalization of mortality in some but not all studies. This data has lead to a number of consensus statements regarding targets for the management of acromegaly, the most recent of which state that the target for therapy in acromegaly should be a GH of <2.5μg/liter for normalization of mortality, <1.0μg/liter during an OGTT for biochemical control and <0.4μg/liter for remission and IGF-I in the age related reference range. Importantly, it should be highlighted that the studies assessing the role of GH and IGF-I in mortality have invariably used the last available GH/ IGF-I as being the level of exposure experienced by the patient from diagnosis until the date of the last measurement. Such an approach is clearly biased as GH/ IGF-I levels tend to decline with time from diagnosis. Inevitably taking the last available measurement as being indicative of exposure since diagnosis underestimates
the level of exposure to GH/IGF-I. Examples illustrating this general concept are shown Figures 6.1 and 6.2. From a pathophysiological perspective one would assume that patients who had elevated GH levels for longer would be at greater risk of mortality than those with persistently lower levels, but to date, no study has assessed this.

Our hypothesis was that the current method of assessing mortality risk in acromegaly based on the last available GH/IGF-I results in a biased risk associated with levels of GH/IGF-I. Having acquired follow up data over a long period of time in a large cohort of patients with acromegaly we aimed to assess mortality risk using a number of methods of analysis including the previously used last available GH/IGF-I, assessments of cumulative GH exposure and a novel ‘instantaneous GH/IGF-I’ method.

6.3 Patients and Methods

6.3.1 Patients

The West Midlands Acromegaly database was established in 1990 and on the 31st of December 2006, contained retrospective and prospective demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centers across the West Midlands region of the United Kingdom. The region has an overall population of 5.7 million. The median duration of follow up was 14.0 years (IQR 7.9-21) in the entire cohort with a total of 7567 patient years follow up (with GH and IGF-I levels yearly when available). There was no difference in duration of follow up between those who are still alive and those who had died (14.2 years and 13.8 years, respectively).

All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1 μg/litre after oral glucose loading and in most cases an elevated IGF-I). However, a small
number of patients (n=34) had died prior to the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site and the Office of National Statistics. 128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone and 104 received all 3 treatment modalities. 143 received surgery and radiotherapy (of these 104/143 patients also received medical therapy), 68 surgery and medical therapy, 162 radiotherapy and medical therapy (of these 102/162 also received surgery). In total, 237 received radiotherapy, 220 received conventional three-field radiotherapy with a median dose of 45Gy [interquartile range (IQR) 45-47Gy] administered over a median of 25 fractions (IQR 25-30). 10 patients received stereotactic radiosurgery and 7 received Yttrium implants.

All patients were flagged at the National Health Service Central Registers (NHSCR) for vital status and embarkations due to emigration. For each death an attempt was made to obtain the death certificate and underlying causes of death were coded using International Classification of Diseases version 9 (ICD-9). Three hundred and thirty nine patients were alive on the exit date of the study and 162 patients were deceased (data relating to radiotherapy and GH/IGF-I and mortality have been reviewed in 419\textsuperscript{133}.

Median age at diagnosis was 46.6 years (IQR 11.6-84.2) in the entire cohort, 44.2 (IQR 34.6-53.7) in those who were still alive and 53.8 (IQR 44.6-61.8) in those who had died.

6.3.2 Endocrine evaluation

Serum GH levels were measured by an in house RIA in a central laboratory as previously described (the value in mIU/litre was divided by a conversion factor of 2 to obtain μg/litre)\textsuperscript{398}. The limit of detection of the assay is 0.5μg/litre and the interassay CV is 5.7% at 2 μg/litre, 4.3% at 3μg/litre, 5.5% at 7.3 μg/litre and
4.47% at 14.7 μg/litre. Data on GH levels during follow up were available in 470/501 (93.8%) patients. Serum IGF-I was measured using an in house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described \(^4\). The limit of detection of the assay is 2.0nmol/litre. The interassay CV is 5.4-8.4% between 16-104 nmol/litre. IGF-I data were available on 409/501 patients (81.6%) during follow up. The same GH and IGF-I assay and reference range was used during the duration of the study.

### 6.3.3 Statistical Analysis

#### 6.3.3.1 External analysis – Standardized Mortality ratios

Standardized Mortality Ratios (SMRs) for overall mortality, cardiovascular, respiratory, and cerebrovascular deaths were calculated by using Stata statistical software \(^4\). The expected number was estimated by multiplying age, sex and calendar period specific death rates in the general population of England and Wales by the person-years at risk accumulated within the age, sex and calendar-period specific strata corresponding to the patient cohort. SMRs for overall and cause specific mortality were also evaluated by GH and IGF-I level.

#### 6.3.3.2 Internal analysis – Poisson regression

Most of the statistical modeling was internal since such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders. Since GH and IGF-I measurements were available for most patients, the GH value was considered as a time dependent variable. GH values were considered to be constant between two adjacent GH measurements, extrapolated back in time from the most recent measurement.
This instantaneous approach avoids bias due to incorrect allocation of person years as is the case when using the GH-level that is available at the end of the study follow up (i.e. last available GH). The latter approach assumes that the GH level measured at the end of the study prevailed throughout the whole study follow up. Such an approach is biased as the GH tends to decline with time from diagnosis (Figure 6.1 and 6.2).

**Figure 6.1(a).** Clinical course of 3 hypothetical patients (A, B, C) demonstrating that not all patients will arrive at the same last available GH level (point ■) by similar clinical courses.

**Figure 6.1(b).** Shows the difference in cumulative GH exposure (as assessed by area under the curve) between the 3 patients. This highlights the possible error of using last available GH if we hypothesize that the biological effect of excess GH exposure is a key determinant in increased mortality in patients with acromegaly.
cumulative GH and IGF-I levels \(^{428}\). Unless otherwise stated, relative risks were adjusted for radiotherapy, hypopituitarism, attained age, sex, calendar period, and period of follow-up.

### 6.4 Results

#### 6.4.1 Mortality

All cause mortality was significantly increased in patients with acromegaly compared with the general population [SMR 1.7 (1.4, 2.0); \(p<0.001\)]. Similarly the cause specific mortality with a significant increase in cardiovascular [SMR 1.9 (1.6, 2.4); \(P<0.001\)], respiratory [SMR 1.8 (1.1, 2.8); \(P=0.01\)] and cerebrovascular death [SMR 2.7 (1.9, 4.1); \(P<0.001\)], but no increase in death due to cancer [SMR 1.2 (0.9, 1.7); \(p=0.26\)] compared to the general population was noted.

#### 6.4.2 Comparison of last available vs. time-dependent (instantaneous) GH on mortality

Patients were divided into groups according to whether GH was above or below arbitrary cut-off values, and mortality (as relative risk) was assessed. Using the last available GH there was a statistically significant increase in mortality in groups as low as \(\leq 1\mu g/litre\) vs. \(>1\mu g/litre\) (RR 1.8, \(p=0.03\), Table 6.1. This was not the case for GH when using the ‘time-dependent method’, where only GH values of \(\geq 5\mu g/litre\) were suggestive of being associated with an increased risk of mortality (RR = 1.5, \(p = 0.08\), table 1. In all models radiotherapy, gender, attained age, calendar period, follow up and pre treatment GH levels were included as potential confounders.
<table>
<thead>
<tr>
<th>GH μg/litre</th>
<th>RR</th>
<th>CI</th>
<th>P value</th>
<th>Deaths</th>
<th>Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Available GH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;1</td>
<td>1</td>
<td></td>
<td></td>
<td>28</td>
<td>2491.5</td>
</tr>
<tr>
<td>1 to &lt;2.5</td>
<td>1.7</td>
<td>0.9, 3.1</td>
<td>0.08</td>
<td>31</td>
<td>1847.1</td>
</tr>
<tr>
<td>2.5 to &lt;5</td>
<td>1.6</td>
<td>0.8, 3.1</td>
<td>0.16</td>
<td>29</td>
<td>1211.3</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>2.5</td>
<td>1.4, 4.6</td>
<td>0.003</td>
<td>48</td>
<td>1548.4</td>
</tr>
<tr>
<td>&lt;25 to &lt;50</td>
<td>4.3</td>
<td>0.8, 22.2</td>
<td>0.08</td>
<td>3</td>
<td>41.6</td>
</tr>
<tr>
<td>&gt;50</td>
<td>11.8</td>
<td>2.9, 47.1</td>
<td>0.0005</td>
<td>4</td>
<td>96.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instantaneous GH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;1</td>
<td>1</td>
<td></td>
<td></td>
<td>28</td>
<td>1656.0</td>
</tr>
<tr>
<td>1 to &lt;2.5</td>
<td>1.6</td>
<td>0.9, 2.9</td>
<td>0.13</td>
<td>31</td>
<td>1601.9</td>
</tr>
<tr>
<td>2.5 to &lt;5</td>
<td>1.3</td>
<td>0.7, 2.6</td>
<td>0.37</td>
<td>30</td>
<td>1324.1</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>1.9</td>
<td>1.0, 3.6</td>
<td>0.04</td>
<td>53</td>
<td>2115.1</td>
</tr>
<tr>
<td>&lt;25 to &lt;50</td>
<td>2.1</td>
<td>0.4, 10.1</td>
<td>0.36</td>
<td>3</td>
<td>192.9</td>
</tr>
<tr>
<td>&gt;50</td>
<td>7.1</td>
<td>1.9, 27.0</td>
<td>0.0037</td>
<td>5</td>
<td>200.1</td>
</tr>
</tbody>
</table>

Table 6.1. All cause mortality in patients with acromegaly according to whether a patient was above or below arbitrary GH cut off using two methods of analysis (last available and instantaneous method of analysis). Data adjusted for radiotherapy, gender, attained age, follow up, calendar year and pre-treatment GH levels.

6.4.3 Patients were then divided into groups based on ranges of GH

Using the last available GH, levels >5μg/liter were associated with significantly increased mortality levels (Table 6.2). This was still evident with last available GH values from 1 to <2.5μg/liter (RR 1.7, p=0.08). However, when the instantaneous GH method of analysis was used the RR of mortality at each level was lower and the associated p value larger. This was also true for the likelihood ratio test for a trend in mortality with increasing GH levels (Table 6.2).
In all models radiotherapy, gender, attained age, calendar period, follow up and pre treatment GH levels were included as potential confounders.

<table>
<thead>
<tr>
<th>GH µg/litre</th>
<th>RR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Available GH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.5 vs. &gt; 0.5</td>
<td>1.6</td>
<td>0.9, 2.9</td>
<td>0.12</td>
</tr>
<tr>
<td>≤1 vs. &gt; 1</td>
<td>1.8</td>
<td>1.1, 2.9</td>
<td>0.03</td>
</tr>
<tr>
<td>≤1.5 vs. &gt; 1.5</td>
<td>1.6</td>
<td>1.0, 2.6</td>
<td>0.04</td>
</tr>
<tr>
<td>≤2 vs. &gt; 2</td>
<td>1.6</td>
<td>1.0, 2.4</td>
<td>0.05</td>
</tr>
<tr>
<td>≤2.5 vs. &gt; 2.5</td>
<td>1.5</td>
<td>1.0, 2.4</td>
<td>0.07</td>
</tr>
<tr>
<td>≤5 vs. &gt; 5</td>
<td>1.7</td>
<td>1.1, 2.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

| Instantaneous GH |
| ≤0.5 vs. > 0.5 | 1.4  | 0.7, 2.5 | 0.32 |
| ≤1 vs. > 1    | 1.5  | 0.9, 2.5 | 0.094 |
| ≤1.5 vs. > 1.5| 1.4  | 0.9, 2.2 | 0.16 |
| ≤2 vs. > 2    | 1.4  | 0.9, 2.1 | 0.16 |
| ≤2.5 vs. > 2.5| 1.2  | 0.8, 1.9 | 0.42 |
| ≤5 vs. > 5    | 1.5  | 0.9, 2.4 | 0.08 |

Table 6.2. All cause mortality in patients with acromegaly according to range of GH, using two methods of analysis (last available and instantaneous method of analysis). Data adjusted for radiotherapy, gender, attained age, follow up, calendar year and pre-treatment GH levels.

6.4.4 Comparison of last available IGF-I vs. instantaneous IGF-I

Irrespective of using last available or instantaneous method when IGF-I was divided into levels according to arbitrary cutoffs (Table 6.3) or quartiles (Table 6.4) there was no significant increase in mortality with higher levels. In all models radiotherapy, attained age, gender, calendar year and follow up period were included as potential confounders.
included as potential confounders.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>RR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Available IGF-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
<td>0.49, 1.84</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>0.79</td>
<td>0.39, 1.61</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>1.3</td>
<td>0.7, 2.42</td>
<td>0.40</td>
</tr>
<tr>
<td>p trend</td>
<td>0.366</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Instantaneous IGF-I |     |            |         |
| 1                   | 1   |             |         |
| 2                   | 1.16 | 0.68, 1.99 | 0.58    |
| 3                   | 0.91 | 0.52, 1.61 | 0.76    |
| 4                   | 1.06 | 0.61, 1.86 | 0.83    |
| p trend  | 0.95 |             |         |

Table 6.3. All cause mortality in patients with acromegaly according to the level of IGF-I using two methods of analysis (last available and instantaneous method of analysis). Data adjusted for radiotherapy, age, gender, calendar year and follow up.
<table>
<thead>
<tr>
<th>IGF-I (nmol/litre)</th>
<th>RR</th>
<th>CI</th>
<th>P value</th>
<th>Deaths</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last Available IGF-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>1</td>
<td></td>
<td>31</td>
<td>2089.7</td>
<td></td>
</tr>
<tr>
<td>25-49</td>
<td>0.85</td>
<td>0.50, 1.42</td>
<td>0.5307</td>
<td>28</td>
<td>20101.0</td>
</tr>
<tr>
<td>50-74</td>
<td>1.28</td>
<td>0.65, 2.52</td>
<td>0.4811</td>
<td>13</td>
<td>594.2</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.55</td>
<td>0.79, 3.02</td>
<td>0.2016</td>
<td>14</td>
<td>293.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p trend 0.194</td>
</tr>
</tbody>
</table>

| Instantaneous IGF-I |     |             |         |        |              |
| 0-24               | 1   |             | 34      | 1893.3 |              |
| 25-49              | 1.19| 0.7, 1.9    | 0.48    | 35     | 1939.7       |
| 50-74              | 0.94| 0.5, 1.7    | 0.84    | 18     | 1014.0       |
| >75                | 1.5 | 0.8, 2.8    | 0.21    | 18     | 968.8        |
|                   |     |             |         |        | p trend 0.43 |

Table 6.4. All cause mortality in patients with acromegaly according to quartile of IGF-I using two methods of analysis (last available and instantaneous method of analysis). Data adjusted for radiotherapy, age, gender, calendar year and follow up.
6.4.5 The Effect of cumulative GH on mortality

When the effect of cumulative exposure of GH on the risk of mortality was assessed (having adjusted for attained age, gender and calendar period and pre-treatment GH) there was a trend to increased mortality in patients who had the greatest exposure to GH as assessed by elevated GHU year exposure (p for trend = 0.06). When radiotherapy was introduced into the model the trend decreased (p for trend = 0.15), Table 6.5.

<table>
<thead>
<tr>
<th>Cumulative exposure to GH (GHU-years)</th>
<th>No. of Deaths</th>
<th>No. of Patient years</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
<th>Relative Risk (95% CI) With Radiotherapy in Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-49</td>
<td>6</td>
<td>407</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td>20</td>
<td>993</td>
<td>1.3 (0.5, 3.4)</td>
<td>0.536</td>
<td>1.1 (0.4, 2.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-199</td>
<td>28</td>
<td>1438</td>
<td>1.7 (0.7, 4.1)</td>
<td>0.249</td>
<td>1.4 (0.6, 3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>31</td>
<td>1442</td>
<td>2.0 (0.8, 5.4)</td>
<td>0.127</td>
<td>1.7 (0.7, 4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500-999</td>
<td>15</td>
<td>752</td>
<td>2.1 (0.8, 5.4)</td>
<td>0.142</td>
<td>1.7 (0.6, 4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000+</td>
<td>7</td>
<td>390</td>
<td>2.0 (0.7, 6.0)</td>
<td>0.224</td>
<td>1.4 (0.5, 4.5)</td>
</tr>
</tbody>
</table>

Table 6.5. Effect of level of cumulative exposure to GH on all cause mortality and effect of radiotherapy on this effect. GHU = GH units. Likelihood Ratio Test for linear trend in relative risks p=0.06. Adjusted for: attained age, sex, calendar period, assuming pre-treatment GH level existed for 8 years prior to diagnosis.
6.5 Discussion

We have shown that the widespread method of assessing mortality risk in patients with acromegaly based on last available GH leads to biased estimates of the increased relative risk of mortality at any GH level compared an unbiased time-dependent approach. We have again documented that IGF-I did not predict mortality. For the first time, we show that increased cumulative exposure to GH leads to a trend towards increased relative risk of mortality, but this relationship was diluted once radiotherapy was included in the model. Both radiotherapy and ACTH deficiency are associated with increased mortality in this patient cohort. Hypopituitarism per se is also associated with reduced life expectancy (SMR’s 1.5-2.5) \(^{118}\). These observations have far reaching therapeutic implications; in an attempt to lower GH levels to existing targets, we often use radiotherapy or repeat surgery which although frequently effective in reducing GH/IGF-I has other detrimental effects, including hypopituitarism. While we would not argue against the importance of reducing GH levels in patients with acromegaly \(^{133,134,137,264,266}\), our data indicate that the GH cut-offs suggested in current consensus guidelines may lead to the increased use of radiotherapy or repeat surgery which may themselves cause adverse outcomes.

6.5.1 Impact of GH levels on mortality in acromegaly

In the early 1990’s, two studies demonstrated that the increased mortality associated with acromegaly can be decreased if treatment is successful in reducing last available GH levels to less than 5mU/L (2.5μg/L), whether this is measured as the mean of a growth hormone day profile or as a random growth hormone level \(^{134,137}\). In the first of these studies by Bats et al, in a cohort of 79

189
patients with acromegaly, the SMR fell from 2.6 to 2.0 if treatment reduced GH levels to under 10mU/L (5µg/L) \(^{134}\). Even more significant was the fact that mortality was reduced to normal if post-treatment GH levels of less than 5mU/L (2.5µg/L) were achieved. The second study by Rajasoorya et al in a cohort of 151 patients with acromegaly showed both on univariate and multivariate analysis that higher GH levels were associated with reduced survival \(^{137}\).

Over the last two decades a number of studies have reported similar findings reaching a consensus in showing that post-treatment GH values of less than 2.5µg/L restores SMR to normal and providing an evidence base for targeted reduction of GH concentrations \(^{55,140,271,272}\). However, GH cut off points of 2.5µg/L for normalization of mortality and <1µg/L to define biochemical control of acromegaly have been arbitrarily adopted, with little scientific basis for this selection. In our own West Midlands Acromegaly cohort, comparison of crude death rates per 1000 population suggested that a latest GH of 2µg/L may be a more appropriate treatment target, with a step-up in the death rate once GH exceeded 2µg/L \(^{133}\). Data from Holdaway et al. suggest a further improvement in outcome if GH can be lowered to under 1µg/L \(^{264}\). Similar results were seen in this current study; using a latest GH cut-off value as low as <1 vs >1 µg/litre appearing to show improvement in survival. In a recent meta-analysis focusing on the relationship between biochemical measurements and mortality during follow-up after treatment for acromegaly, mortality was close to the expected level when last available GH was <2.5µg/L (SMR 1.1, 95% CI 0.9-1.4), but was significantly elevated in those with last available GH >2.5µg/L (SMR 1.9, 95% CI 1.5-2.4), the RR for a serum GH >2.5 µg/L was 1.7 (P<0.05) \(^{273}\). On this background therefore, the consensus is that the target for normalization of mortality in acromegaly should be reduction of GH values to less than 2.5µg/L.
However, we feel these data may be an overestimation of the effect of GH on mortality; when we used a more appropriate instantaneous method of analysis we did not see as great relative risks of mortality or statistical significance as in the biased method using the last available GH method. There was a trend toward significance for a greater GH cumulative exposure being associated with increased mortality in acromegaly (which given that this is a rare disease may be clinically relevant albeit not statistically significant). This is the first time the effect of cumulative exposure to GH has been assessed in patients with acromegaly and strengthens the already strong argument that GH concentrations are a factor driving mortality in this patient cohort.

6.5.2 Impact of IGF-I levels on mortality in acromegaly

IGF-I is now widely used as a first line investigation for the diagnosis and therapeutic monitoring of patients with acromegaly. Indeed, the introduction of GH-antagonists as medical treatment for acromegaly necessitates the use of IGF-I in the biochemical monitoring of patients treated with these agents. However, the relationship between mortality and last available IGF-I level is not as strong as it is for the last available GH. Swearingen et al reported that in a cohort of 162 patients (12 deaths), those patients who were surgically cured, defined by a normal IGF-I, had mortality similar to that of the general population of the United States, while those with active disease as defined by a persistently elevated IGF-I had reduced life expectancy for the period that the IGF-I was elevated. A further study also concluded that IGF-I normalization reduced mortality to expected levels, however serum IGF-I was not an independent predictor of mortality when both GH and IGF-I measurements were included in the multivariate analysis, and was only significant when looking at SD scores >2 for IGF-I compared to normal IGF-I levels. In the recent meta-analysis by
Holdaway et al., those with normal IGF-I had mortality rates close to the expected values for the general population (SMR 1.1, 95% CI 0.9, 1.4), whereas the SMR for those with elevated IGF-I at last follow-up remained significantly increased (SMR 2.5, 95% CI 1.6, 4.0). The risk ratio for an elevated serum IGF-I was 2.3 (P<0.05) \(^{273}\). However, it should be noted that two of the largest studies, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between post-treatment IGF-I levels and mortality (RR 1.2, CI 0.71-2.02, p=0.05) and (0.46, CI 0.17-1.26, p=0.13), suggesting last available serum IGF-I may not be as reliable a predictor of future mortality in acromegaly as last available GH \(^{133,266}\). In our study, we assessed the role of IGF-I on future mortality by a number of methods including dichotomous (normal vs. elevated), quartiles of IGF-I and IGF-I according to biochemical cut-offs after adjusting for a number of potential cofounders. We did not find any relationship between IGF-I and mortality risk in patients with acromegaly whether using the last available or the instantaneous IGF-I method of analysis.

This study highlights that although normalization of GH and IGF-I has been, and should continue to be a target of therapy in acromegaly alongside tumour volume control and alleviation of symptoms that a risk benefit assessment for each patient is essential. If normalization of GH and IGF-I is at the cost of exposing the patient to pituitary radiotherapy or inducing hypopituitarism (in particular ACTH deficiency) then the risk of remaining at an elevated GH/IGF-I must be weighed up against the possible detrimental effects of this therapy. This is particular relevant given the significant effects of medical therapy on biochemical control \(^{164,210,464}\) (and in the case of somatostatin analogue therapy tumor volume reduction) \(^{161}\).

Importantly, patients with acromegaly have abnormal glucose metabolism, blood pressure, cardiac structure and lipid profiles \(^{207}\). No study to date has studied
the effect of modern vascular risk factor reduction on mortality in acromegaly. One could speculate that the improvement in the last two decades in SMR for patients with acromegaly may reflect greater awareness of these complications and the introduction of better therapies for glucose control, lipid abnormalities and treatment of blood pressure and cardiac abnormalities such as left ventricular hypertrophy rather than reductions in GH/IGF-I per se.

6.6 Conclusion

In conclusion, our study emphasizes the misleading bias of using the latest available GH and IGF-I levels to predict mortality. These have probably overestimated true risk and adoption as consensus "cures" may, paradoxically, have lead to increased risk through radiotherapy and hypopituitarism-related mortality. An unbiased method, using time-dependent (instantaneous) GH values suggests that higher GH cut-offs of 5μg/L may be acceptable. Our study again highlights the limitations of IGF-I in predicting outcome. Further work is required to formulate GH targets for normalization of mortality taken into account this newer method of analysis. Therapy for each patient should be individualized and future detrimental outcomes depending on treatment modalities be assessed on a risk benefit basis.
Chapter 7

General Conclusions and Discussion
Acromegaly is a rare condition associated with increased morbidity and mortality. As a result of its low incidence large studies are difficult and often involve a national or multinational approach, which may have limitations. The West Midlands Acromegaly Study had data on over 500 patients with acromegaly in a defined region in the United Kingdom. The GH and IGF-I assays were centralised to a single laboratory and therefore the problem of multiple assays with multiple reference ranges, which is often a limitation of national or multinational studies, is avoided. Follow up data including biochemical data, treatment responses, degree of endocrine replacement therapy; morbidity and mortality were recorded for a median of 15 years.

The method of optimum follow up of patients with acromegaly is one of debate. The options include the oral glucose tolerance test (OGTT), growth hormone day curve (GHDC) and fasting GH and IGF-I sample. There are cost and service implications for the OGTT and GHDC, whereas the fasting GH sample is more economical. On the basis of the data reported in this thesis, in patients who have a basal fasting GH <2.5 µg/litre, there is no added diagnostic benefit in performing an OGTT or GHDC given the close association between basal fasting GH and nadir/ mean during OGTT/ GHDC. Similarly, in those patients with a fasting basal GH is >5 µg/litre there is no added benefit in performing an OGTT or GHDC as the probability of nadir/ mean GH being suppressed to <2.5 µg/litre is low. However, if the basal GH is between 2.5-5 µg/litre then an OGTT or GHDC should be performed as a basal fasting GH has a poor correlation with GH nadir/ mean in this range. The results of this thesis also highlight the large discordance between disease activity assessed by GH and IGF-I and this discordance is exaggerated by radiotherapy. With the weight of evidence supporting GH versus IGF-I as a mortality outcome measure, the pitfalls of measuring only IGF-I to monitor disease activity in acromegaly are
self-evident. More research is needed, particularly in the group who have reached their target for GH but in whom IGF-I remains elevated to assess if these patients require further therapy or are at risk of increased morbidity/mortality.

The results of medical therapy for acromegaly have been reported in a number of clinical trials. We assessed the results of using these agents in a clinical practice rather than clinical trial setting. We found that in routine clinical practice somatostatin analogues lead to similar levels of GH and IGF-I control reported in clinical trials. Although results of reviews of clinical practice are never truly as robust as randomised control trials they are also important as the can give an idea of what happens outside the tightly monitored clinical trial environment (often difficult to attain in clinical practice). These results also show that dopamine agonists may still have a role in patients with mildly active disease, however more research is required into the risk of cardiac valve dysfunction secondary to dopamine agonists, particularly as patients with acromegaly are already at increased risk of valve dysfunction. There is controversy as to whether dopamine agonists should only be used in patients who co-secrete or co-immunostain with prolactin but we have demonstrated that neither basal prolactin concentrations nor co-immunostaining with GH and prolactin predict a more favourable response in GH/IGF-I to dopamine agonist therapy. Therefore, dopamine agonists should not solely be used in patients with hyperprolactinaemia. Prior therapy with surgery or radiotherapy do not have a significant effect on the subsequent response of GH /IGF-I to dopamine agonist therapy. Similarly previous radiotherapy or surgery does not have an impact on GH response to somatostatin analogues, however, prior radiotherapy is associated with a lower IGF-I response to somatostatin analogues.
Hypopituitarism has been associated with increased mortality, however the studies reporting this have excluded patients with acromegaly and Cushing's disease due to the inherent increase in mortality in these conditions. We assessed the role of pituitary dysfunction and its treatment on mortality in patients with acromegaly. We found that patients who were ACTH deficient had higher mortality rates, even after controlling for GH, IGF-I and radiotherapy exposure. There has been a move in recent years to decrease the dose of hydrocortisone used in the treatment of ACTH deficiency as the classic replacement dose of 20mg hydrocortisone in the morning and 10mg in the afternoon/ evening have been associated with morbidity, however until this study there has been no data to show an increase in mortality. We have shown that higher daily doses of hydrocortisone are independently associated with increased mortality. Therefore the aim should be to have patients on the lowest dose of hydrocortisone therapy that keeps them asymptomatic of adrenal insufficiency. Further studies are needed to see if this is also true in non-acromegalic patients with hypopituitarism and to assess the optimum therapy.

We have also shown in a large patient cohort that conventional fractionated radiotherapy is independently associated with increased risk of mortality in patients with acromegaly and this is predominantly due to an increase in cerebrovascular disease. It is too early to say if newer, more focused radiotherapy methods will result in a decrease in mortality due to this treatment and studies may take some time before they can report this. Therefore, until these data are available the risk benefit ratio for radiotherapy should be discussed individually with each patient.

In all the studies assessing the role of GH and IGF-I in mortality to date the last available GH measurement has been used to assess risk of mortality. We have shown that this may be statistically biased. Using these measurements have
probably over estimated true risk and the adoption of these targets as consensus for "cure" or 'normalisation of mortality' may, paradoxically, have lead to increased risk through radiotherapy and hypopituitarism-related mortality. A statistically less biased method, using time-dependent (instantaneous) GH values suggests that higher GH cut-offs of 5µg/L may be acceptable. Our study again highlights the limitations of IGF-I, whatever the statistical method used, for predicting outcome. Therapy for each patient should be individualized and future detrimental outcomes depending on treatment modalities should be assessed on a risk benefit basis.

None of the studies published to date take into account the significant improvements in cardiovascular risk reduction that has taken place over the last 20-30 years including increased prescription of antiplatelet therapy, antihypertensives (and lower target blood pressure) and statin therapy, all of which one would assume have a significant role to play in reducing cardiovascular mortality in patients with acromegaly as in the general population.

Further work is needed to assess the relative roles of these all of the above risk factors in the premature mortality seen in patients with acromegaly and also to assess the relative importance of newer risk factors (radiotherapy, hypopituitarism and glucocorticoid over-replacement) compared to excess exposure to GH and IGF-I.
References


49. Fedele, M., et al. Transgenic mice overexpressing the wild-type form of the HMGA1 gene develop mixed growth hormone/prolactin cell pituitary


406. Seth, J., Ellis, A. & Al-Sadie, R. Serum growth hormone measurements in clinical practice: An audit of performance from the UK National


421. Clark, P.M., Neylon, I., Raggatt, P.R., Sheppard, M.C. & Stewart, P.M. Defining the normal cortisol response to the short Synacthen test:


426. Statcorp Stata Statistical, S., Vol. Relaese 9 (College Station, TX, Statcorp LP, 2005).


437. Kalsas, G.A., *et al*. Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in


451. Ayuk, J., Stewart, S.E., Stewart, P.M. & Sheppard, M.C. Efficacy of Sandostatin LAR (long-acting somatostatin analogue) is similar in patients with untreated acromegaly and in those previously treated with surgery and/or radiotherapy. Clin Endocrinol (Oxf) 60, 375-381 (2004).


Appendix A

Published Manuscripts arising from this thesis
Monitoring disease activity using GH and IGF-I in the follow-up of 501 patients with acromegaly

M. Sherlock*, A. Aragon Alonso*, R. C. Reulent†, J. Ayuk*, R. N. Clayton‡, G. Holder§, M. C. Sheppard*, A. Bates‡ and P. M. Stewart*

*Centre for Endocrinology, Diabetes and Metabolism, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TH, UK, †Department of Public Health and Epidemiology, Centre for Childhood Cancer Survivor Studies, University of Birmingham, Birmingham B15 2TH, UK, ‡Department of Postgraduate Medicine, University of Keele, Harthill, Stoke-on-Trent, ST4 7QU, UK, §Department of Clinical Biochemistry, University Hospital Birmingham NHS Trust, Birmingham B29 6JD, UK, and ¶Birmingham Heartlands and Solihull NHS Trust, Birmingham B9 5SS, UK

(Received 22 July 2008; re-turned for revision 30 July 2008; finally revised 24 September 2008; accepted 29 September 2008)

Summary
Context The aims of treatment in patients with acromegaly are to achieve serum GH/IGF-I concentrations associated with cure or normalization of mortality and alleviation of symptoms.

Objective and methods Using the West Midlands Acromegaly database (n = 501) we investigated the reliability of basal fasting GH in predicting nadir or mean GH during oral glucose tolerance test (OGTT) or GH day curve (GHDC), respectively, the degree of discordance between disease activity measured by GH and IGF-I values and the effect of radiotherapy on the above relationships. In total 773 OGTT and 507 GHDC were performed.

Results Basal fasting GH was strongly correlated with nadir/mean GH on OGTT/GHDC (r = +0.87, P < 0.0001, r = +0.93, P < 0.0001, respectively). A basal GH < 2.5 μg/l was associated with a nadir/mean GH during OGTT/GHDC < 2.5 μg/l in 98.6% and 88.2% of cases, respectively.

Elevated IGF-I was seen in 32.4% and 46.4% of patients with GH nadir values during OGTT < 1 and < 2.5 μg/l, respectively, and in 21.2% and 45.9% of GHDC with mean GH < 1 and < 2.5 μg/l, respectively. Radiotherapy increased the discordance in GH and IGF-I as markers of disease activity at GH < 2.5 μg/l (elevated IGF-I-values when OGTT nadir GH < 2.5 μg/l; radiotherapy 55.0% vs. no radiotherapy 36.9%, P = 0.002).

Conclusions There is a close relationship between a basal fasting GH < 2.5 μg/l and nadir/mean GH < 2.5 μg/l during OGTT/GHDC. There is a large discordance between disease activity when assessed by GH and IGF-I which is further increased by radiotherapy. These observations illustrate the challenge of defining appropriate biochemical end-points to achieve control of disease and normalization of mortality in acromegaly.

Introduction
Acromegaly is a disabling disease characterized by excess GH secretion and circulating IGF-I concentrations. In addition to significant morbidity, acromegaly is associated with increased mortality which has been demonstrated in a number of retrospective studies with standardized mortality ratios between 1.3 and 3 (comprising over 5000 patients and 1000 deaths).1-4 This increase in mortality can be normalized if GH levels are decreased,5-8 we and others have previously described normalization of mortality if GH can be reduced to < 2.5 μg/l.5,6,8-11 The evidence for using IGF-I as a predictor of outcome is not as robust. To date only two studies have provided support for the use of IGF-I as a predictor of long term outcome, and the observed number of deaths in both these studies was small.4,8 The most recent consensus statement for cure of acromegaly has defined the criteria for remission as a normal age related IGF-I and a GH < 1 μg/l during an oral glucose tolerance test (OGTT).10 Many endocrinologists have adopted a target GH for normalization of mortality as < 2.5 μg/l1-4 and a recent meta-analysis of the effect of lowering GH values has shown that GH values < 2.5 μg/l are associated with a normalization of mortality (standardized mortality ratios 1.1, 95% CI 0.9-1.4).11

The method of assessing GH during follow up in patients with acromegaly varies widely across the endocrine community. Many have adopted the suppression of GH following a glucose load (OGTT) as the gold standard for follow up. Other investigators use a 5 point GH day curve (GHDC) or a single random/basal GH measurement. IGF-I should be measured at the same time as GH secretion is assessed.12 The OGTT and GHDC require time and resources, both in terms of personnel and multiple assays; whereas a single random fasting GH level can be performed easily at a clinic visit or in the phlebotomy department and only requires one sample, similar to IGF-I which measures integrated GH secretion.
Radiotherapy is widely used in the treatment of acromegaly and has been shown to be effective in decreasing GH and IGF-I levels. Using data from the West Midlands Acromegaly database \((n = 501)\) we examined a number of issues surrounding the biochemical follow-up of patients with acromegaly. First, did a basal fasting GH reliably predict the nadir GH during an OGTT or mean GH during a GHDC in the assessment of disease activity during follow-up in patients with acromegaly? Second, what was the degree of discordance between disease activity measured by GH and IGF-I values and finally does exposure to radiotherapy have any effect on the above relationships?

Patients and methods

The West Midlands Acromegaly database was established in 1990 and on the 31 December 2006, contained demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centres across the West Midlands region of the UK. The region has an overall population of 5.7 million. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1 µg/l after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (34) had died prior to the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site.

In total 128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone, 143 surgery and radiotherapy, 68 surgery and medical therapy, 162 had radiotherapy and medical therapy and 104 received all the three. Median duration of follow-up was 13.9 years (inter-quartile range 7.9–21.0 years).

Endocrine evaluation

Serum GH levels were measured by an in house RIA in a central laboratory as previously described (the value in mIU/l was divided by a conversion factor of 2 to obtain µg/l). The limit of detection of the assay is 0.5 µg/l and the interassay CV is 5.7% at 2 µg/l, 4.3% at 3 µg/l, 5.5% at 7.3 µg/l and 4.47% at 14.7 µg/l. Assessment of GH secretion after treatment differed between units within centres in the West Midlands. GH levels were recorded as a nadir of five GH assessments over two hours following administration of 75 g oral glucose (2-h 75 g-OGTT), the mean of a GH day profile (the average of five GH measurements taken at 2-h intervals) or a random/basal GH measurement performed in an outpatient setting. Data on GH levels during follow-up were available in 470 out of 501 (93.8%) patients. Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described. The limit of detection of the assay is 2.0 nmol/l. The interassay CV is 5.4–8.4% between 16 and 104 nmol/l. Reference ranges were derived from adults with no known or suspected endocrine disorders. Reference range values were 14–48 nmol/l at 21–30 years \((n = 71)\), 13–37 nmol/l at age 31–45 years \((n = 123)\) and 8.9–32 nmol/l \((n = 75)\) above 45 years. IGF-I data were available on 409 out of 501 patients (81.6%).

Statistical analysis

Positive and negative predictive values were calculated for basal GH with respect to GH nadir during OGTT and mean during GHDC. GH nadir during OGTT and mean during GHDC < 1 µg/l and < 2.5 µg/l were considered as true positive with relation to disease remission and levels known to normalize mortality, respectively. Differences in predictive values and changes in discordance levels dependent on radiotherapy were assessed by the \(\chi^2\)-test. Correlation coefficients comparing basal GH and GH nadir during OGTT/mean during GHDC are reported as Spearman's correlation coefficients. A \(P\)-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism, San Diego, CA. We performed an Altman-Bland analysis to quantify agreements between basal GH and nadir/mean GH during OGTT/ GHDC. This involves plotting a difference of measured values vs. an average of the same values (these calculations were performed on log transformed data).

Results

The association between basal fasting GH and nadir GH during OGTT/mean GH during GHDC

In total there were 773 OGTT performed on 282 patients and 507 GHDC performed on 109 patients during follow-up. This included 480 (62.1%) OGTT and 436 (86%) GHDC performed in patients who had received radiotherapy and 293 (37.9%) OGTT and 71 (14%) GHDC in patients who were radiotherapy naive. In the analysis of OGTT data if the basal GH was also the nadir reading then the next lowest reading was taken to avoid bias. In analysis of all tests performed the basal GH was strongly correlated with mean GH during GHDC \((r = 0.95, P < 0.0001)\) and with nadir GH during OGTT \((r = 0.87, P < 0.0001)\) (Fig. 1). The concordance between basal GH and nadir/mean GH during OGTT/GHDC are represented by Altman-Bland plots (Fig. 2). In the Altman-Bland analysis of log basal GH vs. log GH nadir during OGTT the bias was -0.18 and the 95% limit of agreement -0.68 to 0.31. In the Altman-Bland analysis of log basal GH vs. log GH mean during GHDC the bias was 0.004 and the 95% limit of agreement -0.31 to 0.32. The predictive value of a basal fasting GH indicating degrees of disease activity with respect to GH nadir/mean during OGTT/ GHDC are represented in Table 1. In the 208 patients who recorded a nadir GH during OGTT < 1 µg/l 112 (53.8%) had a basal GH < 1 µg/l and 96 (46.2%) had a basal GH > 1 µg/l. Of these 96 patients had a basal GH < 2.5 µg/l, leaving 28 out of 208 (13.5%) patients with a nadir GH on OGTT < 1 µg/l having a basal > 2.5 µg/l, of these 28 subjects 12 had a raised IGF-I.

Discordance between disease activity as assessed by GH values and IGF-I status

The discordance between disease activities as assessed by IGF-I values and nadir/mean GH during OGTT/GHDC was examined. IGF-I values were categorized into being within, above or below the age specific local reference range. For this purpose only OGTT and
Fig. 1 Correlation between basal GH and GH nadir/mean during oral glucose tolerance test (OGTT) and GH day curve (GHDC) in all patients.

Fig. 2 Altman-Bland analysis of comparison between basal GH and GH nadir during oral glucose tolerance test (OGTT) (2a) and basal GH and mean GH during GH day curve (GHDC) (2b). Dotted lines represent 95% limits of agreement.

Table 1. The predictive value of basal GH indicating degrees of disease activity with respect to GH nadir on OGTT and mean GH on GHDC

<table>
<thead>
<tr>
<th>GH µg/l</th>
<th>GH Nadir OGTT &lt; 2.5</th>
<th>GH Nadir OGTT &gt; 2.5</th>
<th>GH Mean GHDC &lt; 2.5</th>
<th>GH Mean GHDC &gt; 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal GH &lt; 2.5</td>
<td>287/291 (98.6%)</td>
<td>4/291 (1.4%)</td>
<td>149/169 (88.2%)</td>
<td>20/169 (11.8%)</td>
</tr>
<tr>
<td>Basal GH 2.5-5</td>
<td>85/167 (50.9%)</td>
<td>82/167 (49.1%)</td>
<td>23/130 (17.7%)</td>
<td>107/130 (82.3%)</td>
</tr>
<tr>
<td>Basal GH &gt; 5</td>
<td>35/312 (11.2%)</td>
<td>277/312 (88.8%)</td>
<td>1/208 (0.5%)</td>
<td>207/208 (99.5%)</td>
</tr>
</tbody>
</table>

GHDC results within the database which had IGF-I data recorded on the same day were included. 421 OGTT in 173 patients (83 subjects following radiotherapy, 90 no radiotherapy) and 223 GHDC in 75 patients (54 subjects following radiotherapy, 21 no radiotherapy) had corresponding IGF-I assessments. In total 32-4% of patients with GH nadir values on OGTT < 1 µg/l and 46.4% of patients with a GH nadir on OGTT < 2.5 µg/l had an elevated IGF-I. 21.2% of GHDC with mean GH < 1 µg/l and 45.9% of GHDC with mean GH < 2.5 µg/l had an elevated IGF-I. In patients who had an OGTT, 27.0% with a basal GH > 2.5 µg/l and 18.6% with a nadir GH > 2.5 µg/l during OGTT had a normal IGF-I. In patients who had a GHDC, 13.5% with a mean GH > 2.5 µg/l and 15.4% with a basal GH of > 2.5 µg/l had a normal IGF-I (Table 2). The degree of discordance between GH and IGF-I was similar whether the GH used was basal or mean/nadir GH at all levels during a GHDC. During an OGTT the discordance between GH and IGF-I was similar if basal GH or
Table 2. Discordance between disease activity as assessed by GH (basal or nadir/mean GH during OGTT/GHDC) and IGF-I-values. (χ², Pearson *P < 0.05, **P < 0.002)

<table>
<thead>
<tr>
<th>GH µg/l</th>
<th>Elevated IGF-I</th>
<th>Normal IGF-I</th>
<th>Low IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHDC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal &lt; 1</td>
<td>9/40 (22.5%)</td>
<td>27/40 (67.5%)</td>
<td>4/40 (10%)</td>
</tr>
<tr>
<td>Mean &lt; 1</td>
<td>7/33 (21.2%)</td>
<td>22/33 (66.7%)</td>
<td>4/33 (12.1%)</td>
</tr>
<tr>
<td>Basal &lt; 2-5</td>
<td>46/93 (49.5%)</td>
<td>43/93 (46.2%)</td>
<td>4/93 (4.3%)</td>
</tr>
<tr>
<td>Mean &lt; 2-5</td>
<td>45/98 (45.9%)</td>
<td>49/98 (50.0%)</td>
<td>4/98 (4.1%)</td>
</tr>
<tr>
<td>Basal 2-5-5</td>
<td>45/55 (81.8%)</td>
<td>10/55 (18.2%)</td>
<td>0/55</td>
</tr>
<tr>
<td>Mean 2-5-5</td>
<td>41/51 (80.4%)</td>
<td>10/51 (19.6%)</td>
<td>0/51</td>
</tr>
<tr>
<td>Basal &gt; 5</td>
<td>65/75 (86.7%)</td>
<td>10/75 (13.3%)</td>
<td>0/75</td>
</tr>
<tr>
<td>Mean &gt; 5</td>
<td>68/75 (90.7%)</td>
<td>7/75 (9.3%)</td>
<td>0/75</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal &lt; 1</td>
<td>18/73 (24.7%)</td>
<td>49/73 (67.1%)</td>
<td>6/73 (8.2%)</td>
</tr>
<tr>
<td>Nadir &lt; 1</td>
<td>47/145 (32.4%)</td>
<td>92/145 (63.4%)</td>
<td>6/145 (4.2%)</td>
</tr>
<tr>
<td>Basal &lt; 2-5</td>
<td>78/190 (41.1%)</td>
<td>106/190 (55.8%)</td>
<td>6/190 (3.1%)</td>
</tr>
<tr>
<td>Nadir &lt; 2-5</td>
<td>129/278 (46.4%)</td>
<td>142/278 (51.1%)</td>
<td>7/278 (2.5%)</td>
</tr>
<tr>
<td>Basal 2-5-5</td>
<td>67/109 (61.5%)</td>
<td>41/109 (37.6%)</td>
<td>1/109 (0.9%)</td>
</tr>
<tr>
<td>Nadir 2-5-5</td>
<td>61/84 (72.6%)</td>
<td>23/84 (27.4%)</td>
<td>0/84</td>
</tr>
<tr>
<td>Basal &gt; 5</td>
<td>102/124 (82.3%)</td>
<td>22/124 (17.7%)</td>
<td>0/124</td>
</tr>
<tr>
<td>Nadir &gt; 5</td>
<td>57/61 (93.4%)</td>
<td>4/61 (6.6%)</td>
<td>0/61</td>
</tr>
</tbody>
</table>

Table 3. Effect of radiotherapy on predictive value of basal GH compared to nadir/mean GH during oral glucose tolerance test and GH day curve. (χ², Pearson *P = 0.02, **P < 0.0001)

<table>
<thead>
<tr>
<th>GH µg/l</th>
<th>Radiotherapy</th>
<th>No Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal &lt; 2-5 with Mean GHDC &lt; 2-5</td>
<td>114/133 (85.7%)</td>
<td>36/36 (100%)</td>
</tr>
<tr>
<td>Basal &lt; 1 with Nadir OGTT &lt; 1</td>
<td>45/46 (97.9%)</td>
<td>73/73 (100%)</td>
</tr>
<tr>
<td>Basal &lt; 2-5 with Nadir OGTT &lt; 2-5</td>
<td>142/146 (97.9%)</td>
<td>145/145 (100%)</td>
</tr>
<tr>
<td>Basal 2-5-5 with Nadir OGTT &gt; 2-5</td>
<td>52/111 (46.8%)</td>
<td>32/57 (56.1%)</td>
</tr>
<tr>
<td>Basal &gt; 5 with Nadir OGTT &gt; 2-5</td>
<td>226/233 (95.9%)</td>
<td>72/93 (77.4%)</td>
</tr>
</tbody>
</table>

Table 4. Effect of radiotherapy on the discordance between disease activity assessed by GH and IGF-I concentrations (*P ≤ 0.004)

<table>
<thead>
<tr>
<th>GH µg/l</th>
<th>IGF-I Level</th>
<th>Radiotherapy</th>
<th>No Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GHDC &lt; 2-5</td>
<td>Normal</td>
<td>33/66 (50.0%)</td>
<td>15/31 (48.4%)</td>
</tr>
<tr>
<td>Nadir OGTT &lt; 1</td>
<td>Normal</td>
<td>25/53 (47.2%)</td>
<td>67/92 (72.8%)</td>
</tr>
<tr>
<td>Nadir OGTT &lt; 2-5</td>
<td>Normal</td>
<td>61/137 (44.5%)</td>
<td>82/141 (58.2%)</td>
</tr>
<tr>
<td>Nadir OGTT &gt; 2-5</td>
<td>Normal</td>
<td>17/103 (16.5%)</td>
<td>10/42 (23.8%)</td>
</tr>
</tbody>
</table>

Discussion

These results demonstrate that a basal fasting GH correlates strongly with both nadir/mean GH on OGTT/GHDC in the follow up of a large cohort of patients with acromegaly. We have demonstrated that a basal fasting GH < 2-5 µg/l is strongly predictive of achieving a nadir GH during OGTT and mean GH during GHDC < 2-5 µg/l. Conversely, a basal fasting GH > 5 µg/l is predictive of a failure to achieve a nadir/mean GH during OGTT/GHDC < 2-5 µg/l (i.e., GH levels previously shown to normalize mortality). We have also shown a significant discordance between GH values during OGTT and GHDC indicating remission or associated with normalization of mortality and disease activity assessed by IGF-I. Radiotherapy leads to increased discordance between disease activity defined by GH and IGF-I (when GH < 2-5 µg/l). (Tables 3 and 4, and Fig. 4).

The validity of a single basal or random GH compared to an OGTT or GHDC has been criticized because of the pulsatile nature of GH secretion in normal individuals and the risk of under or over estimating disease activity in acromegaly. Our study, similar to a recent study from Jayasena et al.19 reveals that a basal fasting GH is strongly predictive of a GH nadir on OGTT and other studies have shown a similarly strong correlation between a basal GH and a mean GH during a GHDC.20 Bajuk et al.21 have recently reported a strong correlation (r = 0.93, P < 0.0001) between an 8am single GH sample and mean GH from 24 h sampling (samples taken every 10–20 min) in patients with active acromegaly. However, they suggested caution be exercised due to the low positive predictive value (0.67) that a basal GH < 2-5 µg/l will predict a mean GH < 2-5 µg/l on 24-h sampling. Our correlation is similar (r = 0.8-0.93), however, we took GH levels from patients with both active and cured acromegaly and also sampled 5 times over a 10-h period (the use of 10–20 min sampling is rarely used in clinical practice). In our study there is a strong predictive value of a basal fasting GH < 2-5 µg/l at predicting a nadir/mean GH during OGTT/GHDC of < 2-5 µg/l. A basal GH sample between 2-5-5 µg/l is however, less likely to predict GH levels during OGTT or GHDC and is thus more difficult to interpret.
Fig. 3 Correlation between mean and basal GH during GHDC in radiotherapy naïve patients (3a) and patients following radiotherapy (3b) and nadir and basal GH during OGTT in radiotherapy naïve patients (3c) and patients following radiotherapy (3d). (GHDC, GH day curve; OGTT, oral glucose tolerance test).

disease activity from basal GH values between these levels. Previous concerns regarding the validity of a single basal fasting GH measure do not seem to be born out in clinical practice, providing caution is exercised in interpreting basal GH values between 2.5 and 5 μg/L. Based on this data, a basal fasting GH is a useful initial test of disease activity and is less time consuming than either an OGTT or GHDC for both patient and staff, however, if a basal GH is between 2.5 and 5 μg/L then the patient should go on to have a formal OGTT/GHDC. One limitation of our study is that OGTT and GHDC performed on the same patients are never truly independent, even if they have been performed after long intervals. However, this is the largest series over a long timeframe of OGTT/GHDC in patients with acromegaly reported, and as such provides important observations for clinical practice.

When IGF-I levels are stratified into low, normal or high according to age related reference ranges we have shown a significant discordance between disease activity assessed by IGF-I and the nadir/mean GH during OGTT/GHDC. Of all 32.4% of subjects who had a GH nadir < 2.5 μg/L during an OGTT had an elevated IGF-I (similar values were seen for GHDC). Conversely, in patients with a basal/nadir GH > 2.5 μg/L during OGTT, 27% and 18.6% had a normal IGF-I, respectively. The high degrees of discordance between disease activity as assessed by GH and IGF-I concentrations has major clinical implications, as the current criteria for the assessment of disease activity are based on both GH and IGF-I measurements.21

Discordance between GH and IGF-I have been reported in earlier studies. Gullu et al.22 showed that 15 of 21 patients with normal basal GH had an elevated IGF-I, and 14 of 21 patients with a GH < 1 μg/L on OGTT still had an elevated IGF-I. However, all patients with GH suppression < 0.3 μg/L on OGTT had a normal IGF-I.23 In other studies when mean GH was < 2.5 μg/L, IGF-I has been reported to be elevated in 13–37.5% of subjects and when GH was > 2.5 μg/L IGF-I was normal in 5–18%.15,24 Freda et al. have reported that 50% of patients who suppress GH < 1 μg/L have an elevated IGF-I.25 All patients with a normal IGF-I had a GH during OGTT < 1 μg/L; however, suppression to < 1 μg/L may be too crude as a cut off of normality, as the normal population all suppressed to < 0.14 μg/L.25
Monitoring acromegaly using GH and IGF-I

is not only dependant on GH but is also regulated by exercise, oestrogen, nutrition, body mass index and insulin, any of which may account for the observed discordance. The main body of epidemiological evidence supports the use of GH as a predictor of excess mortality and the discordance between IGF-I and GH may explain to some degree the less robust evidence supporting IGF-I as a predictor of excess mortality.

We also demonstrated a significant increase in discordance between GH and IGF-I in patients treated with radiotherapy. GH and IGF-I dynamics following radiotherapy for acromegaly have been studied in detail by Peacey et al. In a study of 21 treated acromegalic patients with GH <2 μg/l on OGTT or GHDC a number of important differences occurred in patients who had received radiotherapy, compared to those treated surgically. In the radiotherapy group correlations were found between IGF-I and mean GH valley nadir, GH peak height of GH pulses, mean 24 h GH, basal GH secretion, GH pulse amplitude and GH production rate. Patients in the radiotherapy group also had a greater mean valley GH nadir on cluster analysis and despite similar mean 24 h GH concentrations patients with prior radiotherapy had higher IGF-I levels. It was hypothesized that this elevation in IGF-I levels were due to the altered characteristics of GH release, as the mean trough nadir GH and GH burst amplitude correlate positively with IGF-I. The authors suggested that sustained elevated basal GH release was responsible for determining the elevated IGF-I levels in these patients, despite otherwise safe GH levels. Altered GH dynamics might arise from hypothalamic damage due to radiotherapy, the increased GH trough activity in the radiotherapy group may be secondary to decreased somatostatin tone or GH releasing hormone, leading to a decrease in generation of large pulses and reduced amplitude of GH release. Disruption of somatostatin tone has been shown to lead to a more rapid fall in GH than IGF-I which may explain the increase in discordance between disease activity assessed by GH and IGF-I following radiotherapy.

The use of a basal fasting GH to measure disease activity does mean that additional tests are required to assess glucose tolerance. However, if a basal GH and IGF-I were to be the initial tests of choice,
a fasting glucose and HbA1c could be performed at the same time as a primary screening tool for diabetes.4

On the basis of this data, in patients who have a basal fasting GH < 2.5 μg/L, there is no added diagnostic benefit in performing an OGTT or GHDC given the close association between basal fasting GH and nadir/mean during OGTT/GHDC. Similarly, in those patients with a fasting basal GH is > 5 μg/L there is no added benefit in performing an OGTT or GHDC as the likelihood of nadir/mean GH being suppressed to < 2.5 μg/L is low. However, if the basal GH is between 2.5 and 5 μg/L then an OGTT or GHDC should be performed as a basal fasting GH has a poor correlation with GH nadir/mean in this range (Table 1, Fig. 5).

There is a large discordance between disease activity assessed by GH and IGF-I and this discordance is exaggerated by radiotherapy. With the weight of evidence supporting GH vs. IGF-I as a mortality outcome measure, the pitfalls of measuring only IGF-I to monitor disease activity in acromegaly are self evident.

Acknowledgements
Ipsen Ltd. and Novartis Pharmaceuticals have supported the West Midlands Acromegaly Database. Dr M. Sherlock is funded by the MRC as a Clinical Research Training Fellow.

Authors are indebted to Ms Liz Jablonski who managed the database at the Queen Elizabeth Hospital, Birmingham, Mrs Maureen Brown who managed the database at the University Hospital of North Staffordshire and to the Department of Clinical Biochemistry, University Hospital Birmingham NHS Trust who helped greatly in the analysis of samples for this database.

The following additional investigators contributed patients to the West Midlands Acromegaly Database: D.A. Heath, J.A. Franklin, A. A. Toogood, N. J. Gittoes, R. Walsh, R. Mitchell, A. Johnson (Queen Elizabeth and Selly Oak Hospitals, Birmingham); H. Connor (County Hospital, Hereford); P. Dodson (Heartlands Hospital, Birmingham); P. R. Daggett (Staffordshire District General Hospital); K. Taylor, R. Ryder, S. Jones (City Hospital, Birmingham); E. Hillhouse, F. Vince (Coventry and Warwick Hospital); D. Jenkins (Worcester Royal Infirmary); S. Walford, D. Singh (New Cross Hospital, Wolverhampton); C. Carter (Alexandra Hospital, Redditch); J. Benn (Burton District Hospital); D. Robertson, P. Davies (Sandwell Hospital); T. West (Telford District General Hospital); T. Harvey, A. D. Wright (Manor Hospital, Walsall); and A. Zallin (Wordsley Hospital).

References


Medical Therapy in Patients with Acromegaly: Predictors of Response and Comparison of Efficacy of Dopamine Agonists and Somatostatin Analogues


To subscribe to Journal of Clinical Endocrinology & Metabolism or any of the other journals published by The Endocrine Society please go to: http://jcem.endojournals.org/subscriptions/
Medical Therapy in Patients with Acromegaly: Predictors of Response and Comparison of Efficacy of Dopamine Agonists and Somatostatin Analogues


Centre for Endocrinology, Diabetes, and Metabolism (M.S., E.F.-R., A.A.A., J.A., M.C.S., P.M.S.), Division of Medical Sciences, and Department of Public Health and Epidemiology (R.C.R.), Centre for Childhood Cancer Survivor Studies, University of Birmingham, B15 2TH Birmingham, United Kingdom; Department of Postgraduate Medicine (R.N.C.), University of Keele, Stafford, Stafford, ST4 7QB, United Kingdom; Department of Clinical Biochemistry (G.H.), University Hospital Birmingham National Health Service Trust, B29 6DJ Birmingham, United Kingdom; and Birmingham Heartlands and Solihull National Health Service Trust (A.B.), B9 5SS Birmingham, United Kingdom

Context: Acromegaly is associated with increased morbidity and mortality. Treatment options include surgery, radiotherapy, and medical therapy.

Aims: The objective of the study was to examine the role of prolactin status, prior surgery, and radiotherapy on the response to medical therapy in patients with acromegaly and assess the relative efficacy of dopamine agonist therapy compared with somatostatin analog therapy.

Materials and Methods: A total of 276 patients with acromegaly received either dopamine agonists (DA) and/or somatostatin analogs (SSA). One hundred seventy-two patients had received surgery and 73 radiotherapy prior to receiving medical therapy. One hundred ninety-eight of 276 received DA, and 143 of 276 received SSA. GH and IGF-I values at baseline and after 12 months on therapy were analyzed.

Results: In the DA group, basal prolactin concentration did not predict response to therapy, GH percent reduction: hyperprolactinemia, 26.7% (–10.4 to 48) vs. normoprolactinemia, 34.8% (0.2–53.2), P = 0.58; IGF-I percent reduction: hyperprolactinemia 30.0% (9.2–43.1) vs. normoprolactinemia 16.8% (4–37), P = 0.45. Prior surgery was not associated with any difference in response to DA: GH percent reduction (P = 0.1) and IGF-I percent reduction (P = 0.08). By contrast, prior radiotherapy was associated with an enhanced efficacy of DA response vs. DA, P = 0.02. In the SSA group, there was no effect of prior surgery or radiotherapy on response of GH, but radiotherapy was associated with less marked IGF-I percent reduction (P = 0.05). SSA were more potent than DA at decreasing both GH [62.8% (20.7–85%) vs. 42.4% (−6.5 to 68.6), P < 0.008] and IGF-I [SSA 40.4% (0–64.3) vs. 8% (0–40.8), P = 0.05].

Conclusions: The effects of DA are irrespective of baseline prolactin concentrations. Prior radiotherapy is associated with differences in GH and IGF-I response to DA and SSA therapy. (J Clin Endocrinol Metab 94: 1255–1263, 2009)

Acromegaly is a disabling disease characterized by excess GH secretion and increased circulating IGF-I concentrations. It is associated with increased morbidity and premature mortality, which has been demonstrated in a number of retrospective studies (comprising more than 5000 patients and 1000 deaths) (1–10) reporting standardized mortality ratios between 1.3 and 3. This increase in mortality can probably be normalized if GH levels can be decreased to less than 2.5 μg/liter (2, 3, 6–8).

Abbreviations: BC, Bromocriptine; CBG, cabergoline; CV, coefficient of variation; DA, dopamine agonist; IQR, interquartile range; IA, long acting; LAR, long-acting release; OGTT, oral glucose tolerance test; SSA, somatostatin analog.
Therapy for acromegaly is targeted at reducing excess morbidity and mortality by decreasing GH and IGF-1 levels, ameliorating patient symptoms, and decreasing any local compressive effects of the pituitary adenoma. Currently the therapeutic options for acromegaly include surgery; radiotherapy; and medical therapies such as dopamine agonists (DAs), somatostatin analogs (SSAs), and the GH receptor antagonist pegvisomant.

DA and SSA are used to inhibit GH secretion by pituitary tumors, whereas the GH receptor antagonist, pegvisomant, has no direct effect on GH secretion by the tumor but blocks GH activity at peripheral GH receptors (11). Medical therapy is currently most widely used as secondary treatment for persistent or recurrent acromegaly after unsuccessful surgery, although it can be used as primary therapy for patients in whom surgery is not an option or as short-term therapy preoperatively (12). SSAs have become the first choice medical therapy for the majority of patients with acromegaly due to their efficacy on GH/IGF-1 reduction (a recent meta-analysis reported that SSA reduced GH levels and normalized IGF-I levels in 48 and 42% of acromegalic patients, respectively: 13) and antumoral effect (14–17). Dopamine agonists are not used as frequently as SSAs; this is due to a number of factors including lower reported GH/IGF-I control rates, higher rates of side effects, and decreased effect on tumor shrinkage (18). However, it must be remembered that the majority of the studies regarding the efficacy of DA in acromegaly were performed using the DA bromocriptine (BC), and more recent studies suggest that cabergoline (CBG) may be more efficacious (19). The question whether prolactin levels before DA therapy are predictive of response (i.e. patients with elevated prolactin having a greater decrease in GH and IGF-I after DA therapy) is controversial, and there are conflicting data from small studies, with some concluding that tumors that cosecrete prolactin have a greater response to DA (19–22) and others showing no effect (23–27). Similarly, there is no agreement about the association between a positive GH and PRL immunostaining and a favorable response to DA, with some studies showing this association (24) and others not (25, 26, 28).

Data about potential factors that could have a predictive role in the response to medical therapy (particularly for DA) is scarce (29). The aims of our study were to evaluate the role of baseline prolactin concentrations (and tumor immunohistochemical staining), prior surgery or radiotherapy and pituitary hormonal deficiencies in the response of GH and IGF-1 to DA and SSA therapies in patients with acromegaly. We also wanted to assess the relative efficacy of dopamine agonist therapy compared with somatostatin analog therapy in patients with acromegaly. Finally we wanted to determine the efficacy of SSA in clinical practice compared with that observed in clinical trials (and the relative efficacy of sc vs. long acting preparations of SSA).

**Patients and Methods**

The West Midlands Acromegaly database was established in 1990 and on December 31, 2006, contained demographic and clinical details of 501 patients (273 female) with acromegaly from 16 referral centers across the West Midlands region of the United Kingdom. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to < 1 μg/liter after oral glucose loading and in most cases an elevated IGF-I). However, a small number of patients (n = 34) had died before measurement of IGF-I being part of routine clinical practice within the region in the early 1990s. The study was approved by the local research ethics committee of each site.

A total of 276 (151 female) of 501 patients with acromegaly received medical treatment, 198 patients received DA (71.7%), and 143 patients were treated with SSAs (51.9%). Sixty-five patients received both drugs at the same time (17.4%). In 17 of these 65 patients, one of the drugs was added to the other during the first year of treatment follow up; these 65 patients were excluded from the analysis.

Surgery had been performed in 172 (62.4%) patients and 73 (26.4%) patients had received radiotherapy before starting medical therapy. Patients had received radiotherapy a median of 15 months before the initiation of medical treatment [interquartile range (IQR) 6.75–44.5 months]. Median duration of follow-up was 14.9 yr (IQR 8.5–21.3).

**Endocrine evaluation**

Serum GH levels were measured by an in house RIA in a central laboratory as previously described (30). The limit of detection of the assay was 0.5 μg/liter, the intraassay coefficient of variation (CV) 4.1% and the interassay CV 5.7% at 2 μg/liter. Assessment of GH secretion after treatment differed between units within centers in the West Midlands. GH levels were recorded as a nadir of five GH assessments over 2 h after administration of 75 g oral glucose [2-75 g oral glucose tolerance test (OGTT)], the mean of a GH day profile [the average of five GH measurements taken at 2 h intervals] or a random/basal GH measurement performed in an outpatient setting. Whenever possible, either the nadir GH during an OGTT or mean GH during 5-point GH day curve were used. If these were not available, a random GH sample was used. A random or fasting GH has been previously shown to correlate well with the GH nadir during an OGTT and a mean GH during a GH day curve (31–34). The GH value in milliliters per liter was divided by a conversion factor of 2 to obtain micrograms per liter. Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described (35). The limit of detection of the assay is 2.0 nmol/liter. The interassay CV is 3.9–4.8% between 16 and 104 nmol/liter. Reference ranges were derived from adults with no known or suspected endocrine disorders. Reference range values were 14–48 nmol/liter at 21–30 yr (n = 71), 13–37 nmol/liter at age 31–45 yr (n = 123), and 8.9–32 nmol/liter (n = 75) above 45 yr. Paired data for basal and 1-yr follow-up were available for GH in 227 of 276 patients (82.2%) and IGF-I in 146 of 276 patients (52.9%); however, 52 of 276 (18.8%) had received medical therapy before the availability of IGF-I assessment.

**Statistical analysis**

GH and IGF-I levels before commencing and 1 yr after medical therapy were recorded and the percentage decrease in GH/IGF-I calculated as well as the number and percentage of those achieving less than 2.5 μg/liter GH and a normal age-adjusted IGF-I. Only patients with pre- and posttreatment GH and IGF-I were included in the analysis. Patients were divided into groups according to type of medical therapy prescribed (DA and SSA). To assess the relative role of radiotherapy and surgery and to avoid confounding factors, the response to medical therapy was assessed only in those patients who had prior surgery before commencing medical therapy and were radiotherapy naïve and vice versa. Prolactin levels at baseline and tumor immunohistochemistry were also noted and assessed for a role in the response to medical therapy. Because all data were nonparametric, the Wilcoxon rank sum test was used to compare the groups. P < 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism (San Diego, CA).
TABLE 1. Comparison between baseline prolactin, GH, and IGF-I levels, depending on medical therapy, surgery, and radiotherapy

<table>
<thead>
<tr>
<th>Baseline prolactin (mU/litre)</th>
<th>Baseline GH (µg/liter)</th>
<th>Baseline IGF-I (nmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical therapy</strong></td>
<td><strong>Median (IQR)</strong></td>
<td><strong>Median (IQR)</strong></td>
</tr>
<tr>
<td>DA</td>
<td>371 (185–860)</td>
<td>11.2 (6.5–31.8)</td>
</tr>
<tr>
<td>SSA</td>
<td>294 (163–705)</td>
<td>8 (4.2–15.5)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>337 (168–745)</td>
<td>11 (5.4–27.6)</td>
</tr>
<tr>
<td>No</td>
<td>362 (183–887.5)</td>
<td>9.5 (6.2–18.8)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>296 (168–800)</td>
<td>12.2 (7–40.8)</td>
</tr>
<tr>
<td>No</td>
<td>36b (16b–/)</td>
<td>8.1 (4.7–16.8)</td>
</tr>
</tbody>
</table>

Results

There were no differences in baseline prolactin or IGF-I levels between DA and SSA ($P = 0.47$ and 0.15, respectively) (Table 1). However, baseline GH was higher in the DA group ($P = 0.03$) (Table 1). There were no differences between baseline prolactin, GH, and IGF-I levels in patients who had prior surgery compared with those who were surgically naive (no prior radiotherapy), ($P = 0.5$, 0.34 and 0.5, respectively) (Table 1). In patients who had received prior radiotherapy (but no prior surgery), there was no difference in baseline prolactin or IGF-I levels ($P = 0.53$ and 0.85); however, basal GH levels were higher in the radiotherapy group ($P = 0.02$) than the radiotherapy naive cohort (Table 1). There was no effect of gender on the GH or IGF-I response to DA ($P = 0.54$ and 0.71, respectively) or SSA ($P = 0.57$ and 0.75, respectively). Median prolactin in the normoprolactinemic group was 240 mU/liter (IQR 163–381) and in the hyperprolactinemic group, 1116 mU/liter (IQR 857–1652) ($P < 0.001$).

**DA group**

In the patients receiving DA alone in the first year of medical therapy, BC was used in 159 patients (88.3%), CBG in 20 (11.1%), and pergolide in 1 (0.6%). The median dose of DA was 7.5 mg/d (IQR 2.5–10) for BC and 0.5 mg/wk (IQR 0.5–1.25) for CBG. In the DA group, the median GH was 11.2 µg/liter (6.5–31.8) with a median GH of 7 µg/liter (3.3–15.8) at 12 months, giving a median decrease of 3.4 µg/liter (–0.4 to 10.1) or 42.4% (–0.5 to 86.8). The median decrease of GH at 12 months in the patients taking BC was 42.4% (–1.6 to 68.6%) and in those taking CBG was 36.0% (–3.9 to 83.0), ($P = 0.85$). The median IGF-I at baseline in the DA group was 77.0 nmol/liter (52.0–111.3) and at 12 months was 63 nmol/liter (39.8–84.5), giving a median decrease of 15.8 nmol/liter (2.7–41) or 22.9% (5.3–54.3). The median decrease of IGF-I at 12 months was 23.6% (5.9–47.9) in the BC group and 21.7% (1.6–54.7) in the CBG group ($P = 0.95$). After 12 months of DA therapy, 28% of patients achieved a GH less than 2.5 µg/liter [18 of 118 (15.3%)] and six of 16 (37.5%) of those treated with BC and CBG, respectively ($P = 0.04$). IGF-I was in the normal age-related reference range in 17 of 53 (32.1%) (10 of 39 patients (25.6%) on bromocriptine and seven of 14 patients (50%) on cabergoline, ($P = 0.11$).

We evaluated the influence of previous radiotherapy on the decrease in GH and IGF-I levels in patients who received DA therapy. Radiotherapy before starting DA (without prior surgery) was associated with a greater increase in percent GH reduction radiotherapy group, 53% (28.8–70.9) compared with 3.1% (–66.8 to 66.1) ($P = 0.02$); however, there were insufficient data to analyze the difference in IGF-I reduction (Fig. 1).

Patients treated surgically (without prior exposure to radiotherapy) before starting DA had no change in their sensitivity to DA for GH or IGF-I response ($P = 0.1$ and 0.08, respectively) (Fig. 2).

We found no difference in responsiveness to DA in patients who had an elevated or normal baseline prolactin [hyperprolactinemia group decrease in GH 26.7% (–10.4 to 48)] vs. normal prolactin 34.8% (0.2–53.2), $P = 0.58$, and IGF-I 30% (9.2–43.1) vs. 16.8% (4–37), $P = 0.45$ (Fig. 3).

Data from immunohistochemical staining were obtained in 48 patients in the DA group ($n = 34$ GH immunostaining, $n = 14$ GH and prolactin immunostaining). There was no difference in response of GH ($P = 0.19$) or IGF-I ($P = 0.27$) to DA in patients whose histology showed GH only compared with tumors which contained with GH and prolactin.

**Somatostatin analog group**

In the patients receiving SSA alone ($n = 116$), 73 patients were treated with sc octreotide during the first year of therapy at a median dose of 150 µg/d (IQR 100–300). The remaining 43 patients were treated with long-acting depot SSA [lanreotide 26 and octreotide long-acting release (LAR) 17]. In those treated with octreotide LAR, the median dose was 20 mg monthly (IQR

![FIG. 1. Effect of prior radiotherapy on percentage reduction of GH to DA therapy.](image-url)
20–30), and in those treated with lanreotide LAR, the median dose was 60 mg monthly (QRR 60–90). In the entire SSA group, the median baseline GH was 8.0 μg/l (4.2–15.5) with a median GH at 12 months of 2.8 μg/l (1.6–6.6), giving a median decrease of 3.9 μg/l (-8.1 to -10.1) or 62.8% (20.7–85). The median IGF-I was 97 nmol/l (63.5–118.4) at baseline and 46.8 nmol/l (30.7–71.9) at 12 months, giving a median decrease of 53.5 nmol/l (11.8–71.9) or 50% (16.4–68.4). 48.8% achieved a GH less than 2.5 μg/l, and 45.7% achieved an IGF-I in the normal age-related reference range. SSAs were more potent than DAs at decreasing both GH [62.8% (IQR 20.7–85%) vs 42.4% (IQR 0.5–68.6), P < 0.008] and IGF-I [SSA 50.0% (IQR 16.4–68.4) vs 22.9% (IQR 5.3–54.3), P = 0.05] (Fig. 4). There was no difference in either GH or IGF-I percentage reduction between sc and long-acting (LA) SSA [sc octreotide, 63.5% (21.1–64.3) vs LA, 62.9% (27.5–86.1), P = 0.77] and IGF-I percent [sc octreotide 39.6% (9.8–60.9) vs LA 53.4% (4.4–72.7), P = 0.25].

When percent decrease in GH to SSA analogs was divided into those who had received prior radiotherapy (with previous surgery) or not, no differences were found [radiotherapy 44.2% (11.4–70.6) vs no radiotherapy 59.0% (21–84.5), P = 0.64] (Fig. 5). However, the response in IGF-I levels to SSA was lower in patients treated with radiotherapy before starting the SSA [radiotherapy 15.4% (5.5–72.1) vs no radiotherapy 49.1% (0–78), P = 0.05]. This led to a discordance between disease activity as assessed by GH and IGF-I as 10 of 29 patients (34.5%) who had a GH less than 2.5 μg/l and a raised age-related IGF-I.

No difference was found in GH response to SSA, depending on prior surgery (with no prior radiotherapy) [decrease in GH: surgery group 70.5% (42.5–90.1) vs no surgery group 59.0% (21–84.5), P = 0.39] or IGF-I: surgery group 50.3% (16–65.1) vs no surgery group 49.1% (0–78.1), P = 0.62 (Fig. 6).

Prolactin levels did not influence the response of GH levels to SSA [normal prolactin 62.0% (9–85.2) vs hyperprolactinemia 65.9% (42.8–75.4), P = 0.46] or IGF-I [normal prolactin 31.2% (0–62.4) vs hyperprolactinemia 60.2% (32.1–71.6), P = 0.15].

**Effect of pituitary hormone deficiency on response to medical therapy**

The prevalence of anterior pituitary abnormality at time of starting medical therapy was 44 of 148 (29.7%) for LH/FSH deficiency, 30 of 153 (19.6%) for ACTH deficiency, and six of 164 (3.7%) for TSH deficiency.

In patients treated with DA, there were no statistically significant differences in the decrease of GH levels if the patients had ACTH, TSH, or gonadotrophin deficiency (P = 0.28, 0.53, and 0.11, respectively). However, we found a lower IGF-I reduction in DA therapy if gonadotrophin deficiency was present, 4.5% (-0.36 to 11.52) vs 25.9% (9.4–40.4), P < 0.05 but no differences in IGF-I response in patients with ACTH and TSH deficiency (P = 0.86 and 0.35, respectively).
Similarly, there were no significant differences in patients with ACTH, TSH, and FSH/LH deficiency with respect to GH percent reduction ($P = 0.59$, $0.10$, and $0.94$, respectively) or IGF-I percent reduction in the SSA group ($P = 0.79$, $0.69$, and $0.86$, respectively).

**Discussion**

These results demonstrate that neither basal prolactin concentrations nor coimmunostaining of GH and prolactin predicts a more favorable response in GH/IGF-I to DA. Prior therapy with radiotherapy may have an effect on the subsequent response of GH/IGF-I to DA and SSA. We have shown that efficacy of SSA in clinical practice is similar to that described in clinical trials and that there is no difference in efficacy between sc and LA somatostatin analogs. DA therapy is associated with moderate decreases in GH and IGF-I and therefore may be beneficial in patients with mildly active disease.

Transphenoidal surgery is still considered the first choice of treatment for the majority of patients with acromegaly (36). Surgical outcomes depend on several factors including the size and local invasiveness of the tumor and surgical skill (37, 38). Because the majority of GH secreting pituitary tumors are macroadenomas, patients often do not attain GH or IGF-I levels associated with remission or normalization of mortality after surgery, so adjuvant therapy is often required.

Radiotherapy is widely used in patients with acromegaly and is effective in reducing GH and IGF-I to levels associated with cure or normalization of GH; however, there is often a period of several years before this effect is achieved (39). Despite its beneficial effect on GH/IGF-I levels and tumor growth, the use of conventional radiotherapy in patients with acromegaly has been associated with increased cerebrovascular mortality (2) and increased risk of hypopituitarism (40). As a result of these factors and others (access to surgical/radiotherapy expertise and medical therapy) in this historic cohort, we are aware that there may be a selection or allocation bias; however, patients were treated according to best practice at the particular time point. There is also the possible bias that patients who received 1 yr of medical therapy may have been selected based on a favorable initial biochemical response to SSA or DA therapy based on a formal biochemical challenge test. These tests are not routinely used, and as such, most patients will not have been assessed in this manner. For DA, patients are given an initial low dose of bromocriptine or cabergoline, and then this is usually titrated accordingly. Patients who receive SSA are generally given a short trial of sc octreotide to assess for side effects, but biochemistry is not
checked in a formal octreotide challenge test to assess for response of GH during this trial. If there are no side effects from sc octreotide, then patients are given LA SSA, and effect is assessed between 3 and 6 months followed by appropriate titration of dose as required. Patients would frequently be given up to a year to respond to medical therapy, which has been up-titrated.

Medical therapy can be used as an adjunct to surgery or radiotherapy or as primary therapy for acromegaly.

**DAAs**

DAAs bind to D2 receptors in the pituitary and suppress GH secretion in patients with acromegaly (41). They have been used in acromegaly as an individual treatment or combined with SSA. Bromocriptine was the first DA widely used, normalizing IGF-I and GH levels in 10 and 20% of patients, respectively (18). The utility of DAAs, in particular BC, has been limited by the disappointing rates of biochemical response reported, and significant side effects that may occur with the high doses (40–60 mg daily, which have been previously reported) such as nausea, vomiting, diarrhea, fatigue, and orthostatic hypotension (12). In our patients taking BC, lower doses (median 7.5 mg/d) were used; however, even these relatively low doses achieved GH/IGF-I reductions of 42.4 and 23.6%, respectively. These changes, although not as significant as those with SSA therapy, reduced GH and IGF-I levels in patients receiving DA into the range associated with normalization of mortality in 28 and 32.1% of patients, respectively, and therefore may be of use in mildly active disease.

The second-generation dopamine agonist, CBG, has been demonstrated to be potentially more effective in the treatment of acromegaly, achieving safe GH and IGF-I levels in 46 and 39% of patients, respectively (19). In a recent study, Moyes et al. (42) found that on a median weekly dose of CBG of 1.75 mg, normalization of both IGF-I and GH occurred in 27% of the patients. The greater efficacy CBG may be due to a number of factors including greater biological potency, longer half-life, and fewer side effects, leading to improved compliance when compared with BC. In our patient cohort, CBG was used less frequently than BC and in lower doses than those reported in some studies to be effective in reducing GH/IGF-I (19, 27, 42). The lower rate of prescribing of CBG than BC is probably due to the historic nature of the cohort and also the fact that cabergoline was introduced into clinical practice for patients with acromegaly around the same time as long acting SSA (which may be more likely to be used due to their greater efficacy). In contrast to SSA, there are limited studies that specifically evaluated the effect of previous surgery or radiotherapy on response of GH/IGF-I to DA therapy (27). We found that prior radiotherapy lead to a greater reduction of GH in patients receiving DA therapy. However, there was insufficient data due to the historical nature of this cohort to assess the effect on IGF-I. There was no difference in GH or IGF-I response to DA in patients who had received prior surgery.

The predictive value of prolactin regarding GH/IGF-I response to DA therapy is controversial, and there are conflicting data from small studies, with some studies concluding that tumors that cosecrete prolactin have a greater response to DA (19–22) and other showing no increase (24–27). In our study of a large group of patients receiving DA therapy for acromegaly, we could not find an association between pretreatment prolactin and GH/IGF-I response to DA therapy. Therefore, patients who have a normal prolactin should not be excluded from receiving DA on the assumption that there will be limited GH/IGF-I response. Similarly, our study did not show a correlation between positive GH and prolactin immunostaining and a favorable response to DA. In the literature there are again conflicting data in smaller studies regarding the existence of this association, with some studies showing it (24) and others not (25, 26, 28).

Recently CBG and pergolide have been associated with valvular regurgitation in patients on high-dose DA for Parkinson's disease, and further studies are required to assess whether there is a similar risk in patients taking DA for acromegaly and hyperprolactinemia (43, 44). Over the last year, a number of studies have been reported looking at the effect of lower-dose DA in patients with prolactinoma with conflicting results (45–50). More data are required regarding the safety of doses of DA, which are used in prolactinomas and acromegaly.

**Somatostatin analog therapy**

A recent metaanalysis of prospective studies reported that SSA reduced GH levels to less than 2.5 μg/liter and normalized IGF-I levels in 48–52 and 42–68% of acromegalic patients, re-
spectively (13). Despite our study being retrospective, we found similar responses to SSA (48.8% of patients achieved a GH less than 2.5 μg/l and 45.7% achieved an IGF-I in the normal age related reference range). This is important because it shows that GH and IGF-I reductions seen in clinical trials are possible to achieve in routine clinical practice. We found no difference in efficacy between sc and LA SSA, which has previously been reported in smaller single center studies and one large multicenter study (51–53). Our study shows that this is also the case in clinical practice. However, the convenience of the LA SSA still makes them a more appealing option from the patient perspective.

The added advantage of SSA is their ability to reduce tumor volume (14–17). However, results vary, depending on several factors, such as baseline GH levels and the presence of functioning receptors for somatostatin (54).

We have not found any effect of prior surgery or radiotherapy in the response of GH to SSA; we did, however, find that previous radiotherapy led to a decreased response of IGF-I to SSA therapy. The dynamics of GH and IGF-I secretion after radiotherapy have been studied in detail by Pearcey et al. (55, 56). Patients treated with radiotherapy had a greater mean valley GH nadir on cluster analysis, and despite similar mean 24 h GH concentrations patients with prior radiotherapy had a higher IGF-I value. It was felt that this elevation in IGF-I may be due to the altered characteristics of GH release because the mean trough nadir GH and GH burst amplitude correlate positively with IGF-I; the authors suggest that sustained elevated basal GH release determines the elevated IGF-I levels in these patients with otherwise safe GH levels (55, 56). This hypothesis is strengthened by studies in GH-deficient adults whereby regimens leading to greater interpulse GH levels via multiple daily injections or continuous infusion of GH leads to greater IGF-I production rates than the equivalent amount of GH given as two doses (57). Animal studies also showed that there was an increased hepatic stimulation of IGF-I after continuous GH infusion compared with that seen during pulsatile infusion (however, there was not a greater release in muscle derived IGF-I) (58).

The effect of prior surgery on GH/IGF-I response to SSA is also controversial, with some studies reporting that prior surgery leads to a greater decrease in GH and IGF-I than in surgery-naive patients (59, 60) and others similar to ours reporting no such association (61).

We also assessed the role of pituitary hormone deficiencies in predicting response to medical therapy. It has been shown that glucocorticoids down-regulate somatostatin receptors on pituitary cells in culture (62); however, we did not find any effect of ACTH or any other anterior pituitary deficiencies on efficacy of SSA (or DA) therapies, apart from a lower IGF-I reduction in the patients receiving DA with gonadotrophin deficiency. This may possibly be due to the effect of circulating estrogen levels and different modes of estrogen replacement on the hepatic generation of IGF-I (63). However, because this was a retrospective study, we were unable to assess this. Little can be gleaned from the TSH results due to the low frequency of TSH deficiency in the cohort.

In conclusion, in a large cohort of patients with acromegaly, we have demonstrated that neither basal prolactin concentrations nor common coexisting factors predict a more favorable response in GH/IGF-I to DA. Prior therapy with surgery did not have an effect on subsequent response of GH/IGF-1 to DA therapy, however, prior radiotherapy was associated with an increased GH reduction to DA therapy. Previous however, prior radiotherapy is associated with a lower IGF-I response to SSA. Although results of reviews of clinical practice are never truly as robust as randomized control trials, they are also important because they can give an idea of what happens outside the tightly monitored clinical trial environment (often difficult to attain in clinical practice). The efficacy of SSA in our clinical practice is similar to that described in rigorously designed and executed clinical trials. DA therapy is associated with moderate decreases in GH and IGF-I and therefore may be beneficial in patients with mildly active disease.

Acknowledgments

We are indebted to Ms. Liz Jablonski, who managed the database at the Queen Elizabeth Hospital Birmingham, and the Department of Clinical Biochemistry (University Hospital Birmingham National Health Service Trust), which helped greatly in the analysis of samples for this database. The following additional investigators contributed patients to the West Midlands Acromegaly Database: D. A. Heath, J. A. Franklin, A. A. Toogood, N. J. Gittoes, R. Walsh, R. Mitchell, A. Johnson (Queen Elizabeth and Selly Oak Hospitals, Birmingham); H. Connor (County Hospital, Hereford); P. Dodson (Heartlands Hospital, Birmingham); P. R. Daggett (Staffordshire District General Hospital); K. Taylor, R. Ryder, S. Jones (City Hospital, Birmingham); E. Hillhouse, P. Vine (Coventry and Warwick Hospital); D. Jenkins (Worcester Royal Infirmary); S. Walford, D. Singh (New Cross Hospital, Wolverhampton); C. Carter (Alexandra Hospital, Redditch); J. Bennett (Burton District Hospital); D. Robertson, P. Davies (Sandwell Hospital); T. West (Telford District General Hospital); T. Harvey, A. D. Wright (Manor Hospital, Walsall); and A. Zain (Worthing Hospital).

Address correspondence and requests for reprints to: Professor Paul M. Stewart, Institute of Biomedical Research, Division of Medical Sciences, University of Birmingham, B15 2TH Birmingham, United Kingdom. E-mail: p.m.stewart@bham.ac.uk.

The West Midlands Acromegaly Database was supported by Ipsen Ltd. and Novartis Pharmaceuticals. M.S. is funded by the Medical Research Council as a clinical research training fellow.


References


61. Ayuk J, Stewart SE, Stewart PC, Shipard MC 2004 Efficacy of Sandostatin LAR (long-acting somatostatin analogue) is similar in patients with untreated acromegaly and in those previously treated with surgery and/or radiotherapy. Clin Endocrinol (Oxf) 60:375–381
ACTH Deficiency, Higher Doses of Hydrocortisone Replacement, and Radiotherapy Are Independent Predictors of Mortality in Patients with Acromegaly


To subscribe to Journal of Clinical Endocrinology & Metabolism or any of the other journals published by The Endocrine Society please go to: http://jcem.endojournals.org//subscriptions/
ACTH Deficiency, Higher Doses of Hydrocortisone Replacement, and Radiotherapy Are Independent Predictors of Mortality in Patients with Acromegaly


Centre for Endocrinology, Diabetes and Metabolism (M.S., A.A.A., J.A., M.C.S., P.M.S.), School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom; Centre for Childhood Cancer Survivor Studies (R.C.R., M.M.H.), Department of Public Health and Epidemiology, University of Birmingham, Birmingham B15 2TT, United Kingdom; Department of Postgraduate Medicine (R.N.C.), University of Keele, Harstall, Stoke-on-Trent ST4 7QB, United Kingdom; and Birmingham Heartlands and Solihull National Health Service Trust (A.S.B.), Birmingham B9 5SS, United Kingdom

Context: A number of retrospective studies report that patients with acromegaly have increased morbidity and premature mortality, with standardized mortality ratios (SMR) of 1.3–3. Many patients with acromegaly develop hypopituitarism as a result of the pituitary adenoma itself or therapies such as surgery and radiotherapy. Pituitary radiotherapy and hypopituitarism have also been associated with an increased SMR.

Methods: Using the West Midlands Acromegaly database (n = 501; 275 female), we assessed the influence of prior radiotherapy and hypopituitarism (and replacement therapy) on mortality in patients with acromegaly. Median duration of follow-up was 14.0 yr (interquartile range, 7.9–21 yr).

Results: All-cause mortality was elevated [SMR, 1.7 (1.4, 2.0); P < 0.001]. On external analysis, prior radiotherapy, ACTH, and gonadotropin deficiency were associated with an elevated SMR [radiotherapy SMR, 2.1 (1.7–2.6); P = 0.006; ACTH deficiency SMR, 2.5 (1.9–3.2); P < 0.0005; and gonadotropin deficiency SMR, 2.1 (1.6–2.7); P = 0.037].

On internal analysis, the relative risk (RR) of mortality was increased in the radiotherapy [RR, 1.8 (1.2–2.8); P = 0.008] and ACTH-deficiency groups [RR, 1.7 (1.2–2.5); P = 0.004], but not in the gonadotropin- or TSH-deficiency groups. In the ACTH-deficient group, increased replacement doses of hydrocortisone greater than 25 mg/d were associated with increased mortality compared to lower doses.

Conclusions: Radiotherapy and ACTH deficiency are significantly associated with increased mortality in patients with acromegaly. In ACTH-deficient patients, a daily dose of more than 25 mg hydrocortisone is associated with increased mortality compared to lower doses. These results have important implications for the treatment of patients with acromegaly and also raise issues as to the optimum hydrocortisone treatment regimens for ACTH-deficient patients. (J Clin Endocrinol Metab 94: 4216–4223, 2009)

Abbreviations: CI, Confidence interval; CVA, cerebrovascular accident; IQR, Interquartile range; RR, relative risk; SMR, standardized mortality ratio.
Acronegaly is characterized by excess GH secretion and IGF-I concentrations, most commonly due to a pituitary adenoma. Several studies have reported an increased mortality in patients with acromegaly with standardized mortality ratios (SMRs) ranging between 1.3 and 3 (1–9). Several factors have been associated with this increased mortality, including elevated GH and IGF-I concentrations and radiotherapy. GH has been linked with excess mortality in a number of studies; decreasing GH levels reverses this increased mortality (1, 2, 6, 10). Some studies have also reported an improvement in mortality if IGF-I is normalized (4, 11), whereas others have not (1, 10). External beam conventional radiotherapy for acromegaly decreases GH to less than 2.5 μg/liter in 60% of patients after 10 yr and approximately 75–80% after 20 yr (12). However, in recent years external beam conventional pituitary radiotherapy has been associated with increased mortality in patients with both acromegaly and other pituitary disorders (1, 13). Hypopituitarism has also been associated with increased mortality, predominantly due to cardiovascular deaths (13, 14).

The dose of hydrocortisone replacement in patients with pituitary disease, which traditionally was 30 mg/d in divided doses, has been shown recently to be an overreplacement compared with cortisol production rates in healthy subjects (15, 16). In a recent study, Filipsson et al. (17) assessed the effect of ACTH deficiency and hydrocortisone dose in a large cohort of GH-deficient adults. Patients with ACTH deficiency receiving doses of hydrocortisone greater than or equal to 25 mg/d had an adverse metabolic profile compared with GH-deficient patients on no hydrocortisone replacement and those with ACTH deficiency on lower doses of hydrocortisone (17). Despite these changes in cardiovascular risk profile, there have to date been no studies reporting an increase in mortality associated with higher doses of hydrocortisone replacement in patients with ACTH deficiency. Given the above observations, the aims of our study were to assess the role of radiotherapy, hypopituitarism (in particular the effect of individual pituitary axis deficiency), and the effect of different doses of hydrocortisone replacement therapy on mortality in a large cohort of patients with acromegaly.

**Patients and Methods**

The West Midlands Acronegaly database was established in 1990, and on December 31, 2006, contained demographic and clinical details of 501 patients (275 female) with acromegaly from 16 referral centers across the West Midlands region of the United Kingdom. The region has an overall population of 5.7 million. All patients had a biochemical diagnosis of acromegaly based on current accepted criteria (failure of GH suppression to less than 1 μg/liter after oral glucose loading and in most cases an elevated IGF-I). All patients with samples showing elevated GH or IGF-I in the West Midlands Regional Endocrine Laboratory were flagged as potentially having acromegaly and were appropriately assessed; therefore, we feel that patient capture is good and there are no grounds to assume that selection bias is substantial. However, a small number of patients (n = 34) had died before the introduction of IGF-I to routine clinical practice in the early 1990s. The study was approved by the local research ethics committee of each site and the Office of National Statistics.

A total of 128 patients had received surgery alone, 32 radiotherapy alone, 43 medical therapy alone, and 104 received all three treatment modalities. A total of 143 received surgery and radiotherapy (of these, 104 patients also received medical therapy), 68 surgery and medical therapy, and 162 radiotherapy and medical therapy (of these, 102 also received surgery). In total, 237 received radiotherapy, 220 received conventional three-field radiotherapy with a median dose of 45 Gy [interquartile range (IQR), 45–47 Gy] administered over a median of 25 fractions (IQR, 23–31). Ten patients received stereotactic radiosurgery, and seven received Yttrium implants.

All patients were registered with the Office of National Statistics (ONS), and death certification data from the ONS were reviewed to obtain information relating to cause of death according to ICD-9 criteria. A total of 339 patients were alive on the exit date of the study, and 162 patients were deceased (data relating to radiotherapy and GH/IGF-I and mortality have been reviewed in 419 of these patients previously) (1). Median age at diagnosis was 46.6 yr (IQR, 11.6–64.2) in the entire cohort, 44.2 yr (IQR, 34.6–53.7) in those who were still alive, and 53.8 yr (IQR, 44.6–61.8) in those who had died. Median duration of follow-up was 14.0 yr (IQR, 7.9–21) in the entire cohort, with a total of 7567 patient years, and there was no difference in duration of follow-up between those who are still alive and those who had died (14.2 yr and 13.8 yr, respectively). In total, 178 patients had ACTH deficiency and received hydrocortisone therapy. The daily dose of hydrocortisone (HC) was 1.5 mg in 15 patients (taken as HC 10 mg/5 mg), 20 mg in 29 patients (five taken as HC 10 mg/5 mg/5 mg; 11 as HC 15 mg/5 mg; and 13 as HC 10 mg/10 mg), 25 mg in 14 patients (13 taken as HC 15 mg/10 mg; and one as HC 15 mg/5 mg/5 mg), and 30 mg in 115 patients (four taken as HC 10 mg/10 mg/10 mg; and 111 taken as HC 20 mg/10 mg); five patients received HC doses greater than 30 mg/d.

**Endocrine evaluation**

Serum GH levels were measured by an in-house RIA in a central laboratory as previously described (18) (the value in mIU/liter was divided by a conversion factor of 2 to obtain μg/liter). The limit of detection of the assay is 0.5 μg/liter, and the interassay coefficient of variation is 5.7% at 2 μg/liter, 4.3% at 3 μg/liter, 5.5% at 7.3 μg/liter, and 4.47% at 14.7 μg/liter. Data on GH levels during follow-up were available in 470 of 501 patients (93.8%). Serum IGF-I was measured using an in-house RIA with acid ethanol extraction performed to remove IGF-binding proteins, as previously described (19). The limit of detection of the assay is 2.0 nmol/liter. The interassay coefficient of variation is 5.4–8.4% between 16 and 104 nmol/liter. IGF-I data were available on 409 of 501 patients (81.6%).

The presence or absence of hypopituitarism was defined by proven biochemical deficiency of at least one endocrine axis. The hypothalamic pituitary adrenal axis was deficient if the peak cortisol response to short synacthen testing was less than 550
nmol/litre (20) or less than 500 nmol/litre after insulin-induced hypoglycemia during an insulin stress test. The thyroid axis was deficient if the free $T_3$ concentration was below the local reference range, with an inappropriately low/normal TSH. Hypothalamic-pituitary gonadal dysfunction in males was diagnosed in the setting of a low serum testosterone and inappropriately low/normal gonadotropins. In females, hypothalamic-pituitary gonadal dysfunction was diagnosed in premenopausal females if the patient was amenorrheic (with normal prolactin levels) and in postmenopausal females if the FSH was inappropriately low (<35 IU/litre). The dose and duration of hydrocortisone, $T_4$, testosterone, and estrogen replacement were documented.

Statistical analysis

SMRs for overall mortality, cardiovascular, respiratory, and cerebrovascular deaths were calculated using Stata statistical software (StataCorp, College Station, TX) (21). The expected number was estimated by multiplying age, sex, and calendar period specific death rates in the general population of England and Wales by the person-years at risk accumulated within the age, sex, and calendar period-specific strata corresponding to the patient cohort. SMRs for overall and cause-specific mortality were also evaluated by whether patients were treated with radiotherapy; whether patients were ACTH-, TSH-, or gonadotropin-deficient; and whether patients were treated with hydrocortisone. The dose of hydrocortisone was treated as a time-dependent variable; i.e. if a patient was on a higher dose of hydrocortisone for any given period, then person-years at that level were contributed; however, if the dosage was reduced, person-years were added to the analysis for the lower dose category. Similarly, radiotherapy was assessed in a time-dependent fashion such that patients only entered the radiotherapy group for assessment of risk on the date they started radiotherapy. Most of the statistical modeling was internal because such analysis avoids the problem of whether the study and general population differ through unmeasurable confounders.

Poisson regression

In an internal analysis, a multivariable Poisson regression model was used to calculate relative risk (RR) of mortality based on tumor size; treatment with radiotherapy; ACTH, TSH, or gonadotropin deficiency; and dose of hydrocortisone received, if applicable (22). Unless otherwise stated, RRs were adjusted for GH level, attained age, sex, calendar period, and period of follow-up. To assess the role of GH/I GF-1 level on 11 β-hydroxysteroid dehydrogenase type 1 and mortality in patients on hydrocortisone therapy, an interaction term was added to the above model.

Results

Overall group

All-cause mortality was increased significantly in the overall group of patients compared with the general population [SMR 1.7 (1.4, 2.0); $P < 0.001$]. There was a significant increase in cardiovascular [SMR 1.9 (1.6, 2.4); $P < 0.001$], respiratory [SMR 1.8 (1.1, 2.8); $P = 0.01$], and cerebrovascular death [SMR 2.7 (1.9, 4.1); $P < 0.001$], but no increase in death due to cancer [SMR 1.2 (0.9, 1.7); $P = 0.26$] (Table 1). In the respiratory death category, 16 patients died from pneumonia and four from exacerbations of asthma/chronic obstructive pulmonary disease. There was a significant difference in mortality in patients with macroadenoma [SMR 1.9 (1.6, 2.3)] compared with microadenoma [SMR 1.0 (0.6, 1.7); $P = 0.021$]. On internal analysis having adjusted for GH level, sex, attained age, calendar period, period of follow-up, and pretreatment level of GH, there was also an increase in mortality associated with increased tumor size [microadenoma RR, 1.5 (0.9, 2.6); $P = 0.11$], although this was not significant.

The effect of pituitary irradiation on mortality

There was an increase in all-cause mortality in patients who had received radiotherapy compared with the general population: no radiotherapy [SMR 1.4 (1.1, 1.7)] compared with radiotherapy [SMR 2.1 (1.7, 2.6); $P = 0.006$] (Table 2). On internal analysis, correcting for GH level, sex, hypopituitarism, attained age, calendar period, period of follow-up, and pretreatment level of GH, radiotherapy was associated with a significantly increased RR of mortality [RR 1.8 (1.2–2.8); $P = 0.008$] (Table 2). Among those exposed to radiotherapy, there was a significantly increased risk of cerebrovascular death [SMR 4.1 (2.3, 6.6); $P = 0.034$] (Table 3); there was no significant increase in any other specific cause of death. Of the 90 deaths in the 237 patients exposed to radiotherapy, there were seven deaths (in 17 patients, 41.1%) in radiosurgery/yttrium implant groups.

### Table 1. Cause of death in all patients (n = 501, deaths 162) compared to the general population

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>O</th>
<th>E</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>162</td>
<td>95.9</td>
<td>1.7</td>
<td>1.4, 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>36</td>
<td>29.8</td>
<td>1.2</td>
<td>0.9, 1.7</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>77</td>
<td>39.5</td>
<td>1.9</td>
<td>1.6, 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>20</td>
<td>11.2</td>
<td>1.8</td>
<td>1.1, 2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>25</td>
<td>9.1</td>
<td>2.7</td>
<td>1.9, 4.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

O, Observed; E, Expected.

### Table 2. Effect of radiotherapy on mortality in patients with acromegaly

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>SMR</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.4</td>
<td>1.1, 1.7</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.1</td>
<td>1.7, 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>1</td>
<td>1.8, 2.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>1</td>
<td>1.8, 2.8</td>
<td></td>
</tr>
</tbody>
</table>

External analysis is compared to the general population (SMR standardized for sex, attained age, and calendar period). Internal analysis is adjusted for GH level, sex, attained age, calendar period, hypopituitarism, period of follow-up, and pretreatment level of GH.
TABLE 3. Cause of death in acromegaly cohort divided according to radiotherapy exposure, standardized for sex, attained age, and calendar period

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Radiotherapy</th>
<th>O</th>
<th>E</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>No</td>
<td>72</td>
<td>14</td>
<td>1.4</td>
<td>1.1, 1.7</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>90</td>
<td>21.2</td>
<td>2.1</td>
<td>1.7, 2.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Cancer</td>
<td>No</td>
<td>17</td>
<td>1.1</td>
<td>1.1</td>
<td>0.6, 1.7</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19</td>
<td>1.4</td>
<td>1.4</td>
<td>0.8, 2.2</td>
<td>0.044</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>No</td>
<td>38</td>
<td>1.7</td>
<td>1.7</td>
<td>1.1, 2.4</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>39</td>
<td>2.2</td>
<td>2.2</td>
<td>1.6, 3.1</td>
<td>0.027</td>
</tr>
<tr>
<td>Respiratory</td>
<td>No</td>
<td>9</td>
<td>2.2</td>
<td>2.2</td>
<td>1.1, 3.9</td>
<td>0.342</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11</td>
<td>2.2</td>
<td>2.2</td>
<td>0.7, 7.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>No</td>
<td>9</td>
<td>1.7</td>
<td>1.7</td>
<td>0.8, 3.3</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>4.1</td>
<td>4.1</td>
<td>2.3, 6.6</td>
<td>0.034</td>
</tr>
</tbody>
</table>

P value reflects test of homogeneity in SMRs. O, Observed; E, expected.

Compared with 83 deaths (in 220 patients, 37.7%) in the conventional radiotherapy group.

The effect of pituitary hormone deficiency on mortality

Patients with ACTH deficiency and gonadotropin deficiency had a significantly increased SMR, but patients with TSH deficiency did not (Table 4). However, on internal analysis, having adjusted for sex, attained age, calendar period, period of follow-up, and radiotherapy, only ACTH deficiency was associated with significantly increased mortality [RR 1.7 (1.2, 2.5); P = 0.004] (Table 5). There was no significant linear trend (P trend = 0.515) in RR of mortality with increasing number of pituitary hormone axis deficiency (Supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

The effect of hydrocortisone replacement dose on mortality

Increasing doses of hydrocortisone were associated with an increasing SMR (P for linear trend <0.001) (Table 6). On internal analysis, having adjusted for age, sex, calendar period, period of follow-up, and radiotherapy, there was a significant increase in RR of mortality in patients receiving hydrocortisone daily doses of between 25 and 30 mg [RR 1.6 (1.1, 2.4); P = 0.014] and hydrocortisone daily doses greater than 30 mg [RR 2.9 (1.4, 5.9); P = 0.003] (Table 6). On internal analysis, there was a significant association between an increasing dose of hydrocortisone and mortality as assessed by the likelihood ratio test for linear trend in relative risks (P = 0.002). The main cause of death in the higher dose hydrocortisone group was cardiovascular disease. In the group of patients who were ACTH replete, 26.2% of deaths were due to cardiovascular causes. In the overall group of ACTH-deficient patients, 31.6% of patients died from cardiovascular causes, and there was an increase in cardiovascular death with increasing hydrocortisone dose [HC dose >0 and ≤20 mg/d, 10% cardiovascular mortality; HC dose >20 and ≤25 mg/d, 33.3% cardiovascular mortality; HC dose >25 and ≤30 mg/d, 38.5% cardiovascular mortality; and HC >30 mg/d, 44.4% cardiovascular mortality].

When GH levels were included in the above model as an interaction term with hydrocortisone exposure to account

TABLE 4. Effect of pituitary axis deficiency of mortality compared to the general population, standardized for sex, attained age, and calendar period

<table>
<thead>
<tr>
<th>Factor</th>
<th>O</th>
<th>E</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>No</td>
<td>69</td>
<td>53.8</td>
<td>1.3</td>
<td>1.0, 1.6</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>62</td>
<td>25.1</td>
<td>2.5</td>
<td>1.9, 2.3</td>
</tr>
<tr>
<td>TSH</td>
<td>No</td>
<td>93</td>
<td>57.1</td>
<td>1.6</td>
<td>1.3, 2.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>42</td>
<td>19.7</td>
<td>2.1</td>
<td>1.5, 2.9</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>No</td>
<td>40</td>
<td>28.8</td>
<td>1.4</td>
<td>0.99, 1.9</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>66</td>
<td>31.4</td>
<td>2.1</td>
<td>1.6, 2.7</td>
</tr>
</tbody>
</table>

O, Observed; E, expected.

TABLE 5. Internal analysis of the effect of pituitary axis deficiency of mortality, adjusted for radiotherapy, follow-up time, sex, attained age, and calendar year

<table>
<thead>
<tr>
<th>ACTH</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.7</td>
<td>1.2, 2.5</td>
<td>0.004</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.0</td>
<td>0.7, 1.4</td>
<td>0.829</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>1.2</td>
<td>0.8, 1.8</td>
<td>0.433</td>
</tr>
</tbody>
</table>

TABLE 6. Effect of increasing dose of hydrocortisone (HC) replacement on mortality in patients with acromegaly compared to the general population, standardized for sex, attained age, and calendar period

<table>
<thead>
<tr>
<th>HC daily dose (mg)</th>
<th>SMR</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.35</td>
<td>1.1, 1.7</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>2.26</td>
<td>1.4, 3.7</td>
<td>0.0011</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>2.82</td>
<td>2.2, 3.7</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 ≤ HC ≤ 20</td>
<td>1.3</td>
<td>0.7, 2.6</td>
<td>0.439</td>
<td></td>
</tr>
<tr>
<td>≥20 ≤ HC ≤ 25</td>
<td>1.4</td>
<td>0.6, 3.3</td>
<td>0.429</td>
<td></td>
</tr>
<tr>
<td>25 ≤ HC ≤ 30</td>
<td>1.6</td>
<td>1.1, 2.4</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>HC &gt; 30</td>
<td>2.9</td>
<td>1.4, 5.9</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Linear trend in SMR of mortality with increasing dose of HC therapy, P value for linear trend <0.001. Internal analysis of the effect of increasing daily hydrocortisone replacement doses on mortality in patients with acromegaly is adjusted for sex, attained age, calendar period, period of follow-up, and radiotherapy. Likelihood Ratio Test for Linear Trend in RR, P = 0.002.
for the possible effect of GH on glucocorticoid metabolism of 11 β-hydroxysteroid dehydrogenase type I, this interaction was not statistically significant (P = 0.44). This was repeated with IGF-I instead of GH, but the model did not converge due to lack of power.

Discussion

In a large cohort of patients with acromegaly, we have shown that ACTH deficiency, higher doses of hydrocortisone replacement therapy, and radiotherapy are independently associated with increased mortality. Conventional external beam radiotherapy in acromegaly decreases GH to less than 2.5 µg/liter in 60% of cases after 10 yr and 75−80% after 20 yr (12). However, it has been reported that pituitary radiotherapy is associated with a number of adverse events such as risk of secondary intracranial neoplasms (23), cognitive impairment (24), damage to the optic nerve (25, 26), hypopituitarism (27–29), increased risk of cerebrovascular disease (30, 31), and in some previous studies, increased mortality (1, 13).

Increased cerebrovascular disease and death have been reported in a number of studies after pituitary irradiation. In a series of 156 patients with nonfunctioning pituitary adenoma, increased cerebral infarction rates were found in patients administered higher doses of radiotherapy (31). In a study assessing the role of pituitary radiotherapy in the development of cerebrovascular accidents (CVAs) in 331 patients who received pituitary radiotherapy, it was reported that patients who received radiotherapy had a RR of CVA of 4.1 [confidence interval (CI), 3.6–4.7] compared with the general population (30). On multivariate analysis, the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared with biopsy or no operation, higher doses of radiotherapy, and an underlying diagnosis of acromegaly (30).

In a further study, Brada et al. (32) reported that cerebrovascular mortality was increased in patients who had received pituitary irradiation [accounting for 26% of all death (RR, 4.11; CI, 2.84–5.75)], with an even further increase in females compared with male patients (RR, 6.9 and 2.4, respectively; P = 0.002). Surgery may also play a role in the increased cerebrovascular mortality reported in this study because patients with prior surgery had an increased RR compared with those with no surgery or biopsy alone (radiotherapy RR, 5.19; surgery alone RR, 1.33; P = 0.02) (32).

We have previously shown an increased mortality in 419 patients, 211 of which were treated with radiotherapy for acromegaly in the West Midlands Cohort (1). In patients treated with radiotherapy, overall SMR was 1.58, with an SMR of 4.42 for cerebrovascular death. Similarly, the Finnish national acromegaly database study reported an increased mortality in patients who had received radiotherapy compared with the general population. In 116 of 334 patients treated with radiotherapy, mortality was increased (SMR, 1.69) compared with patients who did not receive radiotherapy (SMR, 0.94) (10).

Radiation leads to damage of both large and small vessels but has a predilection to smaller vessels (33). The vasculature is vulnerable because endothelial cells are radiosensitive, which leads to several ultrastructural changes (33) with resultant increased capillary permeability and intracellular edema that may be followed by platelet and fibrin thrombosis. Larger lesions in arterioles can also occur, leading to myointimal proliferation, foamy macrophage plaques, fibrinoid necrosis of the media or hyalinization of the media leading to narrowing of the vessel lumen (33). There is evidence that these changes may be clinically significant because in a large study of patients with Hodgkin's disease (n = 4665) who received irradiation to the heart, the RR of myocardial infarction was 2.56 times higher than patients who had just received chemotherapy (34).

More than 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiencies within the following decade (27–29). A number of studies have described increased mortality in patients with hypopituitarism compared with age and sex-matched controls (13, 14, 35, 36). In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. In total, nearly 1900 patients have been included in these studies, and approximately 50% had radiotherapy; in two studies, radiotherapy was not associated with increased mortality (14, 35), and in the third study it was not possible to investigate the link between radiotherapy and mortality because nearly all patients had radiotherapy (36). In the largest series in the literature, Tomlinson et al. (13) reported that radiotherapy was associated with significantly increased mortality [SMR, 2.32 (1.7–3.14); P = 0.004] compared with the general cohort of patients with hypopituitarism [SMR, 1.87 (1.62–2.16)]. In particular, patients who had received radiotherapy had an elevated cerebrovascular risk [SMR, 4.36 (2.48–7.68); P = 0.001]. There is no clear answer to date regarding the causal relationship between hypopituitarism and mortality. In the study by Tomlinson et al. (13), only gonadotropin deficiency was associated with increased mortality (sex steroid replacement decreased mortality). Ehrufth et al. (37) compared radiation regimens and duration of symptoms of hypopituitarism in 342 patients treated with surgery and radiotherapy. They found no significant difference between patients who had died from cerebrovascular disease and a matched cohort who had not died for a number of irradiation
parameters such as maximum absorbed dose, maximum biological equivalent dose, field size, and number of fractions. The only difference found was a longer duration of symptoms of hypopituitarism in the patients who had died from cerebrovascular causes. This led to the conclusion that untreated hormone deficiency may be more directly implicated in cerebrovascular mortality than radiotherapy per se. The findings of our study do not support this but rather suggest that both radiotherapy and ACTH deficiency were risk factors for mortality independent of each other.

Recent studies have suggested that patients with primary adrenal failure have an increased risk of mortality compared with the general population (38, 39). Increased cardiovascular event rate (RR, 2.56; CI, 2.18–2.99) has also been described in patients receiving high-dose glucocorticoids (prednisolone ≥7.5 mg/d) (40). However, the association between mortality and secondary adrenal insufficiency from ACTH deficiency is not well described.

In recent years, it has been reported that the cortisol production rate in normal subjects is less than was previously thought (Esteban et al. (15), normal cortisol production rate in young adults, 27.3 μmol/d (equivalent to 5.7 mg/m²/d or approximately 9.9 mg/d); and Kerrigan et al. (16), total daily cortisol production rate, 5.7 ± 0.3 mg/m²/d). Traditionally, the daily dose of hydrocortisone was 30 mg/d, split into two doses (frequently, two thirds in the morning and one third in the evening); given the recent discovery of lower levels of cortisol production rates, this would lead to levels that were supraphysiological. Indeed, in the study by Esteban et al. (15), patients with Cushing’s syndrome had daily cortisol production rates of 30.7 ± 9.3 mg/d. The bioavailability of orally administered hydrocortisone is approximately 95% (41, 42); therefore, 30 mg of hydrocortisone per day could achieve levels similar to those seen in patients with Cushing’s syndrome, albeit with greater peaks and troughs, because the half-life of orally administered cortisol is only 90 min (43). A single morning dose of 15 mg hydrocortisone leads to supraphysiological serum cortisol concentrations 1–2 h after oral administration and a return to subphysiological or undetectable levels 6–8 h later (44, 45). Glucocorticoid replacement dose has effects on a number of clinical parameters including bone metabolism, glucose metabolism, cardiovascular function, and quality of life (46).

Current glucocorticoid replacement regimens cannot mimic the physiological circadian and ultradian rhythm of endogenous cortisol. There is evidence that continuous, prolonged exposure, compared with intermittent short exposure, to glucocorticoids may have different effects on a number of steroid-responsive enzymes and occupancy of the glucocorticoid receptor (46).

Circadian infusions of hydrocortisone can mimic the normal cortisol rhythm, resulting in beneficial effects in patients with Addison’s disease and congenital adrenal hyperplasia (47); using these infusions, it was also possible to reduce the daily dose of hydrocortisone (48). These infusions are obviously cumbersome and not practical; however, over the last few years there has been a push to design orally active, delayed- or sustained-release formulations of hydrocortisone to aid the physiological replacement of hydrocortisone and ultimately to improve quality of life and side effect profiles in patients requiring lifelong glucocorticoid replacement (49).

Filipsson et al. (17) have described an adverse metabolic profile in a cohort of GH-deficient patients on higher doses of glucocorticoid replacement. They found that patients on hydrocortisone replacement had increased total cholesterol, triglycerides, waist circumference, and glycosylated hemoglobin compared with the ACTH-sufficient patients; all these factors are associated with increased cardiovascular morbidity. Importantly, subjects who had hydrocortisone-equivalent doses of less than 20 mg/d did not differ in metabolic endpoints compared with the ACTH-sufficient patients. However, when a hydrocortisone-equivalent dose of more than 20 mg/d was administered, patients had an adverse metabolic profile (17).

Acronegaly is associated with increased rates of hypertension and biventricular hypertrophy as well as metabolic complications such as impairment of glucose tolerance and lipid abnormalities (50). These abnormalities are also seen in patients with glucocorticoid excess in Cushing’s syndrome (51), and one could speculate that in this study the increased mortality seen in patients receiving higher doses of hydrocortisone replacement therapy may be contributed to by the development of subclinical iatrogenic Cushing’s syndrome in these patients. Indeed, patients with Cushing’s disease have been reported to have a cardiovascular SMR of 5 (52), which is due to a combination of abnormalities in blood pressure, glucose and lipid metabolism, and coagulation system (51). Importantly, in a recent study, the length of disease was the only predictor of increased cardiovascular risk after multivariate analysis (51). Patients on higher doses of hydrocortisone replacement therapy are often exposed to elevated circulating cortisol levels (although not as severe as many patients with Cushing’s syndrome) for many decades, which may explain the increased cardiovascular mortality we have reported in our patients on higher doses of hydrocortisone.

At a tissue level, active glucocorticoid availability to the glucocorticoid/mineralocorticoid receptor is determined by the interconversion of hormonally active cortisol and inactive cortisone by isozymes of 11β-hydroxysteroid dehydrogenase (53). Many authors have reported an interaction between the GH/IGF-I system and 11β-hydroxysteroid dehydrogenase 1 both in vivo and in vitro (54). This
interaction may be clinically important because it suggests the appropriate dose of hydrocortisone for patients with controlled acromegaly may be lower than that for patients with active disease, although what the exact dose adjustment should be is unknown. However, in this study GH levels had no impact on the effect of mortality in patients on hydrocortisone therapy, but it must be remembered that this was not a physiological study to assess this, but rather an assessment to ensure that this phenomenon did not bias our results.

Regarding the predictive value of size of tumor and future mortality, although the increase in mortality in patients with macroadenomas was not statistically significant (P = 0.11), on internal analysis the RR was 1.5 (95% CI, 0.9–2.6), this should be interpreted cautiously because the nonsignificance may be related to sample size and the fact that adjusting for a number of variables may have decreased the power.

In conclusion, ACTH deficiency, higher doses of hydrocortisone, and radiotherapy are independently associated with increased mortality. Further work is needed to assess the relative roles of these risk factors in the premature mortality seen in patients with acromegaly and also to assess the relative importance of these risk factors compared with excess exposure to GH and IGF-I. This is the first study to show an increase in mortality in patients with ACTH deficiency on higher doses of hydrocortisone therapy. Further larger studies are required in patients with ACTH deficiency to assess the optimum therapy; however, our results do highlight the deleterious effects of higher doses of hydrocortisone replacement in these patients.

Acknowledgments

The following additional investigators contributed patients to the West Midlands Acromegaly Database: D. A. Heath, J. A. Franklyn, A. A Toogood, N. J. Gittoes, R. Walsh, R. Mitchell, A. Johnson (Queen Elizabeth and Selly Oak Hospitals, Birmingham); H. Connor (country Hospital, Hereford); P. Dodson (Heartlands Hospital, Birmingham); P. R. Daggett (Staffordshire District General Hospital); K. Taylor, R. Ryder, S. Jones (City Hospital, Birmingham); E. Hillhouse, F. Vince (Coventry and Warwick Hospital); D. Jenkins (Hereford Royal Infirmary); S. Walford, D. Singh (New Cross Hospital, Wolverhampton); C. Carter (Alexandra Hospital, Redditch); J. Benn (Burton District Hospital); D. Robertson, P. Davies (Sandwell Hospital); T. West (Telford District General Hospital); T. Harvey, A. D. Wright (Warwick Hospital, Walsall); and A. Zolin (Woodcote Hospital).

We are indebted to Ms. Liz Jablonski, who managed the database at the Queen Elizabeth Hospital, Birmingham; Mrs. Maureen Brown, who managed the database at the University Hospital of North Staffordshire; and to the members of the Department of Clinical Biochemistry, University Hospital Birmingham National Health Service Trust, who helped greatly in the analysis of samples for this database.

Address all correspondence and requests for reprints to: Professor Paul M. Stewart, Institute of Biomedical Research, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom. E-mail: P.M.Stewart@bham.ac.uk.

Ipsen Ltd. and Novartis Pharmaceuticals have supported the West Midlands Acromegaly Database. M.S. is funded by the Medical Research Council as a Clinical Research Training Fellow. R.C.R. is funded by Cancer Research UK as a Graduate Training Fellow.

Disclosure Summary: Authors M.S., R.C.R., A.A.A., M.M.H., J.A., R.N.C., M.C.S., and A.S.B. do not report competing interests. P.M.S. reports being on an educational advisory board for Neon (supported by Novartis). The study database is supported by unrestricted educational grants from Novartis and Ipsen.

References


Mortality in Patients with Pituitary Disease


Centre for Endocrinology, Diabetes, and Metabolism (M.S., J.A., J.W.T., A.A.-A., M.C.S., P.M.S.), School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom; and Birmingham Heartlands and Solihull National Health Service Trust (A.S.B.), Birmingham B9 5SS, United Kingdom

Pituitary disease is associated with increased mortality predominantly due to vascular disease. Control of cortisol secretion and GH hypersecretion (and cardiovascular risk factor reduction) is key in the reduction of mortality in patients with Cushing’s disease and acromegaly, retrospectively. For patients with acromegaly, the role of IGF-I is less clear-cut. Confounding pituitary hormone deficiencies such as gonadotropins and particularly ACTH deficiency (with higher doses of hydrocortisone replacement) may have a detrimental effect on outcome in patients with pituitary disease. Pituitary radiotherapy is a further factor that has been associated with increased mortality (particularly cerebrovascular). Although standardized mortality ratios in pituitary disease are falling due to improved treatment, mortality for many conditions are still elevated above that of the general population, and therefore further measures are needed. Craniohypophysectomy patients have a particularly increased risk of mortality as a result of the tumor itself and treatment to control tumor growth; this is a key area for future research in order to optimize the outcome for these patients. (Endocrine Reviews 31: 0000–0000, 2010)

I. Mortality in Hypopituitarism
A. Introduction
B. Causes of hypopituitarism
C. All-cause mortality in hypopituitarism
D. Specific cause mortality in hypopituitarism
E. Role of ACTH deficiency and glucocorticoid replacement
F. Role of GH deficiency and replacement
G. Role of TSH deficiency and replacement
H. Role of sex steroid deficiency and replacement
I. Role of underlying etiology on mortality in hypopituitarism
J. Other factors contributing to mortality in hypopituitarism

II. Mortality in Acromegaly
A. Introduction
B. Studies of mortality in acromegaly
C. Impact of GH levels on mortality in acromegaly
D. Impact of IGF-I levels on mortality in acromegaly
E. Assay variability
F. Role of pituitary radiotherapy on mortality in acromegaly

G. Role of pituitary dysfunction on mortality in acromegaly
H. Cancer mortality in acromegaly
I. Other factors influencing mortality in acromegaly

III. Mortality in Cushing’s Disease
A. Introduction
B. Mortality studies in Cushing’s disease
C. Factors influencing mortality in Cushing’s disease

IV. Mortality in Craniohypophysectomy
A. Introduction
B. Mortality studies in craniohypophysectomy
C. Factors influencing mortality in craniohypophysectomy

V. Pituitary Radiotherapy and Mortality in Pituitary Patients
A. Introduction
B. Cerebrovascular morbidity and mortality following pituitary radiotherapy
C. Hypopituitarism following pituitary radiotherapy
D. Mechanisms of radiation injury
E. Secondary oncogenesis following pituitary radiotherapy

VI. Summary

Abbreviations: BMI, Body mass index; CI, confidence interval; CRP, C-reactive protein; CRH, conventional radiotherapy; LVA, cerebrovascular accident; LH, luteinizing hormone; LHRH, luteinizing hormonereleasing hormone; M, meningioma; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; PR, partial remission; RR, risk ratio; S, score; SIR, standardized mortality ratio; STR, subtotal resection.

Endocrine Reviews, May 2010, 31(3):0000–0000 edr.endojournals.org

Copyright (C) 2010 by The Endocrine Society
I. Mortality in Hypopituitarism

A. Introduction

The pituitary gland is the master regulator of the endocrine system, controlling adrenal, thyroid, and gonadal function, water balance, lactation, and the GH/IGF-1 axis among other processes. Hypopituitarism is defined as a biochemical deficiency of one or more of the hormones of the anterior or posterior pituitary gland (1). The prevalence of hypopituitarism ranges between 290 and 455 cases per million, with a reported incidence of 42.1 cases per million (2). A recent systematic review of the prevalence of pituitary adenomas revealed a prevalence of 14.4% in postmortem studies and 22.5% in radiological studies, giving an overall prevalence of 16.7% (3). In recent years, a number of studies have revealed an increased prevalence of clinically significant pituitary adenomas in two population studies from England and Belgium ranging from one case per 1064 persons to one case per 1289 persons (4-6). Thus, many patients have pituitary adenomas without any perturbations in endocrine function of the gland. Data from the Swedish Cancer Registry have shown an increasing incidence of pituitary adenomas, with six cases per million being reported in 1958 rising to 11 cases per million in 1991 (7) (Fig. 1) (incidence in this study was from cancer registry data, the majority of these patients having pituitary adenomas that required surgery). This increase may simply reflect improvements in medical diagnostics, imaging, and clinical surveillance rather than increasing incidence per se.

The underlying pathology leading to hypopituitarism had not changed dramatically with time (Table 1), until the last decade when a number of other causes of hypopituitarism have been described such as traumatic brain injury (8), subarachnoid hemorrhage (8), and cranial irradiation for nonpituitary tumors (9). As a result, the incidence of hypopituitarism is likely to increase further as more patients are assessed for pituitary dysfunction with the above disorders. We will not focus on these conditions specifically with regard to mortality because data are limited, but rather we will include them as a part of the overall hypopituitarism group. Certain conditions that lead to hypopituitarism such as acromegaly, craniopharyngioma, and Cushing’s disease also have increased mortality as a result of the condition itself, and these will be discussed.

Hypopituitarism remains a heterogeneous group of conditions unified by variable hormonal deficiencies (some patients will have single deficiencies, whereas others will be deficient is several axes). Indeed, in the study by Regal et al. (2), 87% had gonadotropin deficiency, 61% GH deficiency, 62% ACTH deficiency, 64% TSH deficiency, and 20% cranial (central) diabetes insipidus (DI), with 15, 23, 19, 15, and 7% of patients having two, three, four, five, and six hormone axis deficiencies, respectively. Table 2 shows the heterogeneity in incidence of individual hormonal axis deficiencies and replacement levels in studies assessing mortality in hypopituitarism (some of the patients in these studies were postmenopausal women, and therefore estrogen replacement is not always indicated). GH deficiency is the most common deficiency in pituitary disease, particularly in patients with multiple axis deficiency such as the patients reported in these studies (10). These studies did not always assess for GH deficiency systematically, nor did they replace all patients who were deficient, and this may explain the lower prevalence of GH deficiency than expected. Furthermore, within any particular underlying etiology, the severity of presentation

![Graph](image-url)
may differ markedly between patients, and this may well impact upon morbidity and mortality.

B. Causes of hypopituitarism

The majority of cases of hypopituitarism result from tumors within the pituitary gland (Table 1) (2, 11, 12). Pituitary tumors are common, and in many cases are discovered incidentally and may have no impact upon pituitary function as shown from the relative prevalence of pituitary adenomas compared with hypopituitarism. Simply, the presence of a tumor within the pituitary gland does not equate to hypopituitarism; the diagnosis of hypopituitarism is dependent upon appropriate and often dynamic endocrine testing that is interpreted in the context of appropriate pituitary imaging. Nonfunctioning pituitary adenomas represent the commonest cause of hypopituitarism, at approximately 50% of cases (Table 1). However, the clinical presentation and natural history even within this potentially homogenous cohort may differ (2, 12). Specifically, within the elderly population (>65 yr) the incidence of craniopharyngioma is decreased (13), but nonfunctioning adenomas remain the commonest tumor within the pituitary. The diversity of the underlying diagnosis, combined with the rarity of some underlying diagnoses offers a considerable challenge in understanding and interpreting all-cause and specific mortality data that relate to hypopituitarism.

C. All-cause mortality in hypopituitarism

The standardized mortality ratio (SMR) is a measure of observed numbers of death in a study population compared with the expected numbers of deaths if the age- and sex-specific rates were the same as those of the standard population. In essence, it measures how much more (or less) likely a person is to die in the study population compared with someone of the same age and gender in the standard population, with a value of 1 meaning the patients are as equally likely to die as the normal population, a larger value meaning they are more likely to die, and a value less than 1 meaning they are less likely to die.

For internal analysis within cohorts (not compared with general population), the risk ratio (RR) is used, which allows a good indication of the strength of association between exposure and disease outcome (RR = risk in exposed group/risk in unexposed group). Poisson regression analysis allows us to compare rates between two exposures or indeed more than two exposure groups and allows us to examine the effect of an ordered or continuous exposure variable. In addition such analysis controls for the confounding effects of one or more variables and the effects of exposures that change over time (14).
Analysis of mortality with hypopituitarism is complex and challenging due to the diversity of underlying etiologies and treatment modalities. The challenge in interpretation is further complicated by the low numbers of deaths reported in the published studies, ranging from 41 to 842 patients (Table 3). In the cohorts discussed within this section, mortality within the immediate postoperative period has been removed, as have patients with acromegaly and Cushing’s disease; these will be discussed in Sections II and III, respectively, because these conditions per se are associated with increased mortality independent of hypopituitarism.

In the vast majority of studies presented to date, all-cause mortality is increased in patients with hypopituitarism when compared with age- and sex-matched controls (Table 3 and Fig. 3). Rosén and Bengtsson (11) were the first to identify increased mortality in hypopituitary patients. In their retrospective analysis of 333 consecutive patients diagnosed with hypopituitarism, they observed a SMR in the overall group of 1.81 (observed 104/expected 57.4). When divided by gender, the SMR for males was 1.47 (observed 63/expected 42.9) and for females, 2.82 (observed 41/expected 14.5) (11) (Fig. 2). Subsequently, several other cohort studies have been published (Table 3 summarizes all studies to date assessing mortality in patients with hypopituitarism). With one exception (15), SMR is increased in men, ranging from 1.2 to 3.36 (7, 11, 12, 16–20), and is elevated in women, ranging from 1.3 to 4.54. In all cases, SMR values are higher in women than those seen in men (7, 11, 12, 15–20). A recent meta-analysis examined all published studies and concluded that the SMR associated with hypopituitarism in men is 2.06 [95% confidence interval (CI), 1.94–2.20] and in women 2.80 [95% CI, 2.59–3.02] (21) (Fig. 4), this increase in SMR in women is statistically significant (P < 0.0001). In clinical terms, this leads to an age of death in the entire pituitary cohort ranging between 64.5 and 72.3 yr (7, 16), in men being 56.2–65 yr (12, 16, 17) and in women 52.0–66 yr (12, 16, 17).

The impact of gender upon all-cause mortality is clear, but the underlying reasons remain obscure. However, these SMR data do not imply that the underlying condition is more severe in men than women or that men respond better to specific treatment. The higher SMR in women may simply reflect that hypopituitarism removes the natural survival advantage that women have over men in the general population. A possible explanation may be under diagnosis of hypopituitarism in women because many of the diagnostic tests are not gender specific. Indeed, in the study by Nielsen et al., diagnosis of adrenal, thyroid, and gonadal deficiency and panhypopituitarism was higher in men (52, 49, 73, and 33%, respectively) than
women (30, 30, 46, and 17%, respectively) (15). There is evidence, however, in healthy postmenopausal women that oral estrogen replacement therapy is associated with increased mortality predominantly due to breast cancer and cardiovascular/thromboembolic diseases (22). In women who take oral estrogens, there is also evidence of GH resistance at the level of the liver to IGF-I generation (23) and elevations in total circulating cortisol as a result of elevated corticosteroid-binding globulin (24). GH itself modulates tissue glucocorticoid exposure through modulation of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 (25).

The time since diagnosis does not seem to impact upon mortality (12, 18), but age itself is an important factor. SMRs are highest in the youngest patients, with mortality in elderly patients in some cohorts no different from age- and sex-matched controls (Fig. 5). Again this may not reflect differing degrees of severity of the underlying condition with age but may simply reflect age-related mortality rates within the control population. The year of diagnosis is important, as judged by historical databases showing higher SMR in patients who were diagnosed in the more distant past, with a negative correlation between the first year of inclusion in study and SMR ($r = -0.65; P = 0.017$) (21). However, when data were analyzed according to gender, the negative correlation was significant for men only (men, $r = -0.65; P = 0.03$; women, $r = 0.58$, $P = 0.18$) (Fig. 6).

D. Specific cause mortality in hypopituitarism

This has been an important step in enhancing our understanding of factors that contribute to increased mortality in patients with hypopituitarism. Furthermore, an appreciation of specific cause mortality can help to target appropriate therapy in an attempt to modify risk. However, several important limitations need to be realized. First, much of the reported data are based on death certiﬁcation and not on postmortem ﬁndings, and therefore complete accuracy of cause mortality cannot be ascertained. Indeed, several studies have reported the potential inaccuracies of death certiﬁcate data compared with autopsy data (26–28). This is particularly the case for cardiovascular (29, 30), respiratory, and gastrointestinal death (26); however, recording of cancer death is usually concordant (26). Second, in many cases, subgroup analysis is based upon very small numbers of observed deaths, and therefore a very small number of excess deaths can seemingly translate to dramatic changes in SMR (Table 3).

1. Vascular death

In most studies (11, 12, 18, 20), but not all (15, 16, 31), vascular and cardiovascular mortality is increased, with SMRs up to 18.4 in the youngest female patients with adult onset hypopituitarism (however, it should be highlighted that this increased SMR was based on four deaths) (19). The main cause of mortality
in the study by Rosén and Bengtsson (11) was vascular disease with SMR in the overall group of 1.95 (observed 60/expected 30.8), and in males SMR 1.7 compared with 2.7 in females; however, the risk quotient was not significantly higher in women than men. Similarly, the main causes of the increased mortality in the study of Tomlinson et al. (12) were cardiovascular deaths (SMR = 1.62; \( P < 0.0001 \)), but cerebrovascular (SMR = 2.55; \( P < 0.0001 \)) and respiratory (SMR = 2.03; \( P = 0.002 \)) deaths were also increased.

The finding that in some studies vascular mortality was not increased is interesting. Within 391 patients diagnosed with hypopituitarism (patients with Cushing’s disease and acromegaly excluded) who all underwent autopsy (although not formal dissection in all cases), cerebrovascular death was increased in both males (odds ratio (OR), 2.02) and females (OR, 1.73) with a particular increase in cerebral hemorrhage (male OR, 4.6; female OR, 4.8) but no difference from the general population for cerebral infarction (31). Data relating to the exposure to radiotherapy in this group were not reported. However, deaths related to ischemic heart disease were lower (notably in women) than those in age- and sex-matched controls (male SMR, 0.44; female SMR, 0.27) (31). In the two studies by Bates et al. (16, 17), vascular mortality was not increased. In the first unselected hypopituitary cohort, whereas the vascular SMR was increased (1.35; 95% CI, 0.84–2.07; \( P = 0.11 \)), this failed to reach statistical significance, perhaps due to the relatively small size of the cohort (n = 172) (16). In the subsequent study, mortality was assessed in a cohort of patients who had all undergone pituitary surgery. SMR for vascular mortality was significantly lower than controls at 0.7 (95% CI, 0.5–1.1; \( P = 0.03 \)) (17). The SMR for cardiovascular death was 0.5 (95% CI, 0.2–1.0; \( P < 0.01 \)) in women and 0.9 (95% CI, 0.5–1.4; \( P = 0.26 \)) in men (17). The discrepancies between studies could perhaps reflect overreporting of cardiovascular disease-related deaths on death certification in the absence of autopsy, as well as the selection of patients who are suitable for surgical intervention.

The mechanisms that underpin the increase in cardiovascular mortality are not fully understood. The role of GH deficiency has been widely speculated and is dealt with in Section 1.F. Importantly, most of the large cohort studies that have examined mortality in hypopituitary patients have been in patients with either documented or presumed GH deficiency (patients were not on GH replacement in the vast majority of cases). It is important to note that to date there are no data reporting normalization of mortality after GH replacement. Indeed, the number of patients
required to adequately power such a study suggests that such data will not be forthcoming in the near future.

Not all studies have had sufficient numbers to allow the analysis specifically of cerebrovascular mortality. However, where data are presented, cerebrovascular disease-specific SMRs range between 1.73 and 4.9 (7, 12, 18–20, 31) (Table 3). Furthermore, there is evidence to suggest that those patients diagnosed at a younger age have increased cerebrovascular mortality (18). Interpretation of the published data is challenging and in many situations is complicated by the use of radiotherapy and its effects (some studies report radiotherapy rates ranging from 25–88.4% (12, 18–20) (Table 3), whereas others do not (7, 31). The contribution of radiotherapy to mortality in pituitary disease is discussed in Section V. Other possible contributing factors to explain the increased vascular mortality are outlined below.

a. Insulin sensitivity. The studies of cardiovascular risk in hypopituitarism have been either cross-sectional studies comparing patients on conventional replacement to control subjects or interventional studies primarily examining the impact of GH replacement therapy. Patients on conventional replacement therapy exhibit abnormalities of protein, fat, and carbohydrate metabolism that contribute to the abnormal body composition observed. Lean mass is reduced, and fat mass is increased. There is a propensity to central obesity, and intraabdominal or visceral fat deposition is significantly increased compared with control subjects with similar body mass index (BMI) (32, 33). In the general population, increased visceral adiposity is associated with the metabolic syndrome: insulin resistance or diabetes mellitus, hypercholesterolemia, and hypertension (34, 35).

Although blood glucose and plasma insulin levels are similar to those seen in controls, patients treated for pituitary disease have been shown to be insulin resistant. Johansson et al. (36) used the euglycemic clamp to assess insulin sensitivity in 15 patients and 15 controls matched for age, gender, and BMI. The glucose infusion rate required to maintain normal glucose levels was significantly lower in the patients than in controls (3.9 ± 0.5 vs. 9.9 ± 0.7 mg/kg body weight/min; P = 0.001). When corrected to account for the differences in body composition, the difference was more profound (5.8 ± 0.8 vs. 13.9 ± 0.9 mg/kg lean body mass/min; P < 0.001).

b. Lipid abnormalities. In some hypopituitary cohorts, patients have adverse fasting lipid profiles, including low high-density lipoprotein (HDL) cholesterol, increased triglycerides, and decreased low-density lipoprotein (LDL) particle size; increased BMI (up to 32% being clinically obese BMI >30 kg/m²), and waist circumference (37–41). Importantly, in the large cohort studies characterizing metabolic phenotype, interpretation of the data is hampered by lack of age-, sex-, and demographically matched controls. The serum lipid profile is abnormal in patients on conventional pituitary hormone replacement, with elevated total and LDL cholesterol and triglyceride levels (37, 42–47). Serum levels of HDL cholesterol have been reported as either unchanged (44, 47) or decreased (43, 45, 46) in hypopituitarism. In the largest study to date, a centralized laboratory was employed to examine the fasting lipid profile in 2589 patients (48.8% female; age, 44.2 ± 14.6 yr) before commencing GH replacement (38). The mean (±SD) total, HDL and LDL cholesterol were 6.1 ± 1.3, 3.7 ± 1.1, and 1.2 ± 0.4 mmol/liter respectively. The total cholesterol was above the target level of 5.2 mmol/liter in 71% of patients (66% of males and 75% of females); HDL was below the target level of 1.2 mmol/liter in 49% (46% of men, 49% of premenopausal women, and 57% of postmenopausal women). The ratio of total cholesterol to HDL was increased above 4.5 in 59% of patients (69% of men, 44% of premenopausal women, and 55% of postmenopausal women). Triglycerides were above the target value in 57% of men, 49% of premenopausal women, and 60% of postmenopausal women. The frequency of an abnormal lipid profile increased with age in both sexes. Total cholesterol was also increased in the presence of smoking, diabetes mellitus, and epilepsy and in patients taking lipid-lowering drugs. The HDL concentration decreased with increasing BMI, waist:hip ratio, and waist circumference and was also lower in patients who smoke, had diabetes mellitus, or took lipid-lowering agents.

c. Blood pressure. The data regarding the prevalence of hypertension in patients with hypopituitarism compared with the general population are conflicting. Rosén et al. (45) described an increased prevalence of hypertension in patients with hypopituitarism, but a number of other studies have found no difference (48–50), and some studies have found that patients with hypopituitarism have lower blood pressure than controls (51–54). The majority of data would suggest that hypertension is not a major feature of hypopituitarism and is unlikely to play a major role in the associated vascular morbidity.

d. Vascular structure and function. The development of athropomatous disease is a gradual process that has been studied using a variety of structural and functional measures and serological markers. The earliest detectable change is in the intima media thickness (IMT), which increases as lipids are deposited in the intima of large arteries. Carotid
IMT can be measured using ultrasound and is a predictor of myocardial infarction and cerebrovascular accident (CVA) in adults over 65 yr of age (55). The carotid IMT is significantly increased in adults with hypopituitarism compared with age-matched controls (40, 56, 57); however, this is not the case in adolescents with untreated GH deficiency (58). Major blood vessels dilate to accommodate the pulse pressure generated by the heart to smooth the flow of blood through the arterial system. As vascular disease develops, these vessels become stiffer and are less likely to dilate in response to the pressure wave or to stimuli such as acetylcholine. This is dependent upon nitric oxide generation by nitric oxide synthase. Impaired vascular reactivity is thought to promote further endothelial damage facilitating the atherogenic process. Patients with hypopituitarism on conventional replacement therapy have impaired large vessel reactivity and evidence of impaired nitric oxide generation (59).

Impaired endothelial function promotes adhesion of leukocytes to the endothelium that migrate through it and produce an inflammatory response (60). This is mediated via adhesion molecules that are expressed on the luminal surface of the endothelium. Serum levels of C-reactive protein (CRP), IL-6, and TNF-α are increased in patients with hypopituitarism (61–62). Adhesion molecules such as intercellular adhesion molecule-1, E-selectin, and P-selectin are reported to be elevated in patients with hypopituitarism, although these findings appear to be variable. Furthermore, in vitro studies demonstrate that monocytes collected from these patients show increased adhesion to bovine endothelial cells (64).

Fibrinolytic activity is an important contributor to cardiovascular risk; reduced activity is associated with venous thromboembolic disease, stroke, and ischemic heart disease. One of the major regulators of the fibrinolytic system is plasminogen activator inhibitor-1 (PAI-1), which regulates tissue plasminogen activator through inhibition (65). PAI-1 levels are elevated in patients with hypopituitarism (66–69). Devin et al. (66) demonstrated that the 24-h fibrinolytic profile was abnormal in hypopituitarism, reporting a 62% increase in PAI-1 antigen levels ($P < 0.05$) and a 24% reduction in tissue plasminogen activator levels ($P = 0.003$). In addition, the normal circadian rhythm of PAI-1 was lost. Thus, hypopituitarism treated with conventional replacement therapy (but not GH) is a prothrombotic state that may contribute to the increased cardiovascular mortality observed in patients, and this has been shown to be improved by GH replacement in some studies (68, 69). Circulating levels of AMDA (asymmetrical dimethylarginine), an endogenous nitric oxide synthase antagonist, are elevated in hypopituitary patients independent of GH deficiency (70). In addition, in hypopituitary women, inflammatory cytokines that have been implicated in the pathogenesis of cardiovascular disease including IL-6 and CRP and remain elevated in women after correcting for BMI (71).

2. Malignancy

Where data have been reported, malignant causes of death have included tumors within the gastrointestinal tract, pancreas, liver, bone, central nervous system, lungs, skin, breast, urogenital tract, and lymphohemopoietic system (7, 31). The data have been somewhat conflicting as to whether mortality secondary to malignancy is different in patients with hypopituitarism compared with the general population. In the earliest reports (11, 16), deaths related to malignancy were lower than expected, notably in men, although the actual number of deaths was very small [three male deaths in each of those studies with 10.1 (11) and 5.7 (16) expected, respectively]. Larger studies have reported either no increase in malignant deaths (12, 18, 21, 31) or a significant increase (7, 16, 19, 20) with SMRs up to 12.2 in the youngest patients, reflecting the rarity of malignant diagnoses in the control cohort (19). Differences in control populations may be important, bearing in mind the prevalence of specific cancer types within certain populations. Also, patients with a pituitary adenoma may have an inherent increased risk of malignancy. Overall, the lack of consensus within the literature may reflect differences in the specific populations (and control cohorts) that have been studied as well as differences in treatment modalities and power of studies to assess this outcome. The effects of radiotherapy on future development of secondary intracranial malignancy are discussed in Section V.

3. Respiratory and respiratory tract infections

Respiratory mortality remains a poorly defined area in most studies. Only three studies have quoted specific respiratory mortality, and the data are contradictory. Mortality was increased in both males and females in one study (overall SMR, 2.55; $P < 0.0001$) (12); increased in males but not females in another study (SMR, 1.48, and 95% CI, 1.02–2.14; vs. SMR, 0.818, and 95% CI, 0.53–1.3) (31); and increased in females but not males in another study (SMR, 1.9, and 95% CI, 0.57–1.57; vs. SMR, 0.98, and 95% CI, 0.57–1.57) (7). Although there are theoretical reasons as to why hypopituitary patients may be more vulnerable to respiratory tract infections, including the role of glucocorticoid replacement and potential defects in immune function, there is still little evidence to suggest that this translates to increased respiratory mortality. There is some evidence within the literature to suggest that hypopituitary patients may be more susceptible to life-
threatening infection (72). In a retrospective case note series, severe infections including those affecting the respiratory tract were more common in neurosurgically treated hypopituitary patients compared with control-treated patients without pituitary hormone deficiencies. This was a small retrospective study, and the control group may not be entirely appropriate, but the results do provide an indication of increased susceptibility to infection (72). Mukherjee et al. (73) found that the immune response to pneumococcal vaccine and other markers of humoral immunity was abnormal, particularly in patients with low prolactin and IGF-I. This impaired immune function may contribute to the mortality attributed to respiratory disease, particularly in patients with craniofacial anomalies who are likely to have severe hypopituitarism including prolactin deficiency. Replacement of dehydroepiandrosterone (DHEA), which is frequently deficient in patients with hypopituitarism, may have a positive effect on immune function in patients with Addison’s disease (74), and there is much in vitro work suggesting that DHEA may have an immunomodulatory role (75) (it must be noted that many of these studies have used supra-physiological DHEA levels), but to date the evidence for this effect in patients with hypopituitarism is lacking. The hypothalamic pituitary-gonadal axis has also been shown to be a key regulator of immune function in both experimental and clinical studies. Both GnRH and sex steroids appear to be important modulators of both B and T cell function; however, it should be highlighted that there are conflicting results in some clinical studies. This area has been reviewed in detail by Tanriverdi et al. (76).

E. Role of ACTH deficiency and glucocorticoid replacement

1. Dosage of glucocorticoid replacement

Patients with primary adrenal failure in addition to those with hypopituitarism have an increased risk of premature mortality compared with the general population (77, 78). This increased mortality is predominantly due to cardiovascular, respiratory, and cancer mortality (77, 78). However, the association between mortality and secondary adrenal insufficiency is not as robust. Sherlock et al. (79) have recently shown that in a cohort of patients with acromegaly, the RR for mortality in the ACTH-deficient group [RR, 1.7 (95% CI, 1.2, 2.5); P = 0.004] was significantly greater than the ACTH-replete group. Increasing doses of hydrocortisone were associated with an increasing SMR (P for linear trend, <0.001). On internal analysis, having adjusted for age, sex, calendar period, period of follow-up, and radiotherapy, there was a significant increase in RR of mortality in patients receiving daily hydrocortisone doses between 25 and 30 mg [RR, 1.6 (95% CI, 1.1, 2.4); P = 0.014] and daily hydrocortisone doses greater than 30 mg [RR, 2.9 (95% CI, 1.4, 5.9); P = 0.003] (79). The rate of cardiovascular death was also increased with increasing doses of hydrocortisone therapy. In the group of patients who were ACTH replete, 26.2% of deaths were due to cardiovascular causes. In the overall group of ACTH-deficient patients, 31.6% of patients died from cardiovascular causes, and there was an increase in cardiovascular death with increasing hydrocortisone dose (hydrocortisone dose >0 and ≤20 mg/d, 10% cardiovascular mortality; hydrocortisone dose >20 and ≤25 mg/d, 33.3% cardiovascular mortality; hydrocortisone dose >25 and ≤30 mg/d, 38.5% cardiovascular mortality; and hydrocortisone dose >30 mg/d, 44.4% cardiovascular mortality) (79). Similarly, within the general population, the use of glucocorticoids was associated with a relative risk for a cardiovascular event in patients receiving high-dose glucocorticoids of 2.56 (95% CI, 2.18 to 2.99) (80).

Traditionally, the daily dose of hydrocortisone was 30 mg/d split into two doses (two thirds in the morning and one third in the evening). In recent years, it has been reported that the cortisol production rate in normal subjects is less than was previously thought. Esteban et al. (81) (using stable isotope dilution chenspray liquid chromatography/mass spectrometry) showed that the normal cortisol production rate in young adults can be estimated to be 27.3 μmol/d (equivalent to 5.7 mg/m²/d or approximately 9.9 mg/d). This was supported by deconvolution analysis data from young males who on average had a total daily cortisol production rate of 5.7 ± 0.3 mg/m²/d (82). In recent years, endocrinologists have tried to decrease glucocorticoid replacement doses in patients to levels that remain safe but do not lead to overtreatment. Nevertheless, it is possible that subtle increased glucocorticoid exposure over time might contribute to morbidity and increased mortality as observed in patients with Cushing’s syndrome.
were also the ones with the lowest IGF-I SDS score (SDS) at baseline. However, Dunne et al. (51) reported no changes in weight, glucose, or HbA1c in patients after decreasing their hydrocortisone dose from 30 to 15 mg/d for 3 months.

2. Mode of glucocorticoid delivery

Twice or thrice daily doses of glucocorticoids are recommended to mimic the normal circadian rhythm and changes to circulating cortisol, but this is rarely achieved. The bioavailability of orally administered hydrocortisone is approximately 95% (86, 87), and its half-life is 60–90 min. A single morning dose of 15 mg hydrocortisone leads

FIG. 7. Hydrocortisone equivalent doses in ACTH-deficient patients with GH deficiency before GH replacement. The broken line represents a dose response analysis within the glucocorticoid-treated groups. A. Waist circumference. $P < 0.001$ vs. AS. B. Total cholesterol. $P < 0.0001$ vs. AS. C. Triglycerides. $P < 0.001$ vs. AS. D. LDL cholesterol. $P < 0.05$ vs. less than 20 mg/d. HC, Hydrocortisone; AS, ACTH sufficient. [From H. Filipsson et al.: J Clin Endocrinol Metab 91:3954–3961, 2006 (85). Permission granted by The Endocrine Society. © 2006, The Endocrine Society.]
to supraphysiological serum cortisol concentrations 1–2 h after oral administration and a return to subphysiological or undetectable levels 6–8 h later (86, 88, 89). There is evidence that continuous, prolonged, compared with intermittent short exposure to glucocorticoids may have different effects on a number of steroid responsive enzymes (90). Pulsatility is also important because it has significant effects on the occupancy of the glucocorticoid receptor (90). Circadian iv infusions of hydrocortisone can mimic the normal cortisol rhythm via a programmable pump resulting in beneficial effects in patients with Addison’s disease and congenital adrenal hyperplasia (91); using sc infusions, it was also possible to reduce the daily dose of hydrocortisone (92). These infusions are obviously cumbersome and not practical; however, over the last few years there has been a push to design orally active delayed or sustained release formulations of hydrocortisone to reproduce “physiological replacement” (93). Johannsson et al. (94) recently showed that a novel modified release once daily oral hydrocortisone preparation (Duocort) produced a diurnal plasma cortisol profile that mimicked the physiological serum cortisol profile. Similar results are reported with a preparation originating from Sheffield, UK (Chronocort) (95, 96).

The metabolic fuel profile of 10 patients who were treated with conventional doses of glucocorticoid therapy (median, 22 mg; range, 10–30 mg/24 h) were assessed compared with 13 age-, gender-, and BMI-matched controls. In the patient group, there was decreased glucose, nonesterified fatty acid, and 3-hydroxybutyrate overnight, and this was associated with decreased integrated levels of total and free plasma cortisol and 24-h urine cortisol excretion. Indeed, the decreased glucose and nonesterified fatty acid continued throughout the 24-h period of testing (97). In a further study, morning replacement doses of glucocorticoid resulted in higher glucose levels, which were correlated with the maximal plasma cortisol levels (98).

In a further study, Howlett (89) assessed the glucocorticoid replacement in 130 patients requiring hydrocortisone replacement therapy for ACTH deficiency (in total 174 day curves were performed: 63 on twice daily and 109 on thrice daily glucocorticoid replacement). Optimum replacement was defined as achieving a 0.900 h cortisol within the reference range (after taking morning hydrocortisone on awakening), and 1230 h and 1730 h cortisol above 50 nmol/liter and ideally above 100 nmol/liter. Fifteen percent of patients on twice daily hydrocortisone replacement regimens achieved optimal replacement, compared with 60% on thrice daily regimens. When regimens were compared, the patients who received 10/5/5 mg achieved optimal replacement in 66% (mean quality score, 3.62), 10/10/5 mg in 50% (mean quality score, 3.32), and 20/10 mg in 10% (mean quality score, 2.48) (89). Dunne et al. (51) assessed whether lowering the dose of hydrocortisone replacement from 30 to 15 mg/d in a hypopituitary cohort was associated with improvements in blood pressure and other markers of cardiovascular function. After 3 months on the lower dose of hydrocortisone, there was no change in blood pressure, glucose, or HbA1c; however, there was a significant improvement in forearm blood flow (51).

3. Tissue metabolism of glucocorticoids

At the tissue level, glucocorticoid action is modulated by isozymes of 11 β-HSD, types 1 and 2. 11 β-HSD 2 is a nicotinamide adenine dinucleotide-dependent enzyme predominantly located in tissues that express the mineralocorticoid receptor (MR); it acts as a dehydrogenase [i.e., converting active (cortisol) to inactive (cortisone) glucocorticoids]. This action protects the MR from illicit binding of cortisol, which has similar affinity for the MR as for the glucocorticoid receptor (99). 11 β-HSD 1 is a bidirectional enzyme; however, in vivo it acts predominantly as an oxidoreductase enzyme (due to reduced nicotinamide adenine dinucleotide phosphate cofactor supply from the endoplasmic reticulum located enzyme hexose-6-phosphate dehydrogenase) (100). Thus, it converts inactive (cortisone) to active (cortisol) glucocorticoids within tissues. 11 β-HSD 1 is modulated by many factors, including GH/IGF-I, thyroid hormone, insulin, glucocorticoids, and sex steroids (101). Thus, in patients with hypopituitarism, there may be alterations in tissue-specific exposure to glucocorticoids independent of circulating values. This is particularly relevant in patients with GH deficiency (see Section 1.6).

F. Role of GH deficiency and replacement

The majority of studies to evaluate a role for GH have been performed in patients with hypopituitarism who are also receiving replacement with sex steroids, glucocorticoids, T₄, and desmopressin where appropriate. However, abnormal findings of these studies have been attributed in many cases to untreated GH deficiency leading to the supposition that patients should receive GH replacement therapy to correct these abnormalities and potentially reduce cardiovascular mortality to normal.

There is now a substantial body of evidence that indicates that GH replacement therapy has a beneficial effect upon many of the parameters outlined above. Body composition improves consistently with GH replacement. Lean mass increases, and fat mass decreases significantly. Studies utilizing computed tomography (33), waist-hip ratio (38, 102, 103), or simply waist circumference (38) have
demonstrated a significant reduction in central adiposity. The fasting lipid profile improves with reductions in total and LDL cholesterol and an improvement in the total: HDL cholesterol ratio (38, 43, 44, 104, 105). A study of 1206 patients who received GH treatment for 2 yr demonstrated an average reduction in total and LDL cholesterol levels of 0.4 mmol/liter (95% CI, −0.4 to −0.3; P < 0.0001) and 0.4 mmol/liter (95% CI, −0.4 to −0.3; P < 0.0001), respectively, with a further reduction reported after 2 yr of treatment (38). Although there was a small but significant reduction in HDL cholesterol, the ratio of total: HDL cholesterol improved by 0.3 (95% CI, −0.1 to −0.2; P < 0.0001). Serum triglyceride levels were not affected by GH treatment.

GH treatment in hypopituitary adults also impacts upon endothelial function, the inflammatory process, and fibrinolytic profile. GH replacement results in increased excretion of nitric oxide metabolites in the urine; however, it is not clear whether this reflects greater production or decreased inactivation of nitrous oxide (59). The markers of inflammation, CRP, IL-6, and TNF-α also fall during GH replacement therapy (64, 106). Perhaps as a consequence of the reduction in inflammation and improvement in nitric oxide metabolism, the reactivity of the blood vessels also improves (56, 107). Measurement of the carotid IMT also demonstrates a significant improvement during therapy (56, 57, 108). Although these studies have been of relatively short duration, one study compared the outcome of patients after 10 yr of treatment and demonstrated that the beneficial changes in lipid profile, body composition, and carotid IMT were sustained over that period (109).

These changes all reflect beneficial effects on recognized markers of cardiovascular risk. However, GH replacement produces changes in some parameters that may have an adverse effect upon cardiovascular outcome. Although GH replacement therapy results in a reduction of central fat mass, insulin resistance is increased. In one study of 90 patients, there was an increase in HbA1c levels from 4.9 ± 0.05 to 5.07 ± 0.06% (P < 0.001). Plasma glucose levels rose from 4.72 ± 0.06 to 5.15 ± 0.07 mmol/liter (P < 0.001). These changes were evident after 6 months of treatment and were sustained for 2 yr (110). Lipoprotein (a) is an independent marker of cardiovascular risk that increases significantly during GH replacement (111–113). Despite these changes, which in isolation would suggest a negative impact on cardiovascular risk, the balance of the effect of GH on overall cardiovascular risk appears to be positive, as is evident from the beneficial effects upon vascular structure and function.

The beneficial effects upon the cardiovascular risk profile provided by GH replacement therapy in GH-deficient adults would imply a reduction in expected cardiovascular mortality in that population, but there are currently no data demonstrating directly that GH replacement therapy reduces cardiovascular mortality in hypopituitary adults. Long-term, postmarketing surveillance studies supported by the pharmaceutical industry are in place that may answer this important question in the future.

There is evidence that GH increases the clearance of cortisol by inhibition of 11β-HSD1 (thus preventing conversion of inactive cortisone to active cortisol) (114). There are in vitro data to indicate that this is through the direct action of IGF-I, not GH (115). Clinically, patients starting on GH may need a slight increase in glucocorticoid replacement dose, or patients who are ACTH replete before GH replacement may need retesting once they are on GH treatment (116). However, in GH-deficient patients, cortisol bioavailability is increased in key tissue such as liver, fat, and muscle. This might explain some of the reported deleterious effects of GH deficiency (abnormal lipid profile, increased fat mass, low muscle mass, and increased BMI/waist:hip ratio).

G. Role of TSH deficiency and replacement

Adequacy of thyroid hormone replacement in patients with hypopituitarism is difficult to assess because the normal negative feedback mechanisms are disrupted and serum TSH levels cannot be used as a marker to determine the correct dose of T4. Instead, one has to rely upon measures of the serum T4 level. There is no true consensus about which level of T4 a patient with pituitary disease should be diagnosed with secondary hypothyroidism. Classically, secondary hypothyroidism was diagnosed in the setting of a low T4 level with an inappropriately low TSH in a patient with pituitary disease. However, there is increasing evidence that, although the population may show a spectrum of TSH and T4 values, within any individual levels of TSH/T4 remain remarkably constant over a year (117). Therefore, if a patient has set their “thyrostat” to a high T4 and pituitary surgery decreases this significantly but still is within the normal range, does this mean they are at the same risk of central hypothyroidism as someone who has a low T4 that does not change after pituitary surgery? Further work is needed to ascertain the best diagnostic criteria for secondary hypothyroidism, and there is urgent need for tissue measures of T4 action other than TSH. Lower limits of reference ranges are used, suggesting that many patients may have secondary hypothyroidism and not be adequately replaced. In the normal population, a suppressed TSH level (a marker of thyroid hormone excess) is associated with an increased risk of atrial fibrillation (118), placing the individual at increased risk of embolic events, such as stroke. Furthermore, in a population study, deaths from cardiovascular disease were significantly increased in subjects who had a sup-
pressed TSH level but a normal free T_4_ concentration (119). Thus, mild overtreatment with T_4_ in patients with hypopituitarism may contribute to the increased cardiovascular mortality observed. This risk may be augmented by the prothrombotic state of patients with hypopituitarism (67). It should be highlighted that in the general population there is still debate regarding increased mortality in patients with thyroid dysfunction (120), and there are little data regarding this in patients with pituitary disease.

H. Role of sex steroid deficiency and replacement

Data regarding the role of estrogen and testosterone replacement therapy on mortality in patients with hypopituitarism are weak, and as such we extrapolate findings from studies in the general population, with the caveat that there may be several confounders such as GH therapy/deficiency and altered body composition in patients with hypopituitarism. For many years the use of sex-steroid replacement in normal, postmenopausal women was advocated for the amelioration of menopausal symptoms and the prevention of bone loss and cardiovascular disease. This practice was thrown into doubt by two large, randomized, placebo-controlled studies that reported increased cerebrovascular and cardiovascular events and an increased risk of developing breast cancer after prolonged hormone replacement therapy in postmenopausal women (121, 122). This area is beyond the scope of this review; however, increasingly, the literature regarding randomized control trials in this area shows an increase in overall incidence of breast cancer, stroke, coronary heart disease, pulmonary embolism, and, in women older than 65 yr of age, an increase in dementia rates, with a significant decrease in the incidence of colorectal cancer and fractured neck of femur (123, 124). There does not appear to be a change in endometrial cancer incidence (123). A recent study has also reported an increase in death from non-small cell lung cancer in women on estrogen and progesterin therapy (125). Hormone replacement therapy appears to be safer in young women than older cohorts, but more data are needed to fully assess this (124, 126). These findings raised concern in young women of premenopausal age who require sex steroid replacement to manage hypopituitarism or other conditions that result in ovarian failure. Tomlinson et al. (12) demonstrated that mortality was increased in subjects with gonadotropin deficiency that were not receiving sex steroid replacement, whereas mortality in those on sex steroid replacement was similar to patients with an intact axis (Fig. 8). Further reassurance is provided by the low frequency of malignant disease reported in patients with hypopituitarism; one study reported a 50% reduction in deaths from this cause (11).

The role of androgens and, in particular, testosterone in cardiovascular disease has been increasingly reported over the last decade both in the general population and in patients receiving therapy for prostatic carcinoma. In the general population above the age of 40, lower testosterone levels have been associated with increased risk of cardiovascular disease (127); however, this is not the case in all studies (128). The role of androgens and testosterone in the development of cardiovascular disease and coronary artery disease has been extensively reviewed by Liu et al. (129) and by Wu and von Eckardstein (130), respectively. However, it should be noted that the vast majority of studies in this area do not include a hypopituitary cohort. Another controversial area regarding androgen replacement therapy in men is the role of testosterone in the development of prostatic carcinoma. The Endocrine Society has recently published clinical practice guidelines for adult men with androgen deficiency syndromes that include recommendations for monitoring of prostate, hematocrit, and bone mineral density in patients on testosterone therapy (131). However, the role of testosterone replacement therapy in hypogonadal men in the development of prostatic carcinoma above and beyond that seen in the age-matched general population is controversial (132) because the goal of testosterone replacement is to return testosterone to the normal age-related range.

More detailed studies of sex-steroid replacement strategies and their long-term effect on cardiovascular risk factors, malignancy, and outcome in men and women with hypopituitarism are required to ensure that current practice is optimal.

I. Role of underlying etiology on mortality in hypopituitarism

Hypopituitarism encompasses a number of diverse conditions. The mortality associated with acromegaly, Cushing's disease, and the underlying diagnosis of craniopharyngioma is discussed in Sections II, III, and IV, respectively. In the majority of cases, studies have not been able to analyze data with respect to specific etiology due to insuffi-
cient patient numbers and power. However, in two studies, nonfunctioning pituitary adenomas have been analyzed in separate cohort analyses (12, 133). In the study by Lindholm et al. (133), all patients had undergone surgical intervention, and overall mortality was not significantly different from that of the control population. However, 30% had normal pituitary function postoperatively, and even once they had been excluded from the analysis, mortality was not different from control subjects (SMR, 1.21; 95% CI, 0.86–1.70). Importantly, however, this study only included a total of 109 patients. In the study by Tomlinson et al. (12), 573 patients were identified with an underlying diagnosis of nonfunctioning pituitary adenoma. SMR remained significantly elevated compared with an age- and sex-matched population (SMR, 1.70; 95% CI, 1.34–2.15) and deaths were increased in women and were predominantly due to vascular and respiratory causes. When compared against other causes of hypopituitarism (which included craniohypophyseomas in this study), mortality outcome was improved when nonfunctioning adenoma was the underlying diagnosis (SMR, 1.70 vs. 2.34). Although nonfunctioning pituitary adenomas appear to be associated with improved mortality outcome, it is very hard to generalize. Not all nonfunctioning pituitary adenomas behave in the same way, and, as described above, tumor characteristics may have an impact upon mortality outcome (134).

J. Other factors contributing to mortality in hypopituitarism

Tumor characteristics may influence mortality. In a series of 281 patients who underwent operative procedures (transcranial surgery in 96% of cases) and radiotherapy (98% of cases within 6 months of operation), all-cause mortality was increased significantly in those patients that had tumor regrowth compared with those with no tumor regrowth (SMR, 3.74 vs. 1.71). However, hypopituitarism was only diagnosed in 89% of patients within 5 yr of diagnosis, and mortality was increased in the cohort with and without tumor regrowth. Cerebrovascular deaths were increased in both the regrowth and non-regrowth groups, although this only reached statistical significance in the non-regrowth group compared with age- and sex-matched controls, principally due to the total numbers of observed deaths (134).

II. Mortality in Acromegaly

A. Introduction

Acromegaly is caused almost invariably by a GH-secreting pituitary adenoma, although rarely it may be due to a hypothalamic tumor secreting GHRH or ectopic GHRH secretion from a carcinoid tumor. It is a rare condition with an estimated prevalence of around 60 per million and an annual incidence of three or four per million (135).

The clinical features of acromegaly are due to the somatic and metabolic effects of prolonged excess GH/IGF-I exposure or to local effects of an expanding pituitary mass (136). Clinical symptoms include headaches, sweating, symptoms of carpal tunnel syndrome and arthralgia, visual symptoms, and symptoms of pituitary hormone deficiencies. Typical clinical signs include coarse facial features; large, spade-shaped hands; and enlarged feet resulting from soft tissue swelling and bony enlargement. Growth of the mandible results in prognathism and malocclusion, and widened interdental spaces are also common clinical features. Other common features include enlargement of the tongue (macroglossia), swelling of the nasopharyngeal tissue, sleep apnea, lethargy, skin tags, goiter, and colonic polyps. The expanding pituitary mass may cause hypopituitarism, reproductive disorders, and visual symptoms. GH hypersecretion occurring before the epiphyses have fused results in excess linear bone growth and gigantism. Long-term complications include arthropathy, cardiomyopathy, hypertension, and impaired glucose tolerance, and these have been extensively evaluated in a recent review by Colao et al. (137).

B. Studies of mortality in acromegaly

It is now well established that untreated acromegaly is associated with reduced life expectancy. Several retrospective studies have demonstrated a 2- to 3-fold increased mortality in acromegalic patients compared with age- and sex-matched controls. Death is due predominantly to cardiovascular/cerebrovascular disease, respiratory disease, and, in some studies, malignancy (Table 4 and Fig. 9) (138–147). Results from the more recent studies also demonstrated that the high mortality rates associated with acromegaly can be reversed if treatment is successful in reducing GH levels to less than 2–2.5 μg/liter (139–142, 144, 145, 148) (Fig. 10) and in some studies the normalization of IGF-I levels into age-specific reference ranges (142, 148–150) (Table 5). As far back as the 1920s, patients with acromegaly were thought to have reduced life expectancy. In a series of 100 patients with acromegaly studied and reported on in 1966, 50% had died before the age of 50 yr and 89% by the age of 60 yr (151). The causes of death in these early series included diabetic coma, vascular disease, sepsis, and extension of the pituitary tumor.

The excess mortality associated with acromegaly was first accurately qualified and quantified in the series by Wright et al. (146), published in 1970; cause of death in a cohort of 194 subjects with acromegaly was analyzed and compared with those of the general population of England and Wales (Table 4). Fifty-four deaths were observed, compared with 28.5 expected, giving a SMR of 1.9. The increased number of deaths was predominantly due to cardiovascular disease in males, cerebrovascular disease in
TABLE 4. Studies assessing disease-specific mortality rates in patients with acromegaly

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>No. of patients</th>
<th>No. of deaths</th>
<th>Mortality cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright, 1970 (146)</td>
<td>194</td>
<td>55</td>
<td>Total group SMR, 1.8; cause-specific: vascular, 38.5%; respiratory, 18%; malignant, 18%</td>
</tr>
<tr>
<td>Alexander, 1980 (138)</td>
<td>164</td>
<td>45</td>
<td>Total group SMR, 3.3 (male 2.4/5, SMR = 4.8; female 21/81, SMR = 2.6); cause-specific: vascular, 60%; respiratory, 15.5%; malignant, 15.5%</td>
</tr>
<tr>
<td>Nabarro, 1987 (143)</td>
<td>256</td>
<td>47</td>
<td>Total group SMR, 1.3 (&lt;55 yr, 10/53, SMR = 1.9; female 23/137, SMR = 1.7); cause-specific: cardio/cerebrovascular 47/37.2, SMR = 1.3 N/S; vascular, 55%; respiratory, 6%; malignant, 23%</td>
</tr>
<tr>
<td>Bengtsson, 1988 (152)</td>
<td>166</td>
<td>62</td>
<td>Total group SMR, 3.2; cause-specific: vascular deaths 32/9, SMR = 3.6; cancer deaths 15/5.6, SMR = 2.7</td>
</tr>
<tr>
<td>Rajasoorya, 1994 (145)</td>
<td>151</td>
<td>32</td>
<td>Total group SMR, 3.0; cause-specific: cardiovascular SMR 3; cerebrovascular SMR 3; malignancy SMR 1</td>
</tr>
<tr>
<td>Extabe, 1993 (153)</td>
<td>74</td>
<td>10</td>
<td>Total group SMR, 3.2 (1.55–5.93) (male, SMR 7 (2.81–14.4), female, SMR 1.4 (0.29–4.17); cause-specific: vascular, 10 (0.25–55.7); malignancy, 7.1 (2.31–16.6)</td>
</tr>
<tr>
<td>Bates, 1993 (140)</td>
<td>79</td>
<td>28</td>
<td>Total group SMR, 2.63 (1.8–3.9); cause-specific: vascular, 57%; respiratory, 25%; malignant, 11%</td>
</tr>
<tr>
<td>Orme, 1998 (144)</td>
<td>1362</td>
<td>366</td>
<td>Total group SMR, 1.60 (1.44–1.77); cause-specific: vascular, SMR 1.76 (1.47–2.07); P &lt; 0.001; cerebrovascular, SMR 2.06 (1.5–2.76); P &lt; 0.001; respiratory, SMR 1.85 (0.92–1.44); P &lt; 0.001; malignant, SMR 1.16 (0.92–1.44); P = 0.1</td>
</tr>
<tr>
<td>Swearingen, 1998 (149)</td>
<td>149</td>
<td>12</td>
<td>Total group SMR, 1.16 (0.66–2.0); cause-specific: vascular, 5/12; respiratory, 1/12; malignant, 4/12</td>
</tr>
<tr>
<td>Abosch, 1998 (154)</td>
<td>254</td>
<td>29</td>
<td>Total group SMR, 1.28; cause-specific, not available in majority of 20 deaths</td>
</tr>
</tbody>
</table>

| After 2000                |                 |               |                |
| Beauregard, 2003 (141)    | 103             | 18            | Total group SMR, 2.14; cause-specific: vascular, 5/18; malignant, 9/18 |
| Arita, 2003 (344)         | 154             | 11            | Total group SMR, 1.17 (0.54–2.38); cause-specific: vascular, 4/11; respiratory, 2/11; malignant, 2/11 |
| Birnbaum, 2004 (150)      | 164             | 28            | Total group SMR, 1.33 (0.87–1.87); cause-specific: vascular, 7/28; malignant, 13/28 |
| Holdaway, 2004 (142)      | 208             | 72            | Total group SMR, 1.22; cause-specific: vascular, 35/72 (50%); respiratory, 2/76; malignant, 17/72 (24%) |
| Ayuk, 2004 (139)          | 419             | 95            | Total group SMR, 1.26 (1.03–1.54), P = 0.045; cause-specific: cardiovascular, SMR 1.37 (0.98–1.9), P = 0.111; cerebrovascular, SMR 2.68 (1.73–4.15), P = 0.007; respiratory, SMR 1.52 (0.88–2.61), P = 0.219; malignant, SMR 0.91 (0.59–1.39), P = 0.65 |
| Meston, 2004 (148)        | 1219            | 56            | Total group SMR, not available; SMR 1.3 (0.52–2.67) for remission group and 1.38 (0.51–3.0) in persistent disease group; cause-specific: cardiovascular, 26.8%; cerebrovascular, 8.9%; respiratory, 5.4%; malignant, 16.1% |
| Kauppinen-Makinen, 2005 (155) | 334           | 56            | Total group SMR, 1.16 (0.85–1.54); cause-specific: cardiovascular, 23.2% (coronary artery disease); other cardiovascular diseases, (16.1%); cerebrovascular, 14.3%; malignant, 21.4% |
| Trepp, 2005 (162)         | 94              | 13            | Total group SMR, 1.34 (0.71–2.29); cause-specific: cardiovascular, 6/13; malignant, 4/13 |
| Sherlock, 2009 (79)       | 501             | 162           | Total group SMR, 1.7 (1.4–2.0), P < 0.001; cause-specific: cardiovascular, SMR 1.9 (1.6–2.4), P > 0.001; cerebrovascular, SMR 2.7 (1.9–4.1), P < 0.001; respiratory, SMR 1.8 (1.1–2.8), P = 0.01; malignant, SMR 1.2 (0.9, 1.7), P = 0.26 |

females, and respiratory disease in both. There was no increased mortality from malignancies. Factors associated with increased mortality included the presence of hypertension and diabetes mellitus. Even in this early study, it was evident that control or improvement in GH levels could lead to a decrease in mortality rates [deaths: no treatment group, 27 of 55 (49.1%), compared with 28 of 139 (20.1%) in treated group of which five of 11 had surgery, 15 of 81 had radiotherapy, and eight of 47 had multiple treatment modalities]. These findings were confirmed in a number of subsequent series over the following two decades (138, 140, 143, 145, 147, 152, 153). The excess deaths were predominantly due to vascular disease, respiratory disease, and in some studies, malignancy (Table 4).

In recent years, significant advances have been made in the management of acromegaly, resulting in a change in overall mortality rates seen in acromegaly. In epidemiological studies performed over the last decade (139, 141, 142, 144, 149, 150, 154, 155), although mortality in acromegalic patients remains elevated compared with the general population in several studies, the mortality increase is generally less than 2-fold, compared with the 2- to 3-fold mortality rates seen in earlier series (Table 4), and indeed some studies report no increase in mortality. In a recent meta-analysis pooling 16 studies, SMR ranged from 1.16 to 3.31, with a mean weighted SMR of 1.72 (95% CI, 1.62–1.83) (156). A metaregression pointed toward improved survival in more recent studies (SMR of 1.62 in papers published in 1995 onward compared with SMR of...
2.11 in papers published before 1995), presumably due to modern treatment modalities and more strictly defined cure criteria.

In the West Midlands Acromegaly Study, we reported on the outcome in 419 patients with acromegaly, of whom 324 were alive and 95 deceased (139). Compared with the general population, all-cause mortality was significantly increased with an SMR of 1.26 (95% CI, 1.03–1.54). The excess mortality was due predominantly to cerebrovascular disease, with small but nonsignificant increases due to cardiovascular and respiratory disease (Table 4). There was no increase in deaths from malignancy. No significant increase in mortality was identified in patients with a posttreatment GH less than 4 mU/liter (2 μg/liter), but survival was reduced in the cohort failing to achieve this target, with a RR of 1.55 (95% CI, 0.97–2.5; \( P = 0.068 \)). IGF-I data were available in 360 patients, representing 86% of the cohort. No effect of IGF-I on outcome could be demonstrated, with the RR for those patients achieving serum IGF-I within the normal age-related range similar to those who did not [elevated IGF-I RR, 1.2 (0.71–2.020); \( P = 0.5 \)].

C. Impact of GH levels on mortality in acromegaly

However, results from two of these studies also demonstrated that the increased mortality associated with acromegaly can be diminished if treatment is successful in reducing GH hypersecretion to less than 5 mU/liter (2.5 μg/liter), whether this is measured as the mean of a GH day profile or as a random GH level (140, 145). In the first of these studies by Bates et al. (140), in a cohort of 79 patients with acromegaly, the SMR fell from 2.6 to 2.0 if treatment reduced GH levels to under 10 mU/liter (5 μg/liter). Even more significant was the fact that mortality was reduced to normal if posttreatment GH levels of less than 5 mU/liter (2.5 μg/liter) were achieved (Table 5). The second study by Raja-soorya et al. (145) in a cohort of 151 patients with acromegaly showed both on univariate and multivariate analysis that higher GH levels were associated with reduced survival.

The studies discussed above reached a consensus in showing that posttreatment GH values of less than 2.5 μg/liter restore SMR to normal (Table 5), providing an evidence base for targeted reduction of GH concentrations (157–159). However, cutoff points of 2.5 μg/liter and less than 1 μg/liter to define an adequate response to treatment have been arbitrarily adopted, with little scientific basis for this selection (140). In the West Midlands Acromegaly Study, comparison of crude death rates per 1000 population suggested that a GH of 2 μg/liter may be a more appropriate treatment target, with a step-up in the death rate once GH exceeded 2 μg/liter (Fig. 11) (139). Data from Holdaway et al. (142) suggest a further improvement in outcome if GH can be lowered to under 1 μg/liter as opposed to 2.5 μg/liter (Fig. 12). The Finnish Nationwide Survey of Mortality in Acromegaly reported similar findings (155). In a cohort of 334 acromegalic patients with 56 deaths, excess mortality was seen in those with posttreatment GH levels greater than 2.5 μg/liter (SMR, 1.63 (1.1–2.35); \( P < 0.001 \)).

In a recent meta-analysis focusing on the relationship between biochemical measurements...
TABLE 5. Studies assessing the role of GH and IGF-I on mortality in acromegaly

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>Study period</th>
<th>No. of patients</th>
<th>No. of deaths</th>
<th>Total group SMR</th>
<th>SMR if GH above cutoff</th>
<th>SMR if IGF-I above cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bates, 1993 (140)</td>
<td>1961–91</td>
<td>79</td>
<td>28</td>
<td>2.63 (1.8–3.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Orme, 1998 (144)</td>
<td>NA</td>
<td>1362</td>
<td>366</td>
<td>1.60 (1.44–1.77)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Swearengen, 1998 (149)</td>
<td>1978–96</td>
<td>149</td>
<td>12</td>
<td>1.16 (0.66–2.0)</td>
<td>NA; 39 patients used GH and 133 used IGF-I for criteria of cure</td>
<td>Mortality risk if active disease 3.5-fold (1.0–12) (multivariate analysis)</td>
</tr>
<tr>
<td>Aboch, 1998 (154)</td>
<td>1974–92</td>
<td>254</td>
<td>29</td>
<td>1.28</td>
<td>Remission = GH ≤5 ng/ml, remission SMR = 1.01, persistent SMR = 3.1</td>
<td>NA</td>
</tr>
<tr>
<td>Beauregard, 2003 (141)</td>
<td>1970–99</td>
<td>103</td>
<td>18</td>
<td>2.14</td>
<td>Remission SMR = 0.88, persistent SMR = 4.8</td>
<td>Remission SMR = 0.88; persistent SMR = 4.8</td>
</tr>
<tr>
<td>Arita, 2003 (344)</td>
<td>1977–2000</td>
<td>154</td>
<td>11</td>
<td>1.17 (0.54–2.38)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Biermasz, 2004 (150)</td>
<td>1977–2002</td>
<td>164</td>
<td>28</td>
<td>1.33 (0.87–1.87)</td>
<td>Elevated age-related IGF-I, RR 4.78 (1.01–22.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Holdaway, 2004 (142)</td>
<td>1964–2000</td>
<td>208</td>
<td>72</td>
<td>1.22</td>
<td>Multivariate analysis IGF-I not independent variable, but SMR 3.5 (2.8–4.2) when IGF-I SDS &gt;2</td>
<td>NA</td>
</tr>
<tr>
<td>Ayuk, 2004 (139)</td>
<td>Pre 2001</td>
<td>419</td>
<td>95</td>
<td>1.26 (1.03–1.54)</td>
<td>IGF-I not predictive; internal comparison of normal vs. elevated IGF-I RR = 1.2 (0.71–2.02)</td>
<td>NA</td>
</tr>
<tr>
<td>Mestron, 2004 (148)</td>
<td>NA</td>
<td>1219</td>
<td>56</td>
<td>NA</td>
<td>IGF-I not normal, 41 compared with 15 deaths (P = 0.001)</td>
<td>NA</td>
</tr>
<tr>
<td>Kauppinen-Makelin, 2005 (155)</td>
<td>1980–99</td>
<td>334</td>
<td>56</td>
<td>1.16 (0.85–1.54)</td>
<td>IGF-I not predictive; OR 0.46 (0.17–1.26)</td>
<td>NA</td>
</tr>
<tr>
<td>Trepp, 2005 (162)</td>
<td>1971–2003</td>
<td>94</td>
<td>13</td>
<td>1.34 (0.71–2.29)</td>
<td>Remission criteria: normal age-related IGF-I and either OGTT GH &lt;1 ng/ml or random CIR &lt;2.5 ng/ml. Remission SMR, 1.3 (0.52–2.67); persistent SMR, 1.38 (0.51–3.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, Not available.

and mortality during follow-up after treatment for acromegally (160), mortality was close to the expected level when last available GH was under 2.5 μg/liter (SMR, 1.1; 95% CI, 0.9–1.4), but was significantly elevated in those with last available GH above 2.5 μg/liter (SMR, 1.9; 95% CI, 1.5–2.4). The RR for a serum GH greater than 2.5 μg/liter was 1.7 (P < 0.05) (Fig. 13).

Therefore, the fundamental aim of treatment in acromegaly should be reduction of GH values to less than 2.5 μg/liter and possibly even lower to less than 1 μg/liter, although care must be taken that this is not at the expense of inducing GH deficiency and hypopituitarism (which in itself is associated with an adverse outcome; see Section 1). In addition, it must be noted that GH cannot be used to monitor treatment in patients treated with the GH antagonist pegvisomant.

D. Impact of IGF-I levels on mortality in acromegaly

IGF-I is now widely used as a first-line investigation for the diagnosis and therapeutic monitoring of patients with acromegaly (157, 161). Indeed, the introduction of GH antagonists as medical treatment for acromegaly necessitates the use of IGF-I in the biochemical monitoring of patients treated with these agents. However, the relationship between outcome and latest IGF-I levels is not as clear-cut as with latest GH (139, 141, 142, 149, 155)
(Table 5). In the first of these studies (162 patients, 12 deaths) (149), those patients who were surgically cured, defined by a normal IGF-I, had mortality similar to that of the general population of the United States, whereas those with active disease as defined by a persistently elevated IGF-I had reduced life expectancy for the period that the IGF-I was elevated. A further study also concluded that IGF-I normalization reduced mortality to expected levels (142); however, serum IGF-I was not an independent predictor of mortality when both GH and IGF-I measurements were included in the multivariate analysis (142) and was only significant when looking at SDS above 2 for IGF-I compared with normal IGF-I levels. Further issues raised included the use of different IGF-I assays over the study period and a relatively small number of deaths.

In the recent meta-analysis by Holdaway et al. (160), those with normal IGF-I had mortality close to the expected values for the general population (SMR, 1.1; 95% CI, 0.9–1.4), whereas the SMR for those with elevated IGF-I at last follow-up remained significantly increased (SMR, 2.5; 95% CI, 1.6–4.0) (Fig. 14). The RR for an elevated serum IGF-I was 2.3 (P < 0.05). However, it should be noted that two of the largest studies, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between posttreatment IGF-I levels and mortality [RR, 1.2; 95% CI, 0.71–2.02; P = 0.5 (139) and RR, 0.46, 95% CI, 0.17–1.26; P = 0.13 (155)] (Table 5), suggesting that last available serum IGF-I may not be as reliable a marker of mortality in acromegaly as last available GH.

E. Assay variability

There are also methodological problems with using the last available GH/IGF-I in the analysis for mortality because this value is inherently biased and does not take into account prior GH/IGF-I levels. Many studies were also performed using older assays that may not be used in clinical practice today; however, it may take many years to get meaningful data on survival using newer more sensitive assays, and these older studies have to be interpreted with this in mind. Many studies have used multiple assays during the duration of study (142, 150, 155, 162) or multiple assays in different centers in multicenter studies both for GH and IGF-I (155). Some studies do not describe the assays used (144, 148, 149, 154). Both IGF-I and GH assays, even those in use today, are prone to large variability that will impact on the result of the studies (163). Other difficulties include normal age- and gender-matched reference ranges for IGF-I and different GH standards during time (142, 150, 155). For example, in the Finnish national acromegaly study during the years 1980 to 1999, GH measurements were performed in five laboratories using seven assays (these assays were not all calibrated to the same International Reference Preparation) (155). When the assays changed between 1995 and 2000, four laboratories changed to an immunofluorometric assay (measures only 22-kDa forms), and one laboratory changed to a chemiluminescent assay (measures 22- and 20-kDa forms, leading to a 1.4- to 1.5-fold higher value than the immunofluorometric assay). Serum IGF-I was measured by RIA or immunoradiometric assay and various centers used different cutoffs.

In recent years, the use of higher sensitivity immunofluorometric, chemiluminescent, and immunoradiometric assays has been associated with significantly lower nadir GH during oral glucose tolerance test (OGTT) in healthy controls than was previously thought (ranging from 0.029–0.25 μg/liter [164–168], there was also a gender difference noted in some studies). Therefore, with the use of more sensitive assays, the target for GH may decrease over time because they can detect much lower levels of GH compared with older RIA and have redefined normality during an OGTT. There has also been discussion as to whether targets for GH need to be altered as a result of these newer assays; however, it must be noted that it may
be some time before we have adequate follow-up data to assess GH cutoffs to normalize mortality using these newer assays.

F. Role of pituitary radiotherapy on mortality in acromegaly

In the West Midlands study, compared with the general population, the use of external radiotherapy was associated with increased mortality, with an SMR of 1.58 (95% CI, 1.22–2.04; P = 0.005), and when assessed on internal analysis within the acromegaly cohort resulted in a RR of 1.67 (95% CI, 1.1–2.56; P = 0.02) (139). In the Finnish survey, mortality was also increased in patients who had been treated with radiotherapy [SMR, 1.69 (95% CI, 1.05–2.58); P < 0.001] (155). In the Spanish acromegaly registry, patients who died had a twice greater probability of having been treated with radiotherapy than those who had survived (hazard ratio, 2.29; 95% CI, 1.03–5.08; P = 0.026) (148) (Table 6). The role of radiotherapy is further discussed in Section V.

G. Role of pituitary dysfunction on mortality in acromegaly

Although hypopituitarism is associated with increased mortality (see Section I), there is little data on the role of hypopituitarism in patients with acromegaly per se. In the West Midlands study, there was a trend (P = 0.07) toward reduced survival in patients with acromegaly who had a greater number of deficient hypothalamic-pituitary axes compared with those without evidence of hypopituitarism (139). In the recent study by Sherlock et al. (79), neither TSH deficiency nor gonadotropin deficiency was associated with increased mortality in acromegaly on internal analysis (gonadotropin deficiency was associated with increased SMR compared with the general population); however, ACTH deficiency was associated with increased mortality [RR, 1.7 (95% CI, 1.2–2.5); P = 0.004]. The cause of death was predominantly cardiovascular, and higher doses of hydrocortisone therapy were associated with increased mortality (see Section I.E).

H. Cancer mortality in acromegaly

Both IGF-I and GH have well-described mitogenic properties in vitro, and case-controlled studies have found in-
TABLE 6. Studies assessing the role of pituitary radiotherapy in mortality in patients with acromegaly

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>No. of patients</th>
<th>RR</th>
<th>SMR</th>
<th>RR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biermasz, 2004 (150)</td>
<td>164</td>
<td>57 CRT</td>
<td>NA</td>
<td>1.73 (0.77-3.86); age and sex adjusted, 1.169 (0.52-2.65)</td>
<td>Cause of death not known</td>
</tr>
<tr>
<td>Holdaway, 2004 (142)</td>
<td>208</td>
<td>143 CRT, 35 Yttrium</td>
<td>NA</td>
<td>NA</td>
<td>No increase in stroke mortality</td>
</tr>
<tr>
<td>Ayuk, 2004 (139)</td>
<td>419</td>
<td>211 CRT</td>
<td>DXT group, 1.58 (1.22-2.04); P = 0.005</td>
<td>1.67 (1.1-2.56); P = 0.02</td>
<td>Cerebrovascular SMR = 4.42</td>
</tr>
<tr>
<td>Kauppinen-Makelin, 2005 (155)</td>
<td>334</td>
<td>116 CRT</td>
<td>DXT group, 1.69 (1.05-2.58); non-DXT, 0.94 (0.62-1.37); P &lt; 0.001</td>
<td>2.27 (P = 0.08)</td>
<td>6/8 stroke deaths</td>
</tr>
<tr>
<td>Mestrn, 2005 (148)</td>
<td>1219</td>
<td>504 CRT, 27 stereotactic radiotherapy, 9 radiosurgery</td>
<td>HR 2.29 (1.03-5.08)</td>
<td>NA</td>
<td>Cerebrovascular mortality data NA</td>
</tr>
<tr>
<td>Sherlock, 2009 (79)</td>
<td>501</td>
<td>220 CRT, 17 Yttrium/ radiosurgery</td>
<td>2.1 vs. 1.4 for non-DXT (P = 0.006)</td>
<td>1.8 (P = 0.008)</td>
<td>Cerebrovascular SMR 4.1</td>
</tr>
</tbody>
</table>

RT, Radiotherapy treatment; HR, hazard ratio.

Increased serum levels of IGF-I in subjects who had or eventually developed prostate cancer or premenopausal breast cancer (169); therefore, one might anticipate excess malignancies in acromegaly. However, epidemiological studies exploring the link between acromegaly, cancer incidence, and cancer mortality have given rise to conflicting data. Early studies suggested an increased incidence of neoplasia overall, particularly of the breast (143) and colon (170), in patients with acromegaly. More recent studies, however, have failed to confirm these findings and suggest that overall cancer incidence is not increased in acromegaly (144, 171). Orme et al. (144) retrospectively examined the cancer incidence and mortality in a UK cohort of 1362 patients with acromegaly; overall cancer mortality rate was not increased (indeed, if anything it was lower: SMR, 0.76; 95% CI, 0.6-0.95), but there was a significant increase in the colon cancer mortality rate (SMR, 2.47; 95% CI, 1.31-4.22) and a nonsignificant increase in female breast cancer mortality (SMR, 1.60; 95% CI, 0.85-2.74; P = 0.07). An important finding was that the overall mortality rate increased significantly if GH levels were elevated [GH < 2.5ng/ml, SMR, 1.1 (95% CI, 0.89-1.35); GH 2.5-9.9 ng/ml, SMR, 1.41 (95% CI, 1.16-1.68); GH > 10 ng/ml, SMR, 2.12 (95% CI, 1.7-2.62); P for trend < 0.0001]. This was also true for cardiovascular death [GH < 2.5ng/ml, SMR, 1.2 (95% CI, 0.83-1.68); GH 2.5-9.9 ng/ml, SMR, 1.59 (95% CI, 1.15-2.15); GH > 10 ng/ml, SMR, 2.11 (95% CI, 1.42-3.01); P for trend 0.02] and cancer death [GH < 2.5 ng/ml, SMR, 0.96 (95% CI, 0.63-1.41); GH 2.5-9.9 ng/ml, SMR, 0.81 (95% CI, 0.5-1.24); GH > 10 ng/ml, SMR, 1.81 (95% CI, 1.13-2.74); P for trend 0.05]. Most recent studies have found cancer death rates in patients with acromegaly to be similar to those in the general population, suggesting that malignancy is not a significant cause of mortality in patients with acromegaly with modern treatment modalities and strict targets (139, 142, 148, 155). Although the data regarding cancer mortality in patients with well-controlled acromegaly in recent years does not show a significant increase, there is an increasing body of evidence that the incidence of malignant disease may be greater in patients with acromegaly than the general population; however, several confounding factors must be appreciated while interpreting these data. This area has been extensively reviewed by Renehan and Brennan (172) and by Loeper and Ezzat (173).

The exact magnitude of the risk of colon cancer and the role of screening programs remain the subject of much debate (174-177). Full colonoscopy is important because up to two thirds of lesions were right-sided in one study (178). A significant amount of data in the general population suggest that the majority of colorectal carcinomas arise from adenomas, and as such detection and removal of adenomatous polyps should reduce colorectal cancer incidence and mortality (179). Ron et al. (170) assessed the risk of gastrointestinal cancer in 1041 patients with acromegaly reviewed between 1969 and 1985 from all Veterans Affairs (VA) hospitals in the United States and compared them to more than 37,000 veterans discharged from VA hospitals during the same follow-up time. Patients with acromegaly had a standardized incidence ratio for cancer of 1.6 (1.3-1.9) (116 observed cancers compared with 72.8 expected), with a standardized incidence ratio of 2.0 (95% CI, 1.3-2.9) for digestive organ or peritoneal cancers [in particular, esophageal 3.1 (95% CI, 1.3-6.0) and colonic 3.1 (95% CI, 1.7-5.1) neoplasias] (170). However, other large studies of mortality in patients with acromegaly have not reported raised risk of neoplastic deaths. It is likely that the increased risk of colorectal cancer in acromegaly is modest (176). Renehan et al. (176) have suggested that over a 10-yr period, 556 colonosco-
pies would need to be performed to prevent one death. Therefore, the issue of colonoscopy screening in acromegaly remains a contentious one, and further large-scale prospective studies are required.

There has also been interest in recent years with regard to increased thyroid cancer incidence in patients with acromegaly. However, it should be highlighted that the numbers in these studies are very small (and any changes in incidence may lead to a dramatic change in relative risk). Tita et al. (180) assessed thyroid disease in 125 patients in a single center over 25 yr and reported that the prevalence of thyroid cancer is 5.6% (seven of 125) patients compared with the estimated prevalence in the general population (0.093%). However, there are a number of caveats to this study, including the length of study that leads to inherent bias because the criteria for diagnosis of thyroid cancer may have changed. Also, all patients had thyroid ultrasound at diagnosis. This would not be the screening protocol for the normal population, and there was no matched control group. It is known that many patients in the general population have asymptomatic thyroid malignancy. There is a need for further larger studies with matched control populations to assess the risk of thyroid cancer in patients with acromegaly.

I. Other factors influencing mortality in acromegaly

Analysis of the determinants for mortality in acromegaly indicates that approximately 60% of patients die from cardiovascular/cerebrovascular disease and 25% from respiratory disease, and in 15% of patients, the cause of death is attributed to malignancy (171). From published retrospective studies, the major negative determinants for survival are high GH levels and the presence of hypertension, cardiac disease, and diabetes mellitus (171). Other variables found to influence outcome include hypertension, duration of the disorder before treatment, and age. Hypertension and glucose intolerance are important contributory factors to the vascular morbidity associated with acromegaly (181). However, there are few published reports on their impact on mortality in acromegaly and how this correlates with GH and IGF-I levels. Hypertension occurs in approximately one third of all patients with acromegaly, ranging in some series up to 60% (182, 183). The pathogenesis of hypertension in acromegaly is thought to be multifactorial, with an increase in extracellular sodium, a decrease in atrial natriuretic peptide, insulin resistance, and the direct effects of GH/IGF-I on vascular endothelial cells all playing a role (183). Hypertension is considered one of the most relevant negative prognostic factors for mortality in acromegaly (145, 146, 171, 184).

The presence of diabetes mellitus has been demonstrated to be a significant predictor of mortality in some studies (145, 146), but not in others (140, 152). Further studies are required to examine this association and to determine whether diabetes mellitus is primarily responsible for poor outcome or whether glucose intolerance is a surrogate marker for patients with higher GH levels, who are known to have a poor prognosis independently of any other factors.

III. Mortality in Cushing's Disease

A. Introduction

In Harvey Cushing's original series published in 1932, the median survival in untreated Cushing's disease was just 4.6 yr (185). Plotz et al. (186) endorsed these data some 20 yr later, reporting a 5-yr survival of just 50%. Undoubtedly, these reports reflected severe cases of hypercortisolism at a time when surgical and medical management were not as advanced as they are today but were sufficient to label Cushing's as the "killing disease" with premature mortality from infection and cardiovascular/cerebrovascular disease (187). Cushing's disease is rare, with an incidence of 2.4 cases per million (4.7 females and 0.3 males) and prevalence of 29.1 per million (188). The incidence appears to be increasing with time (from 1.5 to 3.9 million per year), and this is most likely explained through greater awareness and improved diagnostic techniques that detect patients with less florid clinical features.

B. Mortality studies in Cushing's disease

Several series have evaluated long-term outcome in treated patients (Table 7) (186, 188–198). Many such series also contain patients with Cushing's syndrome secondary to autonomous adrenal lesions (adenomas, carcinomas), but most reports separately identify and report on patients with Cushing's disease. It should also be highlighted that the treatment algorithms and techniques used in many of these historic studies would not be in keeping with modern clinical practice.

Pikkarainen et al. (196) reported six deaths in 48 Cushing's disease patients followed for a mean of 7.4 yr after treatment. Twenty-five cases were cured after surgery, and 16 also received radiotherapy. SMR was 2.67 (95% CI, 0.89–5.25) in this cohort. SMR was 3.8 (95% CI, 2.5–17.9; P < 0.03) in a Spanish series comprising 49 patients, with vascular mortality (SMR, 5) being the principal cause (188). Dekkers et al. (190) compared outcome in 248 consecutive cases of transsphenoidal surgery, 174 of whom had nonfunctioning pituitary adenomas and 74 of whom had Cushing's disease. Cushing's patients fared significantly worse with an overall SMR of 2.39 (95% CI, 1.22–
<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>Patients</th>
<th>Follow-up years</th>
<th>Type of surgery</th>
<th>Initial remission rates</th>
<th>Long-term mortality numbers</th>
<th>SMR</th>
<th>Surgical mortality</th>
<th>RT</th>
<th>F:M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plotz, 1952 (186)</td>
<td>33 CD patients and 189 cases from literature</td>
<td>1932–51</td>
<td>18 pituitary RT, 10 adrenal surgery, 2 adrenal RT</td>
<td>5/33</td>
<td>17 died within 5 yr of onset of symptoms</td>
<td>NA</td>
<td>5</td>
<td>18/33</td>
<td>4.3:1</td>
</tr>
<tr>
<td>Welbourn, 1985 (198)</td>
<td>79 CD</td>
<td>1953–80</td>
<td>B/L adrenalectomy</td>
<td>NA</td>
<td>Total 20, 55% cardio/cerebrovascular</td>
<td>SMR NA; actuarial mortality: 1 yr, 67.3%; 5 yr, 79.2%; 10 yr, 71.9%; 20 yr, 61.6%</td>
<td>3/79</td>
<td>16 (20.3%)</td>
<td>2:1</td>
</tr>
<tr>
<td>Guillain, 1988 (192)</td>
<td>64 CD</td>
<td>1978–85</td>
<td>TSS</td>
<td>42 (70%)</td>
<td>NA</td>
<td>NA</td>
<td>1 meningitis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Burse, 1990 (189)</td>
<td>57 CD; B. Nelsons</td>
<td>NA</td>
<td>TSS</td>
<td>83%</td>
<td>NA</td>
<td>NA</td>
<td>2 (3.1%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Grabner, 1991 (191)</td>
<td>109 CD</td>
<td>1950–87</td>
<td>B/L adrenalectomy</td>
<td>All but 5</td>
<td>Total 29, &gt;50% CVS</td>
<td>NA</td>
<td>8 (7%), 3 MI, 2 PE, 1 CNS bleed, 1 Addisonian crisis, 1 sepsis</td>
<td>17 (15.6%)</td>
<td>3:1</td>
</tr>
<tr>
<td>Etsabe, 1994 (188)</td>
<td>49 CD</td>
<td>1975–92</td>
<td>46 TSS</td>
<td>87.5%</td>
<td>5 Total, 3 CVS, 1 infection, 1 post op</td>
<td>All 3.8 (2.5–17.9), women 4.1 (2.9–41), CVS 5 (3.4–48.6)</td>
<td>NA</td>
<td>1 post op</td>
<td>16 (32.7%)</td>
</tr>
<tr>
<td>O'Riordan, 1994 (195)</td>
<td>Total = 50; 25 CD, 18 ectopic, 7 adrenal hyperplasia</td>
<td>1980–91</td>
<td>B/L adrenalectomy</td>
<td>All</td>
<td>Total 15</td>
<td>SMR NA; actuarial mortality in CD: 1 yr, 98%; 3 yr, 98%; 5 yr, 96%</td>
<td>All = 2; 1 Addisonian crisis, 1 extensive metastases</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pikkarainen, 1999 (196)</td>
<td>Total = 74; 43 CD, 4 ectopic, 26 ACTH independent</td>
<td>1981–94</td>
<td>TSS or adrenalectomy</td>
<td>33.8%</td>
<td>Total 10</td>
<td>1.68 (0.81–3.09) in all; CD 2.67 (0.89–5.25)</td>
<td>NA</td>
<td>CD 16 (37.2%)</td>
<td>6.4:1</td>
</tr>
<tr>
<td>Swearingen, 1999 (197)</td>
<td>161 CD</td>
<td>1978–96</td>
<td>TSS</td>
<td>90% of micro, 65% macro</td>
<td>6 Total, 2 CVS, 2 CVA</td>
<td>0.98 (0.44–2.2); actuarial survival: 5 yr, 99%; 10 yr, 93%</td>
<td>Nil</td>
<td>NA</td>
<td>2.5:1</td>
</tr>
<tr>
<td>Lindholm, 2001 (194)</td>
<td>Total = 166; CD 99, adrenal tumors 48, cancer associated 16, others 3</td>
<td>1985–95</td>
<td>90/99 had TSS and 5 yr follow-up data</td>
<td>Permanent cure 45/68, failure 20/68 (11 cure after additional surgery, 9 persistent disease)</td>
<td>Overall group, 23/139</td>
<td>Overall 3.68 (2.3–5.3); CD proven, 1.7 (0.68–3.5); CD unproven, 11.5 (5.7–20.5); adrenal adenoma, 3.5 (0.95–8.9)</td>
<td>3 post op</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Hammer, 2004 (193)</td>
<td>289 CD</td>
<td>1975–98</td>
<td>TSS</td>
<td>82%</td>
<td>29</td>
<td>Actuarial survival: remission 5 yr, 99%; 10 yr, 96%; 15 yr, 85%; persistent disease: 5 yr, 95%; 10 yr, 95%; 15 yr, 84%</td>
<td>3 MI</td>
<td>30</td>
<td>4.8:1</td>
</tr>
<tr>
<td>Dekkers, 2007 (190)</td>
<td>74 CD</td>
<td>1977–2005</td>
<td>TSS</td>
<td>80%</td>
<td>12 Total, 5 CVS</td>
<td>2.39 (1.12–3.9); remission 1.8 (0.71–3.37); persistent 4.38 (1.38–9.07)</td>
<td>NA</td>
<td>14 (18.9%)</td>
<td>3:1:1</td>
</tr>
</tbody>
</table>

**CD**: Cushing’s disease; **ectopic**: ectopic ACTH secretion; **TSS**: transphenoidal surgery; **B/L**: adrenalectomy; **biateral adrenalectomy; F:M**: female: male ratio; **NA**: not available; **CVS**: cardiovascular; **RT**: radiotherapy; **MI**: myocardial infarct; **PE**: pulmonary embolism; **CNS**: central nervous system; **micro**: microadenomas; **macro**: macroadenomas; **Nelsons, Nelsons syndrome**.
3.9) compared with 1.24 (95% CI, 0.85–1.74) in the non-functioning adenoma group. In terms of therapy, a Danish study reported just one death in 45 patients with Cushing’s disease who were cured after surgery, compared with six deaths in 20 patients with persistent hypercortisolism (SMR, 0.31 vs. 5.06) (194). Similar conclusions were published from Swearengen et al. (197) in Boston who reported normal 5- and 10-yr survival rates in 161 patients after transphenoidal surgery; 90% of the cohort were apparently cured after surgery. Normal long-term survival was also documented in a large series (n = 248) from Ann Arbor, Michigan (193). However, increased mortality was observed in a small number of patients who had recurrent/persistent disease. The overall conclusion from the published literature is that mortality is increased in patients with Cushing’s disease, but with effective therapy long-term survival is no different from the background population. By contrast, persistent/recurrent disease is associated with poor outcome, data which collectively provide an evidence base for early and aggressive intervention. It is important to remember that these conclusions are drawn from relatively small series with small numbers of deaths (therefore, even high SMR values often have very wide CIs). It remains to be seen whether the reported ongoing and deleterious cardiovascular risk factors (IMT, metabolic abnormalities) many years after “cure” in these patients translate into poor outcome in larger multicenter/national series (199). In the interim, aggressive treatment of cardiovascular risk abnormalities (hypertension, hyperlipidemia, insulin resistance) with conventional therapies is warranted if these are present.

C. Factors influencing mortality in Cushing’s disease

1. Hypertension

Hypertension is present in approximately 80% of patients with endogenous Cushing’s syndrome and rises to 95% in patients with ectopic ACTH secretion (187, 200, 201). In keeping with the loss of cortisol circadian rhythm, there is also a loss of blood pressure circadian rhythm such that hypertension due to Cushing’s syndrome is associated with a loss of the nocturnal fall in blood pressure (202). Faced with the known actions of glucocorticoids, it is relatively easy to link hypercortisolism to premature vascular mortality. Glucocorticoids increase blood pressure through several mechanisms (203), including the mineralocorticoid action of cortisol, activation of the renin-angiotensin system, potentiation of vasoconstriction through increased β-adrenergic receptor sensitivity to catecholamines, and suppression of vasodilatory actions (203). The resultant effect of these changes is an increase in peripheral vascular resistance, plasma volume, cardiac output, and renovascular resistance (203). Sleep apnea and insulin resistance in patients with Cushing’s syndrome have also been reported as playing a role in the development of hypertension (204, 205).

In one study assessing the underlying pathophysiology of elevated blood pressure in 12 patients with Cushing’s syndrome secondary to an adrenal adenoma compared with six control subjects, patients with Cushing’s syndrome had increased angiotensinogen levels and decreased plasma renin concentration, but no difference in plasma renin activity or plasma aldosterone (despite this, the angiotensin-converting enzyme inhibitor captopril, but not an angiotensin II antagonist, was effective in decreasing blood pressure). The study also described decreased urinary prostaglandin E2 and kaliurea in patients with Cushing’s syndrome, which are known to be depressor systems and therefore may have a role to play in increased blood pressure seen in Cushing’s syndrome. Pressor responses to norepinephrine and angiotensin II were significantly enhanced in this study. All 12 patients had normal blood pressure 1 yr after adrenal adrenalectomy (206).

In Cushing’s disease, the highest cortisol secretion rates are associated with the greatest sodium retaining "mineralocorticoid" effects through saturation of the renal protective enzyme 11β-HSD type 2, which normally inactivates cortisol to cortisone within the renal tubule, protecting the MR from cortisol excess (201). Persistence of hypertension after treatment of hypercortisolism is associated with increased mortality (188). Blood pressure was shown to fall significantly in a childhood/adolescent study, with normalization of diastolic and mean blood pressure 3 months after effective therapy (207); interestingly, there was no correlation between blood pressure pretreatment and cortisol concentrations. As outlined in recent clinical guidelines statements, further outcome studies are urgently required to inform an evidence base for treating patients with Cushing’s disease, particularly when hypercortisolism and/or clinical symptoms/signs are mild (208).

2. Other cardiovascular risk factors

This increase in blood pressure along with other factors may play a key role in the altered left ventricular characteristics and function of patients with Cushing’s syndrome. Muehse et al. (209) recently described decreased left ventricular end-diastolic diameter and left ventricular end-systolic diameter, but increased left ventricular interventricular septum diameter, left ventricular posterior wall diameter, relative wall thickness, and left ventricular mass index in patients with Cushing’s syndrome compared with age-, gender-, and blood pressure-matched controls, leading to reduced systolic performance and diastolic dysfunction. Baykan et al. (210) have also reported left ventricular diastolic dysfunction in patients with Cushing’s syndrome; serum cortisol was positively correlated with Tei index (a measure of global cardiac dysfunc-
tion) and negatively with ejection fraction. These cardiovascular changes may not revert to normal after remission of Cushing’s syndrome. Faggiano et al. (211) showed that 1 yr after remission of Cushing’s disease, patients still had abnormal LDL cholesterol, IMT, systolic lumen diameter, and distensibility coefficient than the age- and gender-matched control group, but not BMI-matched controls (albeit with improvement in all these values compared to when the patients had active Cushing’s disease). Colao et al. (199) assessed cardiovascular risk in patients with Cushing’s disease who had been in remission for 5 yr and compared them to an age- and gender-matched population. Patients who were in remission from Cushing’s disease still had higher BMI, waist:hip ratio, systolic and diastolic blood pressure, fasting glucose and insulin, total and LDL cholesterol, fibrinogen, and lipoprotein (a) than controls. This was associated with an increased carotid IMT and diastolic peak velocity and a decreased systolic/diastolic lumen diameter and distensibility coefficient (199). When the groups were matched for BMI, Cushing’s disease patients still had higher waist:hip ratios, diastolic blood pressure, fibrinogen levels, HDL cholesterol, common carotid artery IMT, and diastolic peak velocity and decreased diastolic lumen diameter and distensibility coefficient.

Hypercortisolemia has been associated with a hypercoagulable state, and several studies have described an increased risk of thromboembolic disorder in patients with Cushing’s syndrome. Van Zaane et al. (212) have recently performed a systematic review in this area, and although much of the data are based on small numbers, it is clear that glucocorticoid-induced hypercoagulability leads to venous thrombosis in patients with Cushing’s syndrome, particularly in postoperative patients. Hypercoagulability was suggested by high levels of factor VIII, factor IX, and von Willebrand factor and evidence of enhanced thrombin generation (212). A risk of 1.9–2.5% was reported for venous thromboembolism not provoked by surgery, with an increased risk in the postoperative period (212).

Hypercortisolism leads to hyperglycemia and insulin resistance and stimulates hepatic gluconeogenesis and glycogenolysis. In vivo glucocorticoids reduce glucose uptake by reducing glucose transporter 4 translocation and increasing lipolysis (213). Assessment of lipid status in clinical studies of patients with Cushing’s disease is not well defined, but patients have a low HDL cholesterol and elevated total and LDL cholesterol (199). The above abnormalities also contribute to hepatic steatosis, which occurs in 20% of patients with Cushing’s syndrome (214).

3. Infection risk

With the actions of glucocorticoids known, it is relatively easy to link hypercortisolism to premature mortality secondary to infection. In terms of infection risk, glucocorticoids suppress the inflammatory response and are immunosuppressive, and Cushing’s syndrome has been suggested to be a transitory immune deficiency state (215). Indeed, there are many case reports and studies reporting opportunistic infection in Cushing’s syndrome with infections such as pneumocystis (216, 217), aspergillus (218), other invasive fungal infections (219), mycobacterium (220), cytomegalovirus (221), cryptocoecal (222), and no-cardial infections (223). Glucocorticoids influence the traffic of circulating leukocytes and inhibit many functions of leukocytes and immune accessory cells (224). They suppress the immune activation of these cells and inhibit the production of cytokines and other mediators of inflammation (224). They particularly suppress type I helper T cells and stimulate apoptosis of eosinophils, and they inhibit the expression of adhesion molecules and their corresponding receptors (224).

With the exception of the association between cortisol secretion rate and renal mineralocorticoid action (201), there are no data linking vascular risk factors or immune markers to absolute levels of cortisol per se. Nevertheless, the assumption is made that the severity of Cushing’s (as translated to the daily cortisol secretion rate) is positively correlated with the mortality risk. This is an important concept when considering the evidence base for therapy in any given patient; the more severe the disease, the greater the potential benefit after therapy (225). However, in terms of underlying etiology of increased mortality, other factors need to be considered.

4. Hypopituitarism

Although pituitary dysfunction has been associated with increased mortality (Section 1), it should be highlighted here that all of these studies excluded Cushing’s patients from analysis. Although the majority of pituitary tumors in Cushing’s disease patients are microadenomas, hypocortisolism per se rather than any mass effects from a tumor, surgical intervention, and/or radiotherapy can result in GH, T4, and sex steroid deficiencies, all of which may be confounders (12). In the study by Lindholm et al. (194), seven of 47 (14.9%) patients had TSH deficiency, seven of 12 (58.3%) men had low testosterone levels, and 10 of 23 (43.5%) premenopausal women had estradiol concentrations below 100 pmol/liter before treatment of Cushing’s disease. However, after treatment 17 patients (49%) were hypogonadal, with 15 having panhypopituitarism (33.3%) (194). Burke et al. (189) reported DI in 25% of patients, gonadotropin deficiency in 48%, TSH deficiency in 28%, and recovery of ACTH function in 47%.
IV. Mortality in Craniopharyngioma

A. Introduction

Craniopharyngiomas are rare epithelial tumors that arise along the path of the craniopharyngeal duct from squamous epithelial remnants of Rathke’s pouch. The pathophysiology and complications that arise from craniopharyngiomas and their treatment has been extensively addressed previously in this journal by Karavitaki et al. (226). Although craniopharyngiomas may arise anywhere along the craniopharyngeal path, the majority of them are located in the sellar/suprasellar region (226) and have a suprasellar component (only 4–6% are intrasellar) (226, 227). Craniopharyngiomas have an incidence of 0.13 per 100,000 person-years that does not vary by gender or race (226) and constitutes 2–5% of adult and 5.3–15% of childhood intracranial tumors (226, 229). They may occur at any age, although a bimodal distribution has been described, with peak incidence rates in children (ages 5–14) and among older adults (ages 65–74) (228). These tumors can be primarily solid, primarily cystic, or more commonly, a combination of both consistencies (227). There are two major histological variants, the commonest being the adamantinomatous type, which is commonly calcified and predominantly affects children, and the papillary or squamous epithelial type, which is rarely calcified and predominantly affects adults (226). Craniopharyngiomas are histologically benign, with only nine cases of malignant craniopharyngiomas reported (230). However, they tend to be locally aggressive, with finger-like attachments that invade adjacent critical structures such as the pituitary, hypothalamus, optic nerves, third ventricle, and blood vessels (231, 232). In fact, craniopharyngiomas are associated with greater tumor-related morbidity than other central nervous system tumors, and most patients present with a combination of neurological, endocrine, and somatic effects that may be permanent or may be exacerbated by treatment (233).

B. Mortality studies in craniopharyngioma

Craniopharyngiomas are associated with significant mortality, with reported overall mortality rates three to five times higher than those of the general population (234, 235). When assessing mortality in patients with craniopharyngioma, it may be important to consider adults and children separately. The overall survival rates (which reflect the effect of multiple treatments) described in exclusive children series range from 83–96% at 5 yr (236–241) and 65–100% at 10 yr (237–248) and average 62% at 20 yr (249). In adults or a mixed-age range population (adults and children) series, the overall survival rates range from 54–96% at 5 yr (228, 232, 235, 239, 240, 250, 251), from 40–93% at 10 yr (232, 234, 235, 239, 240, 250–255), and from 66–85% at 20 yr (235, 254, 255) (Table 8). The lower limits of survival rates usually reflect data from earlier series, before modern advances in microsurgery, neuroimaging, neuroendocrinology, and radiotherapy. It is not clear whether the age at diagnosis represents a survival prognostic factor because some studies have shown that the youngest patients have better survival rates (228, 234, 239, 240, 253); others have found better outcomes in older patients (255, 256), whereas still other studies report no difference between pediatric and adult populations (232, 250, 254, 257, 258).

C. Factors influencing mortality in craniopharyngioma

1. Hypopituitarism

Craniopharyngioma patients have evidence of endocrine dysfunction at presentation and preoperatively in 39–87% of children series (237, 238, 246, 259–261) and 23–95% of mixed adult and children series (232, 235, 240, 250, 251, 254, 262, 263). GH deficiency is reported in 35–100% of patients, FSH/LH deficiency in 10–91%, ACTH deficiency in 21–68%, TSH deficiency in 13–46%, and cranial DI in 6–38% (226, 235, 238, 259, 264–266). Although hypopituitarism is associated with increased mortality, patients with craniopharyngiomas have mortality rates nearly 10 times higher than for other causes of hypopituitarism (12). This highlights the contribution of other factors associated with these tumors to the increased mortality over and above that documented for hypopituitarism per se. Particularly in children, hypoadrenalism and associated hypoglycemia, as well as DI, can lead to significant morbidity and mortality (232, 267, 268).

Hypopituitarism may also result from therapeutic interventions, notably surgery with some degree of hormone deficiency in 73–100% (236, 242, 247, 251, 256, 261, 264, 265, 268, 269) and panhypopituitarism in 44–100% (235, 241, 244, 251, 262, 263, 270, 271). Moreover, previous endocrine insufficiencies do not reverse after surgery (232, 235, 250, 263), except in rare occasions (262, 269, 272). The exact incidence of postradiation endocrine deficiency is difficult to define because the majority of the patients have undergone surgery before irradiation (244). A dose-effect relationship is found, with a significant increase in endocrine dysfunction when maximum doses of radiotherapy exceeded 61 Gy (249). Posttreatment pituitary dysfunction in radiotherapy series (reflecting data from patients receiving surgery plus radiotherapy and radiotherapy only) ranges from 91 to 100% (232, 233, 237, 246, 254, 273) and panhypopituitarism from 80 to 100% (232, 235, 237, 254, 260). The incidence of endocrine complications may be higher in those patients receiving
surgery only (aggressive surgery) vs. those receiving a less extensive surgery and radiotherapy (233), although other studies have shown similar endocrine dysfunction irrespective of the extent of initial surgical resection (236, 250, 269) or type of tumor therapy (226).


2. Therapy

The different therapeutic modalities may also contribute to decreased survival in craniopharyngioma patients. Treatment options include surgery [gross total resection (GTR), subtotal resection (STR), cyst drainage, intracystic bleomycin, or partial removal (PR) with observation], radiotherapy [postoperative conventional external beam radiotherapy, stereotactic radiosurgery, or radiotherapy and intracystic irradiation], or a combination of the above. The two most widely practiced approaches are primary GTR or STR followed by radiation therapy. However, it is difficult to discern which treatment is associated with a better survival rate because there is much heterogeneity among reported groups. Also, there may have been selection bias in the choice of treatment depending on center expertise. Moreover, most studies are retrospective, nonrandomized, and descriptive, with many lacking robust statistical evaluation. The rarity of this tumor limits controlled studies and the experience of any single group or individual in its treatment (233). The variable and extensive nature of its pretreatment morbidity and the competing side effects

<table>
<thead>
<tr>
<th>First author (Ref.)</th>
<th>No. of patients</th>
<th>Follow-up period</th>
<th>Overall survival rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author (Ref.)</td>
<td>(% children at diagnosis)</td>
<td>5 yr</td>
<td>10 yr</td>
</tr>
<tr>
<td>Stripp (232)</td>
<td>75b</td>
<td>1974–2001</td>
<td>96</td>
</tr>
<tr>
<td>Bulow (234)</td>
<td>60 (43%)c</td>
<td>1951–1988</td>
<td>NA</td>
</tr>
<tr>
<td>Pereira (235)</td>
<td>54 (25%)c</td>
<td>1965–2002 (median 10 yr)</td>
<td>95</td>
</tr>
<tr>
<td>Muller (238)</td>
<td>385 (100)c</td>
<td>1980–2001</td>
<td>91</td>
</tr>
<tr>
<td>Regine (239)</td>
<td>58 (31)b</td>
<td>1958–1982</td>
<td>54/64c</td>
</tr>
<tr>
<td>Torrini (241)</td>
<td>54 (100)c</td>
<td>1984–2003</td>
<td>93</td>
</tr>
<tr>
<td>Sung (240)</td>
<td>109 (40)c</td>
<td>1950–1977</td>
<td>67b</td>
</tr>
<tr>
<td>Fisher (236)</td>
<td>30 (100)c</td>
<td>1980–1996</td>
<td>95</td>
</tr>
<tr>
<td>Habrand (237)</td>
<td>37 (100)c</td>
<td>1969–1992</td>
<td>91</td>
</tr>
<tr>
<td>Lin (246)</td>
<td>31 (100)c</td>
<td>1970–2002 (median 6.5 yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Kalaparakal (244)</td>
<td>25 (100)c</td>
<td>1983–1996 (median 10 yr)</td>
<td>100</td>
</tr>
<tr>
<td>Forett (247)</td>
<td>25 (100)b</td>
<td>1980–2002 (median 11 yr)</td>
<td>92</td>
</tr>
<tr>
<td>Scott (246)</td>
<td>61 (100)c</td>
<td>1970–1990</td>
<td>91</td>
</tr>
<tr>
<td>Heteleakis (243)</td>
<td>61 (100)c</td>
<td>1970–1990 (median 10 yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Khafaga (245)</td>
<td>56 (100)c</td>
<td>1975–1996</td>
<td>65</td>
</tr>
<tr>
<td>Devile (242)</td>
<td>75 (100)c</td>
<td>1973–1994 (median 5 yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Regine (249)</td>
<td>19 (100)c</td>
<td>1961–1981 (median 21 yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Karavitaki (250)</td>
<td>121c</td>
<td>1964–2003 (median 8.6 yr)</td>
<td>90</td>
</tr>
<tr>
<td>Van Effenterre (251)</td>
<td>122c</td>
<td>1975–2000</td>
<td>92</td>
</tr>
<tr>
<td>Fahlbusch (253)</td>
<td>148c</td>
<td>1983–1997</td>
<td>92c</td>
</tr>
<tr>
<td>Rajan (255)</td>
<td>173c</td>
<td>1950–1986 (median 12 yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Bartlett (252)</td>
<td>85c</td>
<td>1938–1970</td>
<td>43c</td>
</tr>
<tr>
<td>Pemberton (254)</td>
<td>87c</td>
<td>1976–2002</td>
<td>NA</td>
</tr>
</tbody>
</table>

a Children considered as <16 yr unless otherwise specified.
b Survival rates from diagnosis or initial operation/radiotherapy treatment depending on the study.
c Children considered as ≥20 yr.
d Percentage of children not reported, but patients’ age at diagnosis ranged from 1.5–24.8 yr, with a median of 8.5 yr.
e Children considered as <18 yr.
f Survival rates of 54 and 51% in adults and 84 and 72% in children at 5 and 10 yr, respectively.
g Children considered as ≥15 yr.
h Survival rates of 55 and 40% in adults and 83 and 72% in children at 5 and 10 yr, respectively.
i Patients’ age at diagnosis ranged from 1.1–20 yr with a median of 8.1 yr.
j Children considered as ≥21 yr.
of surgery and radiotherapy make it difficult to evaluate or standardize treatment. The 10-yr survival rates range from 62–100% after GTR (240, 250, 251), 27–86% after STR/PR (240, 250, 251, 276, 277), 74–100% after STR/PR and radiotherapy (232, 240, 250, 276–278), and 81–100% after radiotherapy alone (243, 248, 255). Regarding surgical intervention, perioperative mortality was as high as 33–41% in earlier series before 1950 (279, 280). The introduction of cortisone after 1950 caused prompt improvement in the outcome of surgery, although in a review of a larger series of patients surgically treated after 1950, mortality still varied between 10 and 40% (281). Thanks to the advances of microsurgery, supportive care, and the multidisciplinary management of patients with craniopharyngiomas, the surgical mortality for primary operations reported in studies with mixed age range populations published in the last decade has decreased to 1.1–4.9% (250, 251, 253, 282).

Although it has been suggested that radical excision may cause substantial perioperative morbidity and mortality (226), some studies have reported that the immediate postoperative mortality is not influenced by the extent of surgery excision (234, 250). Tumor recurrence increases the perioperative mortality, but it also increases overall mortality after different therapeutic interventions (234, 240, 249, 250), with overall survival rates ranging between 29 and 86% at 10 yr (240, 250, 270, 283), and 25% at 20 yr (249). The perioperative mortality for surgery after tumor recurrence remains high at 10.5–24% (250, 253, 282). This may be related to the adhesion of the tumor capsule to local structures (241). Variability in studies published in modern series range between 0 and 3.8% (241, 259–261, 285). In combined children and adult/children series, lower surgical mortality rates may be obtained in some (253), but not all (250, 259) transsphenoidal surgery procedures when directly compared with the transcranial approach. However, it is questionable whether the tumors treated using the transsphenoidal and transcranial approach can be compared due to differences in size, extent, and adherence to intracranial structures (251, 253).

3. Hypothalamic damage

Morbidity due to hypothalamic damage includes obesity, cognitive impairment (defective short-term memory and limited concentration span), behavioral abnormalities, defective thirst sensation, sleep disturbances, and thermoregulatory disorders (244, 286). Hypothalamic damage can be due to the tumor itself, surgery, and after radiotherapy (231, 283).

TABLE 9. Contributing mechanisms and risk factors linked to the development of obesity in craniopharyngioma patients

- Lesion/infiltration of hypothalamus (by the tumor and/or its treatment)
- Lesion of ventromedial nucleus (regulator of eating behavior)
- Insensitivity of hypothalamic structures to leptin
- Hypothalamic disinhibition of vaginal output with consequent increased vaginal activity, hyperinsulinemia, and adipogenesis
- Impaired hypothalamic regulation of melatonin rhythm (decreased melatonin levels)
- Extensive surgery
- Hypothalamic radiotherapy >51 Gy
- High BMI SDS before and at the time of diagnosis of craniopharyngioma
- Early and rapid postoperative weight gain
- Recurrence
- Reoperation
- High rate of hydrocephalus requiring a shunt
- High tumor volume (not associated in all studies)
- Reduced physical activity
- Reduced sympathetic tone
- Neurological and visual deficits
- Increased daytime sleepiness and disturbances in the day-night rhythm, in relation to impaired melatonin regulation
- Familial disposition for obesity

Obesity in the general population is associated with increased risk of death (287), and in craniopharyngioma patients, those with severe obesity have reduced survival compared with those with moderate obesity and normal weight (288). Obesity rates vary from 6–30% of craniopharyngioma patients at presentation (232, 237, 247, 250, 256, 259–261, 265, 289), and its incidence increases to 17–62% after surgery (with or without radiotherapy) (232, 235, 237, 241, 244, 246, 247, 259–261, 265, 273, 275, 289, 290). Obesity in patients with craniopharyngioma is multifactorial (Table 9). One of the major causes is the disruption of hypothalamic mechanisms that control satiety, hunger, and energy balance (291). Craniopharyngiomas can be intimately attached to the hypothalamic ventromedial nucleus (241), which regulates eating behavior (292). Lesion of ventromedial areas by aggressive tumors or their treatments can therefore create hyperphagia and obesity (238, 241). Hypothalamic involvement has been associated with the development of obesity in children with craniopharyngioma (286, 292–294). de Vile et al. (295) reported that childhood patients with severe postoperative obesity showed evidence of significant disruption of the normal hypothalamic anatomy assessed by magnetic resonance imaging, with either complete deficiency or extensive destruction of the floor of the third ventricle. Moreover, the extent of surgery and hypothalamic irradiation exceeding 51 Gy have been identified as risk factors for the development of obesity (296). Children with craniopharyngioma who have a higher BMI SDS at the time of diagnosis, as well as those with early and rapid postoperative weight gain, are at highest risk of future
obesity (293, 294, 297). Recurrence (285), reoperation (285, 288), higher rate of a hydrocephalus requiring a shunt (293), and higher tumor volume (288, 293) have also been shown to be linked to the development of obesity, although tumor volume has not been associated with obesity in all studies (289) (Table 9). Other mechanisms may be involved, such as insensitivity of hypothalamic structures to endogenous leptin (298). However, it has also been shown that reduced physical activity, rather than hyperphagia, could be the major factor accounting for obesity in craniopharyngioma patients because the caloric intake in these patients has been found to be similar to that of BMI- and age-matched controls (299). The decreased physical activity and severe obesity could be related to reduced sympathetic tone (300). Other factors such as neurological and visual deficits (299), increased daytime sleepiness, and disturbances of the day-night rhythm may be involved (301).

Decreased melatonin levels are associated with increased daytime sleepiness, BMI, and hypothalamic tumor (301), suggesting an impaired hypothalamic regulation of melatonin rhythm in patients with suprasellar craniopharyngioma (238). A further contributing factor may be increased vagal activity, which leads to hyperinsulinemia and adipogenesis, secondary to hypothalamic disinhibition of vagal output (302). Finally, familial predisposition for obesity could also be a risk factor for the development of severe obesity in craniopharyngioma subjects (293).

The metabolic syndrome is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increase for incident type 2 diabetes mellitus (303). Compared with age-, sex-, BMI-, and pubertal stage-matched healthy controls, craniopharyngioma patients have significantly higher abdominal fat and adverse lipid profile (higher fasting triglycerides and lower HDL cholesterol to total cholesterol ratio), although insulin sensitivity is equally reduced for patients and controls (273). In a Dutch study with both adult and children subjects with craniopharyngioma, a high prevalence of features of the metabolic syndrome such as dyslipidemia, obesity (four times more common), and type 2 diabetes mellitus (twice as common) were also found (235). General obesity and specifically abdominal obesity, together with the adverse lipid profile, and type 2 diabetes could contribute to the increased risk of cardiovascular mortality risk found in craniopharyngioma patients (234, 235).

4. Other factors

"Nontraditional" cardiac risk factors have also been described in patients with craniopharyngioma. A small retrospective study of 12 craniopharyngioma patients found that half of them had at least one abnormality of cardiac structure, function, or rhythm, specifically prolonged QT in 25% of the cohort (304). Besides cardio- and cerebrovascular mortality, other main underlying causes of death in patients with craniopharyngioma are respiratory (12) and infections (235). Finally, it is not clear which other factors may impact on the survival of craniopharyngioma subjects. As already described, it is controversial whether the age at diagnosis has an influence on survival. Similarly, the role of gender as a prognostic factor is not established; some authors report a higher mortality among females (234, 235), but others have not found any gender differences (232, 241, 250, 258). One of the two studies reporting higher mortality rates in females suggested a possible role of estrogen deficiency (235), but the other did not consider that unsubstiuted gonadal insufficiency had a significant impact on enhanced mortality (234). Tumor size could be a prognostic factor because increased survival rates have been shown in tumors under 3 cm (257), and the larger the tumor, the greater will be the damage, both pre-operatively and intra-operatively to vital intracranial structures (256). The histological type as a prognostic factor is also controversial; better 5-yr survival rates have been found in the squamous epithelial type vs. the adamantinous and combined histological types (305), and higher perioperative deaths have also been reported in adult adamantinous tumors (306), but other authors have not found significant differences between the two histological types (307, 308). Several studies have described a more favorable prognosis when tumors lack calcification, especially in adults (257, 306), although no specific pathological feature predicted survival in children (236). In other studies, neither consistency of the tumor (250, 257) nor its location (241, 250) had prognostic importance. In children, the use of modern imaging as well as a good initial performance status (measured according to a functional classification that includes the presence of visual deficits, neurological impairment, and hypopituitarism) have been correlated with enhanced overall survival at 10 yr (237). Finally, it is not clear whether the presence of hydrocephalus constitutes a prognostic factor because increased mortality (256) and lack of association with mortality have been reported (232, 236, 241, 250).

V. Pituitary Radiotherapy and Mortality in Pituitary Patients

A. Introduction

Conventional radiotherapy (CRT) is the most frequently used method of radiation therapy for pituitary tumors. It is most commonly used in patients who have large remnants of pituitary adenomas with evidence of progression after surgery or if surgery does not lead to
normalization of hormone excess. Surgery remains the primary therapy of choice for all pituitary tumors, with the exception of prolactinomas. However, radiotherapy has been shown to be efficacious adjuvant treatment for both tumor (309–317) and endocrine control (318–325). Because stereotactic radiosurgery is only a relatively new therapy, the majority of data regarding efficacy, potential adverse effects of radiotherapy, and in particular effect of radiotherapy on mortality are derived from studies where CRT was used; this review will focus predominantly on studies that used CRT.

B. Cerebrovascular morbidity and mortality following pituitary radiotherapy

Increased cerebrovascular disease and death have been reported in a number of studies after pituitary irradiation. In a series of 156 patients with nonfunctioning pituitary adenoma, increased cerebral infarction rates were found in patients administered higher doses of radiotherapy (326). In a study assessing the role of pituitary radiotherapy in the development of CVA in 331 patients who received pituitary radiotherapy for a number of underlying diagnoses, it was reported that patients who received radiotherapy had a relative risk of CVA of 4.1 (95% CI, 3.6–4.7) compared with the general population (327). On multivariate analysis, the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared with biopsy or no operation, higher doses of radiotherapy, and an underlying diagnosis of acromegaly (327). In a further study, Brada et al. (328) assessed cerebrovascular mortality in 344 patients who had received radiotherapy (79% also had transcranial or transsphenoidal surgery); cerebrovascular disease accounted for 26% of all deaths [33 deaths compared with eight deaths expected (RR, 4.11; 95% CI, 2.84–5.75)], with an even further increase in female patients [RR, 6.9 (95% CI, 4.29–10.6)] compared with males [RR, 2.4 (95% CI, 1.24–4.2); P = 0.002]. Surgery also plays a role in the increased cerebrovascular mortality reported in this study because patients with prior surgery had an increase RR compared with those with no surgery or biopsy alone [RR, 5.19 (95% CI, 3.5–7.42) vs. RR, 1.33 (95% CI, 0.27–3.88); P = 0.02], but there may be several confounders that led to this increase (328).

C. Hypopituitarism following pituitary radiotherapy

More than 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiencies within the following decade (315, 318, 329). The classic pattern of pituitary hormone deficiency to radiotherapy of GH deficiency (100% at 5 yr), gonadotropin deficiency (91% at 5 yr), ACTH deficiency (77% at 5 yr), and TSH deficiency (42% at 5 yr) (329) is not always seen, and deficiencies may occur in any order. Because deficiencies can occur at any time point, even up to 20 yr later, long-term testing is required (309, 315, 330). With CRT, the speed of onset of hypopituitarism is related to the total and fractional doses of radiotherapy (315), and the rate of hypopituitarism increases from time of irradiation.

A number of studies have described an increased mortality in patients with hypopituitarism compared with age- and sex-matched controls, which is covered in Section I (11, 12, 16, 18). In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. In total, nearly 1900 patients have been included in these studies, and approximately 50% had radiotherapy; in two studies, radiotherapy was not associated with increased mortality (11, 16), and in the third study, it was not possible to investigate the link because nearly all patients had radiotherapy [304 of 344 (88.4%) received radiotherapy with an overall cerebrovascular mortality RR of 3.39 (95% CI, 2.27, 4.99); men, 2.64 (95% CI, 1.44–4.42); and women, 4.91 (95% CI, 2.62–8.4)] (18). In the largest series in the literature, Tomlinson et al. (12) reported that radiotherapy significantly increased mortality with an SMR of 2.32 (95% CI, 1.7–3.14; P = 0.004) in the radiotherapy group compared with 1.87 (95% CI, 1.62–2.16) in the general cohort of patients with hypopituitarism. In particular, patients who had received radiotherapy had an elevated cerebrovascular risk [SMR, 4.36 (95% CI, 2.48–7.68); P = 0.001] (Fig. 15). Erfurth et al. (331) compared radiation regimens and duration of symptoms of hypopituitarism in 342 patients treated with surgery and radiotherapy. They compared 32 patients who had died from cerebrovascular disease to 62 matched patients from the cohort who had not died from CVA. They found no significant difference between the

![Fig. 15. Effect of pituitary radiotherapy on total and specific-cause mortality in patients with hypopituitarism. (Reprinted from J. W. Tomlinson et al.: Lancet 357:425–431, 2001 (12), with permission from Elsevier.)](image-url)
two groups for a number of irradiation parameters such as maximum absorbed dose, maximum biological equivalent dose, field size, and number of fractions. The only difference found was a longer duration of symptoms of hypopituitarism in the cerebrovascular mortality group. They concluded that untreated hormone deficiency may be more directly implicated in cerebrovascular mortality than radiotherapy per se. The increase in cerebrovascular mortality after radiotherapy has also been described in patients with acromegaly (Section II).

D. Mechanisms of radiation injury

Radiation injury to the vasculature was first described more than 100 yr ago (332) and has subsequently been reported to be one of the commonest adverse effects of therapeutic radiotherapy. Radiotherapy leads to damage of both large and small vessels, with a predilection to smaller vessels (333) because endothelial cells are radiosensitive (334). In capillaries and sinusoids, irradiation can lead to focal cytoplasmic degeneration, vacuolation, and irregular projections of the cytoplasm to the vessel lumen. In the early stages, this leads to increased capillary permeability and intracellular edema. This may be followed by platelet and fibrin thromboses leading to the detachment of endothelial cells from their basement membrane (332), which may ultimately lead to necrosis of the endothelial cell and wall rupture with resulting loss of a segment of microvessel (335). Less severe damage often results in permanent dilatation and telangetasia; there may also be compensatory endothelial cell proliferation, which, if the insult is not significant, can reestablish microvascular segments (335). Arteriolar lesions can also occur. This is most commonly in the form of myointimal proliferation that leads to narrowing of the lumen, and foamy macrophage plaques may also develop (particularly likely to be due to radiation if they occur in arterioles measuring less than 100 μm in diameter). Fibrin may accumulate in the media or intima of arteriole, leading to fibrinoid necrosis, or the media may be replaced by dense collagen-rich tissues leading to hyalinization of the media (332). Also, some studies have shown an acute lymphocytic vasculitis affecting the media, intima, and adventitia of medium-sized arteries localized to the radiation field leading to fibrous exudate and occasionally thrombosis (333). In arteries measuring more than 100 μm, lesions are observed less frequently than in smaller vessels, and these lesions are similar to those seen in atherosclerosis. However, because the patients are often young and the plaques are limited to the radiation field, one can assume that they may be secondary to the radiation therapy.

These changes may be clinically important, as seen in patients with pituitary radiotherapy who have increased risks of cerebrovascular death but also in other patient groups who receive radiotherapy. A recent retrospective analysis of 4665 Hodgkin’s disease patients who had irradiation to the heart followed up for 7 yr revealed a RR of 2.56 (95% CI, 1.11–5.93) for myocardial infarct, whereas those treated with chemotherapy alone had no increase (336). Another study assessing 2232 Hodgkin’s patients (79% >40 Gy) followed for 9.5 yr, the RR for myocardial infarct in patients treated with radiotherapy alone was 3.8 (95% CI, 2.8–4.8). This RR increased with the latency period and was highest in patients who had been treated with radiotherapy before the age of 20 (337).

E. Secondary oncogenesis following pituitary radiotherapy

Secondary oncogenesis after pituitary radiotherapy is a controversial area. It is impossible to calculate the true incidence of tumors arising after pituitary radiotherapy because most of the literature covers case reports or cross-sectional studies. Another factor to take into account is that patients with pituitary disease receive disproportionately frequent imaging, which historically took the form of recurrent computed tomography scans and, in more recent years, magnetic resonance imaging; a more appropriate control group might be patients treated with surgery alone rather than normal population controls (338) because they also undergo regular surveillance imaging. In some studies, the incidence of secondary neoplasm is as high as 1–2%, occurring with a latency of 8–15 yr (339–341). One study has estimated an incidence of extracranial tumors in non-functioning adenoma patients to be 3.9-fold that of the general population, irrespective of whether or not the patient had radiotherapy (342); therefore, having a pituitary adenoma may lead to some underlying increased susceptibility to tumorogenesis. Secondary intracranial tumors (most commonly gliomas or meningiomas) due to pituitary irradiation are now rarer due to newer techniques that expose a smaller volume of cranial tissue to radiation (343).

VI. Summary

Pituitary disease is associated with increased mortality predominantly due to vascular disease. Control of cortisol secretion and GH hypersecretion (and cardiovascular risk factor reduction) are key in the reduction of mortality in patients with Cushing’s disease and acromegaly, retrospectively. For patients with acromegaly, the role of IGF-I is less clear-cut. Confounding pituitary hormone deficiencies such as gonadotropins and particularly ACTH deficiency (with higher doses of hydrocortisone replacement) may have a detrimental effect on outcome in patients with pituitary disease. Pituitary radiotherapy is an additional fac-
tor that has been associated with increased mortality (particularly cerebrovascular). Although SMRs in pituitary disease are falling due to improved treatment, SMRs for many conditions are still elevated above that of the general population, and as such further measures are needed. Craniohypophysis patients have a particularly increased risk of mortality as a result of the tumor itself and treatment to control tumor growth; this is a key area for future research to optimize the outcome for these patients.

Acknowledgments

Address all correspondence and requests for reprints to: Professor Paul M. Stewart, Institute of Biomedical Research, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom. E-mail: P.M.Stewart@bham.ac.uk.

M.S. is funded by The Medical Research Council as a Clinical Training Fellow. J.W.T. is funded by The Medical Research Council as a Senior Clinical Fellow.

Disclosure Summary: M.S., A.A.-A., A.S.B., and J.W.T. have nothing to declare. J.A. has received lecture fees from Novartis and Ipsen. A.A.T. has received research grants from Novo Nordisk, is a KIMS board member, and has received lecture fees from Pfizer and Novo Nordisk. M.C.S. has received lecture fees from Novartis. P.M.S. has served on an advisory board of Novartis.

References

10. Toogood AA, Beardwell CG, Shalet SM 1994 The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol (Oxf) 41:511–516
25. Stewart PM, Toogood AA, Tomlinson JW 2001 Growth
44. de Boer H, Blok GJ, Voerman HJ, Phillips M, Schouten JA 1994 Serum lipid levels in growth hormone-deficient men. Metabolism 43:199-203
54. Thuesen L, Jorgensen JO, Muller JR, Kristensen BO, Skakkebaek NE, Vahl N, Christiansen JS 1994 Short and
long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults. Clin Endocrinol (Oxf) 41:615–620
61. Andreassen M, Vestergaard H, Kristensen LØ 2007 Concentrations of the acute phase reactants high-sensitivity C-reactive protein and YXL-40 and of interleukin-6 before and after treatment in patients with acromegaly and growth hormone deficiency. Clin Endocrinol (Oxf) 67:909–916


175. Perry I, Stewart PM, Kane K 2003 Colorectal screening guidelines in acromegaly. Gut 52:1387


1992 Sleep architecture and sleep apnea in patients with
Cushing’s disease. Sleep 15:514–518

206. Saruta T, Suzuki H, Handa M, Igarashi Y, Kondo K, Senba
S 1986 Multiple factors contribute to the pathogenesis of
hypertension in Cushing’s syndrome. J Clin Endocrinol
Metab 62:275–279

207. Magiakou MA, Mastorakos G, Zachman K, Chrousos GP
1997 Blood pressure in children and adolescents with
Cushing’s syndrome before and after surgical care. J Clin
Endocrinol Metab 82:1734–1738

208. Biller BM, Grossman AB, Stewart PM, Melmed S,
Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus
AR, Hofland LJ, Klilianski A, Lacroix A, Lindsay JR,
Newell-Price J, Nieman LK, Petersson S, Sonino N, Stella
Treatment of adrenocorticotropin dependent Cushing’s
syndrome: a consensus statement. J Clin Endocrinol Metab
93:2454–2462

209. Mueisan ML, Lupia M, Salvetti M, Grigoletto C, Sonino
N, Boscaro M, Rosei EA, Mantero F, Fallo F 2003 Left
ventricular structural and functional characteristics in
Cushing’s syndrome. J Am Coll Cardiol 41:2275–2279

Assessment of left ventricular diastolic function and Tei
index by tissue Doppler imaging in patients with Cushing’s
syndrome. Echocardiography 25:182–190

211. Faggiano A, Pironello R, Spiezia S, De Martino MC,
Cardiovascular risk factors and common carotid artery
caliber and stiffness in patients with Cushing’s disease
during active disease and 1 year after disease remission. J Clin
Endocrinol Metab 88:2527–2533

212. Van Zante B, Nur E, Squizato A, Dekkers OM, Twickler
MT, Flters E, Gerdes VE, Biller HR, Brandjes DP 2009
Hypercoagulable state in Cushing’s syndrome: a systemat-
ic review. J Clin Endocrinol Metab 94:2743–2750

213. Arnaldi G, Mancini T, Polenta B, Boscaro M 2004 Cardio-
vascular risk in Cushing’s syndrome. Pituitary 7:253–256

214. Rockall AG, Sohaib SA, Evans D, Kaltsas G, Isidori AM,
Hepatic steatosis in Cushing’s syndrome: a radiological
assessment using computed tomography. Eur J Endocrinol
149:543–548

215. Würzburger MI, Prelević GM, Brkic SD, Vukovcica S,
Pendic B 1986 Cushing’s syndrome—transitory immune

216. Kim DS, Park SK, Choi WH, Kim TW, Choi YY, Jeon SC,
Ryu JS 2000 Pneumocystis carinii pneumonia associated
with a rapid reduction of cortisol level in a patient with
ectopic ACTH syndrome treated by octreotide and keto-
conazole. Exp Clin Endocrinol Diabetes 108:146–150

217. Arlt A, Harbeck B, Anlauf M, Alkatout I, Klöppel G,
Fölsch UR, Biewig B, Mönig H 2008 Fatal Pneumocystis
jiroveci pneumonia in a case of ectopic Cushing’s syn-
drome due to neuroendocrine carcinoma of the kidney.
Exp Clin Endocrinol Diabetes 116:515–519

adrenalectomy in paraneoplastic Cushing’s syndrome with
334:497–498

219. Lionakis MS, Kontoyiannis DP 2003 Glucocorticoids and
invasive fungal infections. Lancet 362:1828–1838

220. Hill AT, Stewart PM, Hughes EA, Mcleod DT 1998 Cushing’s
disease and tuberculosis. Respir Med 92:604–606

221. Dutta P, Bhaniali A, Bhat MH, Sinha SK 2005 Cytomeg-
alovirus infection in a patient with endogenous Cushing’s

222. Razavi B, O’Toole J, Schilling M, Razavi M 2000 Cryp-
tococcal meningitis, an endocrine emergency? Lancet 355:
1426

223. Boscaro M, Fallo F, Sonino N 1994 Disseminated nocard-
diosis in a patient with Cushing’s syndrome. J Endocrinol
Invest 17:443–445

224. Chrousos GP 1995 The hypothalamic-pituitary-adrenal
332:1351–1362

225. Nieman LK, Biller BM, Findling JW, Newell-Price J,
Savage MO, Stewart PM, Montori VM 2008 The diagno-
sis of Cushing’s syndrome: an Endocrine Society Clinical
Practice Guideline. J Clin Endocrinol Metab 93:1526–
1540

226. Karavitaki N, Cudlip S, Adams CB, Wass JA 2006 Cria-

9:323–326

228. Bunin GR, Surawicz TS, Witman PA, Preston-Martín S,
Davis F, Brunner JM 1997 The descriptive epidemiology of
cranioophyngioma. Neurosurg Focus 3:e1

229. Bauchet L, Rigau V, Mathieu-Daudé H, Fabbro-Peray P,
Palenzuela G, Figarella-Branger D, Moritz J, Puget S,
Bauchet F, Pallusseau I, Duffau H, Coubes P, Trétrarre B,
Labrousse E, Dhelemmes P 2009 Clinical epidemiology
for childhood primary central nervous system tumors. J
Neurooncol 92:87–98

230. Boongird A, Laothamatas J, Larbcharoen sub N,
Phudhicharoenrat S 2009 Malignant cranioophyngioma;
case report and review of the literature. Neuropathology
29:591–596

231. Kalaparakul JA 2005 Radiation therapy in the manage-
ment of pediatric cranioophyngiomas—a review. Childs
Nerv Syst 21:808–816

232. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA,
Goldwain JW, Moshang T, Rorke LB, Phillips PC, Sutton
LN, Shu HK 2004 Surgery with or without radiation ther-
apy in the management of cranioophyngiomas in children
and young adults. Int J Radiat Oncol Biol Phys 58:714–
720

233. Merchant TE, Kiehna EN, Sanford RA, Mulher RN,
Thompson SJ, Wilson MW, Lustig RH, Kun LE 2002 Cra-
niophyngioma: the St. Jude Children’s Research Hospi-
53:533–542

Nordström CH, Erfurth EM 1998 Postoperative prognosis
in cranioophyngioma with respect to cardiovascular mor-
tality, survival, and tumor recurrence. J Clin Endocrinol
Metab 83:3897–3904

235. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH,
Biermasz NR, van Thiel SW, Corssmit EP, Smit JW,
Rolfsema F, Romijn JA 2005 High prevalence of long-
term cardiovascular, neurological and psychosocial morbidity after treatment for cranioangiomioma. Clin Endocrinol (Oxf) 62:197–204
269. Honegger J, Buchfelder M, Fahrbuch R 1999 Surgical


291. Daouss C, Dunn AJ, Foy PM, MacFarlane IA, Pinkney JH 2005 Endocrine and neuroanatomic features associated with weight gain and obesity in adult patients with hypothalamic damage. Am J Med 118:45 50


295. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R 1996 Obesity in childhood craniopharyngioma: relation to postoperative hypothalamic damage shown by magnetic resonance imaging. J Clin Endocrinol Metab 81:2734 2737


300. Roth CL, Hunneman DH, Gebhardt U, Stoffel-Wagner B, Reinherz T, Müller HL 2007 Reduced sympathetic metab-


Medical therapy in acromegaly

Mark Sherlock, Connor Woods and Michael C. Sheppard

Abstract | Acromegaly is a rare disease characterized by excess secretion of growth hormone (GH) and increased circulating insulin-like growth factor 1 (IGF-1) concentrations. The disease is associated with increased morbidity and premature mortality, but these effects can be reduced if GH levels are decreased to <2.5 μg/L and IGF-1 levels are normalized. Therapy for acromegaly is targeted at decreasing GH and IGF-1 levels, ameliorating patients’ symptoms and decreasing any local compressive effects of the pituitary adenoma. The therapeutic options for acromegaly include surgery, radiotherapy and medical therapies, such as dopamine agonists, somatostatin receptor ligands and the GH receptor antagonist pegvisomant. Medical therapy is currently most widely used as secondary treatment for persistent or recurrent acromegaly following noncurative surgery, although it is increasingly used as primary therapy. This Review provides an overview of current and future pharmacological therapies for patients with acromegaly.


Introduction

Patients with the rare disease, acromegaly, have excess growth hormone (GH) secretion and increased circulating levels of insulin like growth factor 1 (IGF-1). The disease is associated with increased morbidity and premature mortality; reported standardized mortality ratios range between 1.3 and 3.0. 

This increase in mortality has been reported to be reduced if GH levels can be decreased to <2.5 μg/L and IGF-1 levels are normalized. Life expectancy of patients with acromegaly has also increased over the past few decades, probably because of improvements in the surgical and pharmacological management of this condition.

Therapy for acromegaly is targeted at reducing excess morbidity and mortality by decreasing levels of GH and IGF-1, ameliorating symptoms and decreasing any local compressive effects of the pituitary adenoma. Currently, the therapeutic options for acromegaly include surgery, radiotherapy and medical therapies such as dopamine agonists, somatostatin receptor ligands (SRLs) and the GH receptor antagonist pegvisomant. Medical therapy is used predominantly as secondary therapy for persistent or recurrent acromegaly following noncurative surgery, although it can be used as primary therapy for patients in whom surgery is not an option or as short-term therapy before surgery. Consensus guidelines have described the optimal management and the role of medical therapy in treating patients with acromegaly. This Review outlines currently available and future options for the medical management of patients with acromegaly.

A number of important issues need to be mentioned before interpreting the data with regard to medical therapies in patients with acromegaly. These issues include the heterogeneity in the size and design of studies, whether medical treatment is given as first-line or second-line therapy, and selection bias (Box 1).

Somatostatin receptor ligand therapy

Somatostatin receptor interaction

Somatostatin is a cyclical peptide with a short half-life (2–3 min) that is synthesized in many tissues. When synthesized in the hypothalamus, this peptide plays a key role in GH secretion by inhibiting release but not synthesis of GH via its action on somatostatin receptors (SSRs). Although SSR1, SSR2, SSR3 and SSR5 are all expressed on GH-secreting pituitary adenomas, SSR2 and SSR5 are more abundantly expressed than the other types. In vitro and in vivo studies have shown that expression of SSR2 correlates well with the GH-lowering effect of the SRL octreotide, which suggests that the main GH-lowering effect of this drug is through SSR2. Although SSR5 is expressed at higher levels compared with SSR2, no correlation was found between the expression level of SSR5 and effects of SRLs (including octreotide) on GH secretion in cultured pituitary adenomas from patients with acromegaly. Feelders et al. have reviewed the area of somatostatin receptor specificity in detail.

Pharmacology

Subcutaneous octreotide is administered as a thrice-daily injection as its half-life is 2 h; this multiple daily dosing regimen has limitations, including issues with compliance and therapeutic escape before the next dose is administered. The starting dose is usually 100 μg three times per day, which can be increased in increments to a maximum of 500 μg three times per day. The first long-acting formulation to be synthesized was octreotide long-acting release. This formulation of octreotide is delivered by microspheres, which lead to an increase in the serum level of the drug on day 1 post-injection followed by a
Box 1 | Interpreting data on medical therapies in acromegaly

- Acromegaly is a rare condition and as such the numbers of participants enrolled in studies may be relatively small and studies are often multicenter.
- Applicability heterogeneity exists in study design, patient characteristics and patient selection between studies, so direct comparison and meta-analysis may be difficult.
- Patients who receive the drug as primary therapy should be differentiated from those who receive the drug as secondary therapy.
- Large variances exist between studies in the number of patients who have had surgery and radiotherapy prior to medical therapy; this point is important as it affects the subsequent response to therapy both from the perspective of hormone hypersecretion and tumor shrinkage.
- In studies that assess the effect of therapy on tumor size, wide variation exists in the criteria used to assess tumor shrinkage.
- Duration of therapy and follow-up differs between studies and, as such, they may not be comparable, as some therapies function better the longer the patient receives them; furthermore, the effect of radiotherapy on acromegaly increases with time following therapy.
- In studies assessing the efficacy of somatostatin receptor ligands (SRLs), therapy may be with short-acting octreotide or one of the long-acting SRL preparations and, as such, direct comparison and meta-analysis may be difficult.
- Selection bias may exist for trials involving SRL therapy, because in some cases patients will have demonstrated a response to short-acting SRL therapy as an inclusion criterion for enrolment in the study.

The second long-acting SRL synthesized was lanreotide, which is available in two formulations: lanreotide sustained release and lanreotide autogel® (Société de Conseils de Recherches et d’Applications Scientifiques, Paris, France). Lanreotide sustained release comprises lanreotide incorporated into a biodegradable polymer micro-particle, which leads to a rapid release of the drug 1–2 h after injection followed by a prolonged drug release phase peaking 2 days later.14 Lanreotide sustained release has a mean half-life of 5 days and, therefore, injections are required every 10–14 days.14 Lanreotide autogel® is a depot preparation of lanreotide in a supersaturated aqueous solution.14 Administration of lanreotide autogel® provides a peak concentration on day 1; however, this formulation has a longer half-life (25 days) than lanreotide sustained release.14 The elimination of SRLs, such as octreotide or lanreotide, from the body is predominantly via biliary secretion.

Biochemical control

Subcutaneous octreotide

In a study by Vance et al., treatment with subcutaneous octreotide lead to a decrease in GH and IGF-1 levels in 94% and 92% of patients with acromegaly, respectively.22 These reductions led to a normalization of IGF-1 concentration in 46% of patients and a GH level of <5 μg/l in 45% of patients and were associated with a reduction in tumor size of >20% in 44% of patients.22 In a study by Ezzy et al., 21% of patients on 250 μg subcutaneous octreotide three-times daily and 16% of patients on 100 μg subcutaneous octreotide three-times daily achieved a GH level of <2 μg/l.22 IGF-1 levels were normalized in 68% of patients in the 250 μg group and in 55% of those in the 100 μg group. Tumor shrinkage of >1 mm in diameter occurred in 37% of cases in the 250 μg group and in 19% in the 100 μg group during the 6-month treatment period.22

These studies had limitations that included a non-age-adjusted reference range for IGF-1, open labeling and variable dose escalation (or fixed dose in the study by Ezzy et al.).22,25 A number of studies have reported no difference in efficacy between subcutaneous and long-acting SRLs.24-27 However, subcutaneous SRL therapy has been replaced by long-acting SRL therapy owing to improved compliance and patient preference, but it should be noted that long-acting SRL therapy may be considerably more expensive (depending on the dose of short-acting SRL used).

Long-acting somatostatin receptor ligands

An analysis of prospective studies has reported that long-acting SRLs reduce GH levels to <2.5 μg/l and normalize IGF-1 levels in 48–52% and 42–68% of patients with acromegaly, respectively.23 A retrospective study of long-acting SRL use in clinical practice has reported similar responses (48.8% of patients achieved a GH <2.5 μg/l and 45.7% achieved an IGF-1 in the normal age-related reference range).24 This similarity shows that GH and IGF-1 reductions observed with long-acting SRLs in clinical trials are possible to achieve in routine clinical practice. A 5-year prospective study of 45 patients with acromegaly treated with long-acting SRLs as first-line therapy, reported GH control in 100.0%, IGF-1 control in 97.8% and tumor shrinkage of 74.9% in the octreotide long-acting release group and 78.2% in the lanreotide group.26 Direct comparison of different formulations of SRLs used in clinical trials is difficult for a number of reasons, which have been described in Box 1. Another key factor is duration of therapy; as there is some evidence that control of acromegaly by SRLs may improve with time, independent of dosage change and, therefore, if studies are of different duration they may not be comparable.28,29 In two of the largest studies to assess the efficacy of octreotide long-acting release, 66–75% of patients achieved IGF-1 levels
within the normal reference range and 70–72% achieved GH levels <2.5 μg/l.\textsuperscript{3,4,5}

The findings of these studies may be limited by therapeutic and selection bias, as in the study by Lancerajian et al.,\textsuperscript{12} patients were selected on the basis of known responsiveness to subcutaneous octreotide and in the study by Cozzi et al.\textsuperscript{30} only patients with >20% decreases in GH and IGF-1 levels remained in the study for its full duration. Baldelli et al.\textsuperscript{16} have assessed the efficacy of lanreotide sustained release. In this study, GH and IGF-1 levels were controlled in 77% and 63% of patients, respectively, and 22% of patients had clinically significant tumor shrinkage of >20% in volume.\textsuperscript{17} Verhuel\textit{ et al.} have also assessed the efficacy of lanreotide sustained release; these researchers found that GH was reduced to <2.5 μg/l in 45% of patients, IGF-1 levels were in the normal reference range in 44% and 36% had clinically significant tumor shrinkage of >25% volume.\textsuperscript{18}

The question as to which long-acting SRL is most efficacious and the data comparing octreotide long-acting release and the different preparations of lanreotide are beyond the scope of this Review, but have been extensively reviewed by Murray and Melmed.\textsuperscript{19}

**Antitumoral effects**

The antitumoral effects of SRLs have been extensively reviewed by Bevan in 2005.\textsuperscript{20} The mechanisms by which SRLs inhibit growth and proliferation of tumor cells are complex and include cell-cycle arrest, induction of apoptosis and decreased angiogenesis.\textsuperscript{21} Losa et al.\textsuperscript{22} compared Ki-67 immunostaining (a marker of cell cycling) in 39 patients treated with SRLs and 39 controls who were not treated preoperatively with SRLs, but who were matched for age, sex, tumor size and extension; they reported a decreased Ki-67 index with no increase in apoptosis in the treated patients, which suggests that SRLs have important antiproliferative effects. Further evidence comes from Danila et al.\textsuperscript{23} who have reported that inhibition of cell proliferation by SRLs occurs independently of inhibition of GH secretory pathways.\textsuperscript{24}

The studies that have assessed changes in tumor size following SRL therapy have used different imaging modalities (CT and MRI) and different assessments of tumor shrinkage (tumor diameter or volume). These differences between the studies make comparison of results difficult. Most studies define a 10–25% reduction in tumor volume as clinically significant tumor shrinkage. Studies that have assessed tumor shrinkage include those involving patients on short-acting or long-acting SRLs and those receiving SRLs as a primary or secondary therapy. In the review by Bevan,\textsuperscript{25} 217 of 478 patients (45%) who received SRL therapy experienced tumor shrinkage. The reduction in tumor size was more prevalent in the primary medical therapy group (51%) than the secondary medical therapy group (27%).\textsuperscript{26}

Predictors of tumor shrinkage in patients receiving SRL therapy include prior surgery and radiotherapy; specifically, patients who have received radiotherapy and are surgery naive have the greatest reduction in tumor volume in response to SRL therapy. Data are conflicting with regard to the initial size of the tumor in relation to the amount of shrinkage that occurs with SRL therapy. Some researchers report that microadenomas are more likely to shrink than larger adenomas,\textsuperscript{27} whilst others report that macroadenomas are more likely to shrink than smaller adenomas.\textsuperscript{28,29} Furthermore, other groups report no association between initial tumor size and the subsequent amount of shrinkage following SRL therapy.\textsuperscript{30}

A few studies have suggested that patients who have a biochemical response also have a tumor volume response.\textsuperscript{31,32} In the patients in whom GH levels decreased by >50%, tumor shrinkage was observed in 38%.\textsuperscript{33} By comparison, 29% of the patients who had a <50% reduction in their GH levels experienced tumor shrinkage. Verhuel\textit{ et al.}\textsuperscript{34} reported the greatest tumor shrinkage in patients with the greatest IGF-1 response to SRL therapy. By contrast, a number of other studies did not show any relationship between biochemical response and tumor response.\textsuperscript{35,36,37}

**Primary medical therapy**

Unlike surgery, primary medical therapy cannot cure acromegaly but, as this approach can control hormone hypersecretion, it may be indicated in patients who are unlikely to achieve cure following surgery—namely, those with macroadenomas with clinically significant extension or those who refuse or are poor candidates for surgery. Importantly, even in patients who show favorable biochemical and tumor shrinkage responses with SRL therapy, once the therapy is stopped, the tumor regrows and excess levels of GH and IGF-1 return.\textsuperscript{38,39}

The majority of data regarding primary SRL therapy come from nonrandomized studies rather than from prospective randomized trials of surgery versus SRL therapy. In these studies, SRL treatment as a primary therapy is effective in reducing levels of GH and achieving an IGF-1 in the normal range in approximately two-thirds of patients.\textsuperscript{1,2,3,4,5,6,7}

A review has reported that in 14 studies assessing primary medical therapy in patients with acromegaly (n = 424), 36.6% of patients had clinically significant tumor shrinkage >20%.\textsuperscript{6,36} The wide range in percentages of patients with clinically significant tumor shrinkage in the studies reviewed most probably relates to different definitions of clinically significant shrinkage (range 10–45%) and differences in how this effect was assessed radiologically.\textsuperscript{37}

No difference in tumor shrinkage rates existed between patients treated with subcutaneous or long-acting SRLs (43.0% versus 37.8%).\textsuperscript{40} However, a greater tumor shrinkage rate occurred in patients who received SRL therapy for macroadenomas than for microadenomas.\textsuperscript{38,39,40}

**Pre-operative somatostatin receptor ligand therapy**

In a prospective study by Carlsen et al.,\textsuperscript{41} 30 patients who had primary surgical therapy were compared with 32 patients who had preoperative SRL therapy followed by surgery. No statistically significant increase in biochemical cure was found in the total patient group who received preoperative SRL therapy. However, in the subgroup of patients with macroadenomas, an improved cure rate was observed with preoperative SRL therapy. The authors of this trial
concluded that future well-designed studies were required to further assess the role of preoperative SRL therapy. Lucas et al. assessed the efficacy of primary medical therapy with lanreotide sustained release in 104 patients with acromegaly for 1–3 months prior to transspHENoidal surgery. Overall, 29% of patients had a >20% reduction in size of tumor, whereas 66% had some tumor reduction and 18% had >20% increase in tumor size. Biochemical control was the sole predictor of tumor shrinkage. However, longer studies have shown no relationship between GH response and tumor shrinkage. Univariate analysis of surgical outcomes revealed that predictors of persistent disease following surgery in patients who had received preoperative SRL therapy were younger age, higher levels of GH and IGF-1 at diagnosis, larger preoperative tumor volume and extension into the suprasellar region or cavernous sinus. However, as this study lacked a control group it is difficult to accurately assess the role of preoperative SRL therapy without further randomized, controlled trials. Importantly, some patients enrolled in this study developed cavernous sinus extension during treatment, which may have a negative effect on surgical outcome.

Adverse effects of somatostatin receptor ligands
In clinical trials of SRL therapy, the most frequent adverse effects encountered are gastrointestinal nature, such as nausea, flatulence, cramps and diarrhea, which are mostly mild to moderate in severity and are often transient. Injection site discomfort, pain and erythema is also often described but is rarely severe enough to lead to drug cessation. The other concern relates to the development of biliary abnormalities (including sediment, sludge, microliathis and gallstones); however, these abnormalities are mostly asymptomatic. Clinicians need to be aware of this possible adverse effect, particularly when patients stop SRL therapy, as gallbladder contraction may occur leading to symptoms. Patients with acromegaly have an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus and SRL therapy has also been reported to increase the risk of hyperglycemia (as these therapies impair insulin secretion). Other adverse effects include rarely reported cases of liver function abnormalities, anaphylaxis and hair loss.

Dopamine agonists
Dopamine agonists bind to D2 dopamine receptors in the pituitary gland and suppress secretion of prolactin and GH in patients with acromegaly. They have been used in acromegaly as an individual treatment or in combination with an SRL. Three main dopamine agonist agents are used in the treatment of hyperprolactinemia and GH excess: bromocriptine, cabergoline and quinagolide.

Bromocriptine
Bromocriptine was the first dopamine agonist to be widely used in the treatment of acromegaly. This agonist was associated with moderate success, as it normalized IGF-1 and GH levels in 10% and 20% of patients, respectively. The utility of dopamine agonists, in particular bromocriptine, has been limited by the disappointing rates of biochemical response reported, and clinically relevant adverse effects that may occur with the high daily doses (40–60 mg), such as nausea, vomiting, diarrhea, fatigue and orthostatic hypotension. Sherlock et al. have, however, reported that 42.4% and 23.6% of patients taking lower doses of bromocriptine (median 7.5 mg per day) achieved GH and IGF-1 reductions, respectively. These responses, although not as good as those reported with SRL therapy, reduced GH and IGF-1 levels into the range associated with normalization of mortality in 28% and 32.1% of patients, respectively, and, therefore, may be of use for patients with mildly active disease.

Cabergoline
The second-generation dopamine agonist cabergoline has been demonstrated to be potentially more effective than bromocriptine in the treatment of acromegaly, as treatment normalized GH and IGF-1 levels in 46% and 39% of 64 patients, respectively. Moreover, Moyer and colleagues found that on a median weekly dose of 1.75 mg of cabergoline, normalization of both IGF-1 and GH levels occurred in 27% of patients. The greater efficacy of cabergoline than bromocriptine may reflect a number of factors, including greater biological potency, a longer half-life and less adverse effects, leading to better compliance. Data relating to cabergoline therapy in acromegaly is limited, which most probably relates to the fact that this drug was introduced into clinical practice for patients with acromegaly at around the same time as SRL therapy—which is more likely to be used owing to superior efficacy in both hormonal control and tumor reduction.

In the largest study performed to date that has assessed the efficacy of cabergoline in patients with acromegaly, Abs et al. treated 64 unselected patients with cabergoline for 3–40 months. The majority of patients received 1.00–1.75 mg of cabergoline per week (although some patients received doses of up to 3.5 mg per week). In the 48 patients who had pure GH-secreting tumors, cabergoline normalized IGF-1 levels in 35% and suppressed GH levels to <2 µg/l in 44%. A greater effect was observed in the subset of patients whose tumors co-secreted GH and prolactin, among whom IGF-1 levels were normalized in 50% of cases and GH levels were suppressed to <2 µg/l in 56%.

In this study by Abs et al., patients with relatively low baseline levels of GH and IGF-1 were more likely to respond to cabergoline therapy than those with higher baseline levels. When patients were categorized into those with the highest pre-therapy IGF-1 levels (>750 µg/l) compared to others (<750 µg/l), the rate of normalization of IGF-1 was 22% and 43%, respectively. Combined data from four smaller studies reveal less impressive response levels: IGF-1 levels normalized in 22% of patients treated with cabergoline; however, the rate of response was extremely variable (0–27%).

Data on long-term treatment with quinagolide is not as robust as that for bromocriptine or cabergoline, but available data in small numbers of patients report that IGF-1 levels normalize in between 17% and 43% of patients treated with this drug.
Predictive value of hyperprolactinemia
The data as to whether the co-secretion of prolactin is predictive of response to dopamine agonist therapy—in other words, patients with elevated prolactin levels have a greater decrease in GH and IGF-1 following dopamine agonist therapy—is conflicting. Some studies conclude that tumors that co-secrete prolactin and GH have a greater response to dopamine agonist therapy than those that solely secret GH, whereas others show no effect. Similarly, no agreement exists concerning the association between positive GH and prolactin immunohistochemistry of the tumor and a favorable response to dopamine agonist therapy, with some studies reporting this association and others not. Patients who have a normal prolactin level should, therefore, not necessarily be excluded from receiving dopamine agonist therapy on the assumption that there will be a limited GH and IGF-1 response.

Adverse effects of dopamine agonists
The most frequent adverse effects of dopamine agonist therapy are nausea, constipation, headache, mood disturbance, nasal stuffiness and dizziness. Studies in patients treated with dopamine agonists for prolactinomas have shown less frequent adverse effects with cabergoline than with bromocriptine. Indeed, in the largest study of cabergoline in patients with acromegaly, only 3% of patients had adverse effects that required drug withdrawal (despite relatively high doses).

In the past 5 years, cabergoline and pergolide (which has been removed from the US market) have been associated with an increased risk of cardiac valvular dysfunction in patients receiving high-dose therapy for Parkinson disease. However, patients receiving dopamine agonist therapy for endocrine indications differ from the Parkinson disease cohorts in a number of key respects, including cumulative dose exposure and age. Since these findings were published, a number of studies have assessed the risk of clinically relevant valvular lesions in patients receiving dopamine agonist therapy for hyperprolactinemia, and the majority of which show reassuring results. One study did, however, report increased levels of tricuspid regurgitation. Another key issue in the assessment of this concern in patients with acromegaly is that they often have clinically relevant cardiac abnormalities (myocardial, valvular and conduction system abnormalities) as a result of acromegaly and its co-morbidities (hypertension, left ventricular hyperplasia and type 2 diabetes mellitus). More data are required regarding the safety of dopamine agonist therapy for patients with prolactinomas and acromegaly to assess if there is a similar risk in these patients as for those with Parkinson disease.

Tumor shrinkage on dopamine agonist therapy
Very little data are available regarding tumor shrinkage in patients with acromegaly who are receiving dopamine agonist therapy. Combined results from a number of studies revealed that 29% of patients had some tumor shrinkage and the majority of patients who had tumor shrinkage were also hyperprolactinemic. In the study by Abs et al., 12 of 48 patients (nine with macroadenomas) had radiographically obvious GH-secreting tumors prior to treatment with cabergoline and five of these nine patients had tumor shrinkage (but it was <50%). In one series involving treatment with quinagolide, two of 16 patients had tumor shrinkage. Whether these findings represent a real effect of dopamine agonist therapy or an effect related to prior exposure to radiotherapy is difficult to assess from findings that relate to such small numbers of patients and patients who have heterogeneous characteristics.

Pegvisomant
Pegvisomant is an injectable, genetically engineered, pegylated analogue of human GH that blocks the action of GH at the site of its cognate receptor. Amino acid substitutions in the GH molecule result in structural changes that enable enhanced binding of pegvisomant to the GH receptor, but also prevent the secondary rotational changes of the receptor that are needed for downstream signaling and function. The addition of pegylated glycol units to the molecule (pegylation) extends the half-life of pegvisomant by reducing renal clearance and also decreases immunogenicity of the molecule.

Unlike other medical therapies for acromegaly, pegvisomant acts at the GH receptor rather than at the level of the pituitary adenoma, which makes it an important additional agent in the treatment of acromegaly, particularly when other agents have failed. In terms of cost, pegvisomant is more expensive than dopamine agonist or SRL therapy and as such it is often used as a second-line agent, or in combination with other agents once other treatment options have failed or are poorly tolerated. Pegvisomant therapy results in a reduction in levels of IGF-1 and, as a result, the negative feedback loop to the hypothalamus and pituitary gland is altered and GH levels paradoxically rise. For patients with acromegaly who are treated with pegvisomant, therefore, GH measurements cannot be used to monitor disease activity and IGF-1 becomes the key biomarker, along with clinical signs and symptoms. As IGF-1 is the sole marker of disease activity in response to pegvisomant, knowledge of the limitations and performance of local IGF-1 assays and reference ranges is essential.

Efficacy of pegvisomant
The first clinical study to assess the efficacy of pegvisomant in acromegaly showed a rapid and sustained benefit following 12 weeks of treatment. In this randomized, double-blind, prospective trial, the effect of three different doses of pegvisomant (10, 15 and 20 mg per day) were compared to that of placebo in 112 participants. Significant dose-dependent reductions in IGF-1 levels were observed for the treated groups compared with the placebo group; specifically, 38%, 75% and 89% of patients receiving pegvisomant 10, 15 and 20 mg, respectively, achieved IGF-1 levels within the normal reference range. The reduction in IGF-1 concentrations occurred within the first 2 weeks of treatment (note, however, that patients were loaded with 80 mg of pegvisomant at the start of the study) in 75% of patients and was sustained for the remaining 12-week study period. In keeping with the biochemical response, the clinical response was also impressive with symptoms
of acromegaly being reduced in patients from all three pegvisomant groups. Clinically relevant reductions in soft-tissue swelling, excessive perspiration and fatigue were observed in patients receiving the 20 mg per day dose.

Subsequently, Van der Lely et al.56 performed a study that assessed patients with acromegaly treated with pegvisomant over a longer period (6–18 months).56 In this study, patients started on 10 mg of pegvisomant daily and the dose was titrated every 2 weeks using normal age-adjusted IGF-1 as a target. The maximum dose of pegvisomant used was 40 mg per day. Normal IGF-1 levels were achieved in 97% (87 of 90) of patients receiving pegvisomant for 12 months or more. A dose reduction was required in 11 of 90 patients, as IGF-1 levels fell below their age and sex-matched reference range, thus rendering these patients GH-deficient. Furthermore, many patients with IGF-1 in the normal reference range may be rendered GH-deficient on pegvisomant; this concept has been discussed by Mukherjee et al.65 From a metabolic perspective, pegvisomant therapy also reduced insulin and fasting glucose levels, but no change in HbA1c occurred despite GH levels increasing as IGF-1 levels decreased or normalized.56

Use in SRL-treatment resistance

A number of small studies have assessed the use of pegvisomant in patients whose disease is resistant to SRL therapy. Bonert et al.56 first described six patients who were somatostatin-resistant and in whom normal IGF-1 levels were achieved with pegvisomant treatment. Colao et al.45 reported on 16 patients with acromegaly whose disease was suboptimally controlled on long-acting SRL therapy. All 16 patients had undergone surgery and two had also received radiotherapy. The patients had received the maximum monthly dose of octreotide or lanreotide for at least 24 months prior to enrollment but did not have adequately suppressed GH or IGF-1 levels. Daily pegvisomant was administered and adjusted every 6 weeks to achieve an IGF-1 level within the reference range. Four of the patients were withdrawn from the study owing to poor compliance or protocol violation. After 12 months of treatment with pegvisomant, nine of the 12 remaining patients had normal IGF-1 levels. In the three patients with elevated IGF-1 levels, a >50% decrease from their baseline IGF-1 level had occurred.45

Long-term post-marketing surveillance

ACROSTUDY,56 an international, pharmaceutical-sponsored, surveillance registry, was set up to monitor safety and efficacy of pegvisomant treatment in patients with acromegaly. Data were collected between 2004 and 2009 in 10 countries and included a total of 792 patients. The patient cohort was heterogeneous—387 patients had undergone surgery alone, 19 had received radiotherapy alone and 241 had received surgery and radiotherapy. At enrollment, 83% of patients had already been receiving pegvisomant. The mean duration of pegvisomant therapy was 3.3 years, with 90% of patients receiving pegvisomant as once-daily therapy and 67% receiving pegvisomant monotherapy, specifically, 6% received pegvisomant and a dopamine agonist, 23% received pegvisomant and an SRL and 4% received pegvisomant, an SRL and a dopamine agonist.56

In this observational study, 62% of patients achieved an IGF-1 level within the age-related reference range after 1 year of pegvisomant treatment and this level remained constant thereafter. The authors conclude that this low rate of IGF-1 normalization was probably due to under-dosing of pegvisomant, as many patients with raised IGF-1 levels remained on a modest dose of pegvisomant.56 While it is impossible to be sure of the exact reasons for the lack of dose escalation of pegvisomant, some possibilities include adverse effects of the drug, economic limitations and dosing limitations. The mean weekly dose was 106 mg for patients who responded to treatment with normalization of IGF-1 levels, whereas those with an elevated IGF-1 level were on a mean dose of 113 mg per week. Rates of IGF-1 normalization were similar between the monotherapy group and the groups that received combination therapy with either dopamine agonists or SRLs. The data from this observational study probably more closely reflect the response rates and experience with pegvisomant observed in actual clinical practice than that reported from clinical trials, which have greater clinical investigator input and patient contact.

Tumor growth while taking pegvisomant

Concern exists that pegvisomant may cause tumor growth because it decreases negative feedback by IGF-1 on the pituitary gland and hypothalamus and increases GH levels. Bulik et al.56 published the results of a 24-month prospective trial that assessed tumor volume in 61 patients treated with pegvisomant monotherapy. All patients had received SRL therapy previously, 34.6% had received radiotherapy and 86.9% had undergone surgery. The study participants commenced daily pegvisomant treatment and this agent was adjusted as necessary throughout the trial, with mean dose being about 10 mg and a maximum dose of 50 mg per day. Patients had pituitary MRI scans at 6, 12 and 24 months of therapy. Over the 24-month study period, no statistically significant change in tumor volume occurred in 45 of the 61 patients who completed the study. However, clinically significant tumor growth occurred in three patients within 12 months of commencing pegvisomant; it should be noted that none of these patients had received prior radiotherapy.56

Jimenez et al.56 reviewed the imaging of 43 patients treated with long-term pegvisomant therapy (>18 months) in various clinical trials and also separately looked at the nine patients from a total of 364 patients within clinical trials in whom tumor growth was noted within 12 months of starting pegvisomant. In all, 29 of the 43 patients whose imaging was reviewed had received radiotherapy; 24 patients had a significant clinical reduction in tumor volume and of these, 22 had received radiotherapy previously. Importantly, the nine patients who experienced tumor growth within 12 months of starting pegvisomant had not received prior radiotherapy. Six patients had progressive tumor growth prior to commencing pegvisomant and two had probable rebound tumor expansion after stopping SRL therapy, as the expansion occurred within a short
period of commencing pegvisomant and stopping SRL therapy. In these two cases, the patients have remained on pegvisomant and the tumor has remained stable in size. In summary, a small risk of clinically significant tumor growth occurs while on pegvisomant therapy and such growth appears to be particularly prevalent in patients who have not received prior radiotherapy. Whether this potential increased risk of tumor growth is related to pegvisomant therapy per se or to the natural history of these pituitary adenomas needs further assessment.

Combination of pegvisomant and other agents

Pegvisomant has been evaluated in combination therapy with the more traditional medical therapies such as octreotide and lanreotide. Feenstra et al. looked at the addition of once-weekly pegvisomant to long-acting SRL therapy. This trial had an open-label, 42 week design and involved 26 patients with acromegaly in whom disease activity had not been controlled with maximum doses of long-acting SRLs for at least 6 months. The patients had received 30 mg long-acting octreotide or 120 mg lanreotide autogel before enrolment and continued to take these medications throughout the study period. The starting dose of pegvisomant was 25 mg per week, titrated to achieve IGF-1 levels within the age-adjusted reference range. After 18 and 42 weeks of therapy, 81% and 95% of patients, respectively, had achieved an IGF-1 level within the age-adjusted reference range. The median weekly dose required was 60 mg (range 40–80 mg). No tumor expansion was observed on MRI scans and 10% of patients experienced mild non-progressive liver function test abnormalities. The authors concluded that combined treatment with monthly, high-dose, long-acting SRL therapy and weekly pegvisomant is as effective as daily pegvisomant. They also reasoned that this regimen may have cost benefits for some patients, especially if they do not need large doses of pegvisomant (i.e. >60 mg) and that compliance might improve with weekly versus daily injections of this drug.

Neggers et al. studied 32 patients who had been treated with a maximum dose of long-acting SRL therapy and were then started on combination therapy with pegvisomant. The initial weekly dose of pegvisomant was 40 mg, which was adjusted until patients achieved an IGF-1 level within the age-adjusted reference range. All 32 patients attained the IGF-1 target with a median dose of pegvisomant of 60 mg (range 40–160 mg). No difference in the dose needed was observed between those participants who had undergone surgery and those who were on primary medical therapy. For patients with type 2 diabetes mellitus, metabolic control improved, with HbA1c reductions detected over 6–18 months. A total of 11 patients (34%) experienced transient elevated liver function tests; this adverse effect occurred particularly in patients who also had co-existing type 2 diabetes mellitus (odds ratio 5.1). No increase in tumor size was detected and four patients had a >25% decrease in tumor size.

Once-daily versus once-weekly pegvisomant

Pegvisomant is licensed as a once-daily injection; however, given the long half-life of this drug (~100h), it has been suggested that less frequent dosing might be adequate. Early phase II trials assessed weekly dosing regimens, but phase III trials of the agent used once-daily dosing.

In a study of 10 patients performed by Jehle et al., five patients could be treated successfully with less than daily dosing with pegvisomant. These authors initially administered pegvisomant once daily; their aim was to titrate the dose to achieve an IGF-1 level in the 3rd quartile of the reference range for age and sex. If the IGF-1 level fell below the target range, pegvisomant was administered every second day and then twice-weekly, thereafter, if tolerated. Over a mean follow-up period of 15.3 months, 50% of patients tolerated a regimen of less than daily dosing. The authors concluded that daily dosing of pegvisomant was not essential in all patients and treatment could be tailored in some cases. A subsequent study by Higham et al., assessed the use of once-weekly administration of pegvisomant. In this study, five patients who had stable disease for 3 months on daily pegvisomant were converted initially to a bi-weekly regimen and then to a once-weekly dose. This approach was successful in keeping patients' IGF-1 levels within the age-adjusted reference range and all patients elected to stay on this weekly dose at the end of the study period. Once-weekly dosing of pegvisomant may, therefore, be a therapeutic option and could increase patient compliance with treatment.

Adverse effects of pegvisomant

Pegvisomant is generally well tolerated; adverse effects include mild, self-limiting skin reactions and lipohypertrophy at drug injection sites. Deranged liver transaminase levels have also been reported, but it can be difficult to separate other biliary causes from abnormal liver function tests and it must be remembered that prior SRL therapy can cause cholestasis. Elevations in liver transaminase levels resolve fully on cessation of pegvisomant without any further sequelae and seem to be idiosyncratic. If clinically indicated, a second course of pegvisomant can be considered and some patients have successfully re-started therapy after normalization of liver transaminase levels. Initial pretreatment and subsequent 6-monthly liver function tests are recommended when using pegvisomant. Antibodies to pegvisomant may also be present, although they do not seem to interfere with therapeutic response to pegvisomant or cause adverse effects.

Novel agents

Pasireotide

Pasireotide is a synthetic multireceptor targeting SRL; the drug has high affinity for SSR1, SSR2, SSR3 and SSR5. Somatotroph tumors express SSR1, SSR2, SSR3 and SSR5, and in particular they have a greater abundance of SSR2 and SSR5. The SSR targeting of pasireotide may, therefore, be superior to that of conventional SRLs such as lanreotide and octreotide that primarily target SSR2. A proof-of-concept trial published in 2004 compared a single dose of pasireotide (100 µg or 250 µg) with subcutaneous octreotide. All three interventions significantly reduced GH levels and there was a marked dose-dependent reduction in GH levels between the...
low and higher-dose paresitroid groups. The authors reported three types of response to paresitroid. The first response involved a reduction in GH levels for both octreotide and paresitroid treatment, presumably mediated by SSFR2. In the second type of response, paresitroid was more efficacious than octreotide, presumably because of SSFR5 overexpression. In the last response, octreotide was better than paresitroid, which was presumed to occur as a consequence of high SSFR2 and low SSFR5 expression.

A phase II, multicenter, open label, randomized, crossover trial of paresitroid was then conducted, in which 60 patients with active acromegaly were initially given octreotide for 28 days to assess response to standard treatment. Thereafter, the patients were randomly assigned to 200, 400 or 600 mg paresitroid per day. The primary end point was a binary response based on circulating GH and IGF-I levels and secondary end points included symptoms, signs and MRI findings. After 1 month of treatment, 11 (19%) of 58 patients achieved a full response. The full response rate was as follows for the different doses of paresitroid: 200 μg (14%), 400 μg (12%) and 600 μg (30%). Appreciably more people on the 600 μg dose achieved GH levels <2.5 μg/l when compared with the other doses. After 3 months of treatment, 27% of patients on paresitroid achieved a full biochemical response; 49% had GH levels <2.5 μg/l and 38% achieved a normal IGF-I level.

No significant increase in tumor size occurred with treatment and 20 patients (39%) experienced clinically significant decreases in pituitary tumor volume. A number of mild to moderate gastrointestinal disturbances were reported, with patients developing nausea (25%), diarrhea (22%), abdominal pain (12%) and flatulence (10%). Other adverse events included increased blood glucose levels (7%) and increased HbA1c levels (5%), which led to the development of diabetes mellitus (5%).

The authors conclude that after 3 months of treatment with 200–600 μg paresitroid, one-third of patients achieved full biochemical control and 39% had a reduction in tumor size. Larger phase III trials are awaited to further assess the efficacy of this drug.

Chimeric molecules

A number of in vitro studies have assessed the efficacy of various compounds, which have affinity for multiple SSRIs and dopamine receptors. In one study, patients with GH-secreting tumors that partially responded to octreotide therapy were treated in vitro with different chimeric compounds; the result was a greater reduction in GH secretion than reported with octreotide alone. Future in vitro and clinical studies will determine if these compounds have a role in the management of patients with acromegaly.

Conclusions

Medical therapy has an increasingly important role in the management of acromegaly, both as a primary and secondary therapy. SRL therapy leads to normalization of GH and IGF-I levels in 48–52% and 42–58%, respectively, of patients and may also lead to clinically significant tumor shrinkage. Dopamine agonist therapy might be useful in patients with mild disease and may also be of benefit in some patients who are not hyperprolactinemic, but further data is needed regarding long-term safety in relation to cardiac valve dysfunction. Pegvisomant normalizes IGF-I levels in the majority of cases but does not lead to tumor shrinkage. In summary, the currently available medical therapies, administered as monotherapy or in combination, are effective in a proportion of patients; however, there are still subsets of patients who do not respond to existing medical therapy and the ongoing development of newer medical therapies is essential.

Review criteria

Articles were selected after searching PubMed for articles published between 1990 and 2010, using the search terms “acromegaly”, “medical therapy”, “dopamine agonist”, “octreotide”, “somatostatin analogues”, “somatostatin receptor ligands”, “pegvisomant”, “pasireotide”. Full text articles in the English language were used, when possible. Reference lists of identified papers were reviewed for further leads. As there was a word limit for this review not all papers were included, rather the ones felt to be most pertinent.


Author contributions
M. Sherlock, C. Woods and M. C. Sheppard wrote the article, researched data for the article, provided a substantial contribution to discussion of the content and reviewed/editied the manuscript before submission.
Medical therapy in acromegaly

Mark Sherlock, Conor Woods and Michael C. Sheppard

Abstract | Acromegaly is a rare disease characterized by excess secretion of growth hormone (GH) and increased circulating insulin-like growth factor 1 (IGF-1) concentrations. The disease is associated with increased morbidity and premature mortality, but these effects can be reduced if GH levels are decreased to <2.5 μg/L and IGF-1 levels are normalized. Therapy for acromegaly is targeted at decreasing GH and IGF-1 levels, ameliorating patients' symptoms and decreasing any local compressive effects of the pituitary adenoma. The therapeutic options for acromegaly include surgery, radiotherapy and medical therapies, such as dopamine agonists, somatostatin receptor ligands and the GH receptor antagonist pegvisomant. Medical therapy is currently most widely used as secondary treatment for persistent or recurrent acromegaly following noncurative surgery, although it is increasingly used as primary therapy. This Review provides an overview of current and future pharmacological therapies for patients with acromegaly.


Introduction

Patients with the rare disease, acromegaly, have excess growth hormone (GH) secretion and increased circulating levels of insulin like growth factor 1 (IGF-1). The disease is associated with increased morbidity and premature mortality; reported standardized mortality ratios range between 1.3 and 3.0.1-10 This increase in mortality has been reported to be reduced if GH levels can be decreased to <2.5 μg/L11,12 and IGF-1 levels are normalized.12,13 Life expectancy of patients with acromegaly has also increased over the past few decades,13 probably because of improvements in the surgical and pharmacological management of this condition.

Therapy for acromegaly is targeted at reducing excess morbidity and mortality by decreasing levels of GH and IGF-1, ameliorating symptoms and decreasing any local compressive effects of the pituitary adenoma. Currently, the therapeutic options for acromegaly include surgery, radiotherapy and medical therapies such as dopamine agonists, somatostatin receptor ligands (SRLs) and the GH receptor antagonist pegvisomant. Medical therapy is used predominantly as secondary therapy for persistent or recurrent acromegaly following noncurative surgery, although it can be used as primary therapy for patients in whom surgery is not an option or as short-term therapy before surgery. Consensus guidelines have described the optimal management and the role of medical therapy in treating patients with acromegaly.15 This Review outlines currently available and future options for the medical management of patients with acromegaly.

A number of important issues need to be mentioned before interpreting the data with regard to medical therapies in patients with acromegaly. These issues include the heterogeneity in the size and design of studies, whether medical treatment is given as first-line or second-line therapy, and selection bias (Box 1).

Somatostatin receptor ligand therapy

Somatostatin receptor interaction

Somatostatin is a cyclical peptide with a short half-life (2–3 min) that is synthesized in many tissues. When synthesized in the hypothalamus, this peptide plays a key role in GH secretion by inhibiting release but not synthesis of GH.14 Via its action on somatostatin receptors (SSRs), although SSR1, SSR2, SSR3 and SSR5 are all expressed on GH-secreting pituitary adenomas, SSR2 and SSR5 are more abundantly expressed than the other types.15 In vitro and in vivo studies have shown that expression of SSR2 correlates well with the GH-lowering effect of the SRL octreotide, which suggests that the main GH-lowering effect of this drug is through SSR2.16-18 Although SSR5 is expressed at higher levels compared with SSR2, no correlation was found between the expression level of SSR5 and effects of SRLs (including octreotide) on GH secretion in cultured pituitary adenomas from patients with acromegaly.19-21 Fendlers et al. have reviewed the area of somatostatin receptor specificity in detail.14

Pharmacology

Subcutaneous octreotide is administered as a thrice-daily injection as its half-life is 2 h; this multiple daily dosing regimen has limitations, including issues with compliance and therapeutic escape before the next dose is administered.18 The starting dose is usually 100 μg three times per day, which can be increased in increments to a maximum of 500 μg three times per day.16 The first long-acting formulation to be synthesized was octreotide long-acting release. This formulation of octreotide is delivered by microspheres,18 which lead to an increase in the serum level of the drug on day 1 post-injection followed by a
Box 1 | Interpreting data on medical therapies in acromegaly

- Acromegaly is a rare condition and as such the numbers of participants enrolled in studies may be relatively small and studies are often multicenter.

- Apparent heterogeneity exists in study design, patient characteristics and patient selection between studies, so direct comparison and meta-analysis may be difficult.

- Patients who receive the drug as primary therapy should be differentiated from those who receive the drug as secondary therapy.

- Large variations exist between studies in the number of patients who have had surgery and radiotherapy prior to medical therapy; this point is important as it affects the subsequent response to therapy both from the perspective of hormone hypersecretion and tumor shrinkage.

- In studies that assess the effect of therapy on tumor size, wide variation exists in the criteria used to assess tumor shrinkage.

- Duration of therapy and follow-up differs between studies and, as such, they may not be comparable, as some therapies function better the longer the patient receives them; furthermore, the effect of radiotherapy on acromegaly increases with time following therapy.

- In studies assessing the efficacy of somatostatin receptor ligands (SRLs), therapy may be with short-acting octreotide or one of the long-acting SRL preparations and, as such, direct comparison and meta-analysis may be difficult.

- Selection bias may exist for trials involving SRL therapy, because in some cases patients will have demonstrated a response to short-acting SRL therapy as an inclusion criterion for enrollment in the study.

These second long-acting SRL synthesized was lanreotide, which is available in two formulations: lanreotide sustained release and lanreotide autogel® (Société de Conseils de Recherches et d'Applications Scientifiques, Paris, France). Lanreotide sustained release comprises lanreotide incorporated into a biodegradable polymer microparticle, which leads to a rapid release of the drug 1–2 h after injection followed by a prolonged drug release phase peaking 2 days later. Lanreotide sustained release has a mean half-life of 5 days and, therefore, injections are required every 10–14 days. Autogel® is a depot preparation of lanreotide in a supersaturated aqueous solution. Administration of lanreotide autogel® provides a peak concentration on day 1; however, this formulation has a longer half-life (25 days) than lanreotide sustained release. The elimination of SRLs, such as octreotide or lanreotide, from the body is predominantly by biliary secretion.

Biochemical control

Subcutaneous octreotide

In a study by Vance et al., treatment with subcutaneous octreotide lead to a decrease in GH and IGF-I levels in 94% and 92% of patients with acromegaly, respectively. These reductions led to a normalization of IGF-I concentration in 46% of patients and a GH level of <5 μg/L in 45% of patients and were associated with a reduction in tumor size of >20% in 44% of patients. In a study by Ezrat et al., 21% of patients on 250 μg subcutaneous octreotide three-times daily and 16% of patients on 100 μg subcutaneous octreotide three-times daily achieved a GH level of <2 μg/L. IGF-I levels were normalized in 68% of patients in the 250 μg group and in 55% of those in the 100 μg group. Tumor shrinkage of >1 mm in diameter occurred in 37% of cases in the 250 μg group and in 19% in the 100 μg group during the 6-month treatment period.

These studies had limitations that included a non-age-adjusted reference range for IGF-I, open labeling and variable dose escalation (or fixed dose in the study by Ezrat et al.), A number of studies have reported no difference in efficacy between subcutaneous and long-acting SRLs. However, subcutaneous SRL therapy has been replaced by long-acting SRL therapy owing to improved compliance and patient preference, but it should be noted that long-acting SRL therapy may be considerably more expensive (depending on the dose of short-acting SRL used).

Long-acting somatostatin receptor ligands

An analysis of prospective studies has reported that long-acting SRLs reduce GH levels to <2.5 μg/L and normalize IGF-I levels in 48–52% and 42–68% of patients with acromegaly, respectively. A retrospective study of long-acting SRL use in clinical practice has reported similar responses (48.8% of patients achieved a GH <2.5 μg/L and 45.7% achieved an IGF-I in the normal age-related reference range). This similarity shows that GH and IGF-I reductions observed with long-acting SRLs in clinical trials are possible to achieve in routine clinical practice. A 5-year prospective study of 45 patients with acromegaly treated with long-acting SRLs as first-line therapy, reported GH control in 100.0%, IGF-I control in 97.8% and tumor shrinkage of 74.9% in the octreotide long-acting release group and 78.2% in the lanreotide group.

Direct comparison of different formulations of SRLs used in clinical trials is difficult for a number of reasons, which have been described in Box 1. Another key factor is duration of therapy, as there is some evidence that control of acromegaly by SRLs may improve with time, independent of dosage change and, therefore, if studies are of different duration they may not be comparable. In two of the largest studies to assess the efficacy of octreotide long-acting release, 66–75% of patients achieved IGF-I levels.
within the normal reference range and 70–72% achieved GH levels <2.5 μg/l.3,22
The findings of these studies may be limited by therapeutic and selection bias, as in the study by Lancranjan et al.,31 patients were selected on the basis of known responsiveness to subcutaneous octreotide and in the study by Cozzii et al.,32 only patients with >20% decreases in GH and IGF-I levels remained in the study for its full duration. Baldelli et al. have assessed the efficacy of lanreotide sustained release. In this study, GH and IGF-I levels were controlled in 77% and 63% of patients, respectively, and 22% of patients had clinically significant tumor shrinkage of >20% in volume.33 Verbeke et al. have also assessed the efficacy of lanreotide sustained release; these researchers found that GH was reduced to <2.5 μg/l in 45% of patients, IGF-I levels were in the normal reference range in 44% and 36% had clinically significant tumor shrinkage of >25% volume.34
The question as to which long-acting SRL is most efficacious and the data comparing octreotide long-acting release and the different preparations of lanreotide are beyond the scope of this Review, but have been extensively reviewed by Murray and Melmed.35

Antitumoral effects
The antitumoral effects of SRLs have been extensively reviewed by B-even in 2005.36 The mechanisms by which SRLs inhibit growth and proliferation of tumor cells are complex and include cell-cycle arrest, induction of apoptosis and decreased angiogenesis.37 Losa et al.38 compared Ki-67 immunostaining (a marker of cell cycling) in 39 patients treated with SRLs and 39 controls who were not treated preoperatively with SRLs, but who were matched for age, sex, tumor size and extension; they reported a decreased Ki-67 index with no increase in apoptosis in the treated patients, which suggests that SRLs have important antiproliferative effects. Further evidence comes from Danila et al. who have reported that inhibition of cell proliferation by SRLs occurs independently of inhibition of GH secretory pathways.37
The studies that have assessed changes in tumor size following SRL therapy have used different imaging modalities (CT and MRI) and different assessments of tumor shrinkage (tumor diameter or volume). These differences between the studies make comparison of results difficult. Most studies define a 10–25% reduction in tumor volume as clinically significant tumor shrinkage. Studies that have assessed tumor shrinkage include those involving patients on short-acting or long-acting SRLs and those receiving SRLs as a primary or secondary therapy. In the review by Bevan,39 217 of 478 patients (45%) who received SRL therapy experienced tumor shrinkage. The reduction in tumor size was more prevalent in the primary medical therapy group (51%) than the secondary medical therapy group (27%).39
Predictors of tumor shrinkage in patients receiving SRL therapy include prior surgery and radiotherapy; specifically, patients who have received radiotherapy and are surgery naive have the greatest reduction in tumor volume in respond to SRL therapy. Data are conflicting with regard to the initial size of the tumor in relation to the amount of shrinkage that occurs with SRL therapy. Some researchers report that microadenomas are more likely to shrink than larger adenomas,38 whilst others report that macroadenomas are more likely to shrink than smaller adenomas.39,40,41 Furthermore, other groups report no association between initial tumor size and the subsequent amount of shrinkage following SRL therapy.42 A few studies have suggested that patients who have a biochemical response also have a tumor volume response.43,44 In the patients in whom GH levels decreased by >50%, tumor shrinkage was observed in 88%.45 By comparison, 29% of the patients who had a <50% reduction in their GH levels experienced tumor shrinkage. Verbeke et al.46 reported the greatest tumor shrinkage in patients with the greatest IGF-1 response to SRL therapy. By contrast, a number of other studies did not show any relationship between biochemical response and tumor response.40,43,45

Primary medical therapy
Unlike surgery, primary medical therapy cannot cure acromegaly but, as this approach can control hormone hypersecretion, it may be indicated in patients who are unlikely to achieve cure following surgery—namely, those with macroadenomas with clinically significant extension or those who refuse or are poor candidates for surgery. Importantly, even in patients who show favorable biochemical and tumor shrinkage responses with SRL therapy, once the therapy is stopped, the tumor regrows and excess levels of GH and IGF-1 return.24,44
The majority of data regarding primary SRL therapy come from nonrandomized studies rather than from prospective randomized trials of surgery versus SRL therapy. In these studies, SRL treatment as a primary therapy is effective in reducing levels of GH and achieving an IGF-1 in the normal range in approximately two-thirds of patients.46,47
A review has reported that in 14 studies assessing primary medical therapy in patients with acromegaly (n = 424), 36.6% of patients had clinically significant tumor shrinkage >20%.46 The wide range in percentages of patients with clinically significant tumor shrinkage in the studies reviewed most probably relates to differences in definitions of clinically significant shrinkage (range 10–45%) and differences in how this effect was assessed radiologically.48

Pre-operative somatostatin receptor ligand therapy
In a prospective study by Carlsen et al.,40 30 patients who had primary surgical therapy were compared with 32 patients who had preoperative SRL therapy followed by surgery. No statistically significant increase in biochemical cure was found in the total patient group who received preoperative SRL therapy. However, in the subgroup of patients with macroadenomas, an improved cure rate was observed with preoperative SRL therapy. The authors of this trial
concluded that future well-designed studies were required to further assess the role of preoperative SRL therapy.\(^\text{50}\) Lucas \textit{et al.} assessed the efficacy of primary medical therapy with lanreotide sustained release in 104 patients with acromegaly for 1–3 months prior to transsphenoidal surgery. Overall, 29% of patients had a >20% reduction in size of tumor, whereas 66% had some tumor reduction and 18% had >20% increase in tumor size.\(^\text{51}\) Biochemical control was the sole predictor of tumor shrinkage. However, longer studies have shown no relationship between GH response and tumor shrinkage.\(^\text{52-54}\)

Univariate analysis of surgical outcomes revealed that predictors of persistent disease following surgery in patients who had received preoperative SRL therapy were younger age, higher levels of GH and IGF-1 at diagnosis, larger preoperative tumor volume and extension into the suprasellar region or cavernous sinus.\(^\text{55}\) However, as this study lacked a control group it is difficult to accurately assess the role of preoperative SRL therapy without further randomized, controlled trials. Importantly, some patients enrolled in this study developed cavernous sinus extension during treatment, which may have a negative effect on surgical outcome.\(^\text{51}\)

### Adverse effects of somatostatin receptor ligands

In clinical trials of SRL therapy, the most frequent adverse effects encountered are gastrointestinal in nature, such as nausea, flatulence, cramps and diarrhea, which are mostly mild to moderate in severity and are often transient.\(^\text{18}\) Injection site discomfort, pain and erythema is also often described but is rarely severe enough to lead to drug cessation. The other concern relates to the development of biliary abnormalities (including sediment, sludge, micro- lithiasis and gallstones); however, these abnormalities are mostly asymptomatic.\(^\text{19}\) Clinicians need to be aware of this possible adverse effect, particularly when patients stop SRL therapy, as gallbladder contraction may occur leading to symptoms. Patients with acromegaly have an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus and SRL therapy has also been reported to increase the risk of hyperglycemia (as these therapies impair insulin secretion).\(^\text{52,53}\) Other adverse effects include rarely reported cases of liver function abnormalities, anaphylaxis and hair loss.

### Dopamine agonists

Dopamine agonists bind to D2 dopamine receptors in the pituitary gland and suppress secretion of GH and GH in patients with acromegaly. They have been used in acromegaly as an individual treatment or in combination with an SRL. Three main dopamine agonist agents are used in the treatment of hyperprolactinemia and GH excess: bromocriptine, cabergoline and quinagolide.

### Bromocriptine

Bromocriptine was the first dopamine agonist to be widely used in the treatment of acromegaly. This agonist was associated with moderate success, as it normalized IGF-1 and GH levels in 10% and 20% of patients, respectively.\(^\text{54}\) The utility of dopamine agonists, in particular bromocriptine, has been limited by the disappointing rates of biochemical response reported, and clinically relevant adverse effects that may occur with the high daily doses (40–60 mg), such as nausea, vomiting, diarrhea, fatigue and or/hostile hypotension.\(^\text{55}\) Sherlock \textit{et al.}\(^\text{24}\) have, however, reported that 42.4% and 23.6% of patients taking lower doses of bromocriptine (median 7.5 mg per day) achieved GH and IGF-1 reductions, respectively. These responses, although not as good as those reported with SRL therapy, reduced GH and IGF-1 levels into the range associated with normalization of mortality in 28% and 32.1% of patients, respectively, and, therefore, may be of use for patients with mildy active disease.\(^\text{54}\)

### Cabergoline

The second-generation dopamine agonist cabergoline has been demonstrated to be potentially more effective than bromocriptine in the treatment of acromegaly, as treatment normalized GH and IGF-1 levels in 46% and 39% of 64 patients, respectively.\(^\text{56}\) Moreover, Moyes and colleagues found that on a median weekly dose of 1.75 mg of cabergoline, normalization of both IGF-1 and GH levels occurred in 27% of patients.\(^\text{57}\) The greater efficacy of cabergoline than bromocriptine may reflect a number of factors, including greater biological potency, a longer half-life and less adverse effects, leading to better compliance. Data relating to cabergoline therapy in acromegaly is limited, which most probably relates to the fact that this drug was introduced into clinical practice for patients with acromegaly at around the same time as SRL therapy—which is more likely to be used owing to superior efficacy in both hormonal control and tumor reduction.

In the largest study performed to date that has assessed the efficacy of cabergoline in patients with acromegaly, Abs \textit{et al.}\(^\text{58}\) treated 64 unselected patients with cabergoline for 3–40 months. The majority of patients received 1.00–1.75 mg of cabergoline per week (although some patients received doses of up to 3.5 mg per week). In the 48 patients who had pure GH-secreting tumors, cabergoline normalized IGF-1 levels in 35% and suppressed GH levels to <2 μg/l in 44%. A greater effect was observed in the subset of patients whose tumors co-secreted GH and prolactin, among whom IGF-1 levels were normalized in 50% of cases and GH levels were suppressed to <2 μg/l in 56%.

In this study by Abs \textit{et al.}\(^\text{58}\) patients with relatively low baseline levels of GH and IGF-1 were more likely to respond to cabergoline therapy than those with high baseline levels. When patients were categorized into those with the highest pre-therapy IGF-1 levels (>750 μg/l) compared to others (<750 μg/l) the rate of normalization of IGF-1 was 22% and 43%, respectively. Combined data from four smaller studies reveal less impressive response levels: IGF-1 levels normalized in 22% of patients treated with cabergoline;\(^\text{59,60}\) however, the rate of response was extremely variable (0–27%).\(^\text{38,41}\)

Data on long-term treatment with quinagolide is not as robust as that for bromocriptine or cabergoline, but available data in small numbers of patients report that IGF-1 levels normalize in between 17% and 43% of patients treated with this drug.\(^\text{52,53}\)
**FOCUS ON PITUITARY TUMORS**

Predictive value of hyperprolactinemia

The data as to whether the co-secretion of prolactin is predictive of response to dopamine agonist therapy—in other words, patients with elevated prolactin levels have a greater decrease in GH and IGF-1 following dopamine agonist therapy—is conflicting. Some studies conclude that tumors that co-secrete prolactin and GH have a greater response to dopamine agonist therapy than those that solely secrete GH.\(^{6,12,25}\) whereas others show no effect.\(^{6,12,25,49}\) Similarly, no agreement exists concerning the association between positive GH and prolactin immunohistochemistry of the tumor and a favorable response to dopamine agonist therapy, with some studies reporting this association\(^{6,49}\) and others not.\(^{25,49,50}\) Patients who have a normal prolactin level should, therefore, not necessarily be excluded from receiving dopamine agonist therapy on the assumption that there will be a limited GH and IGF-1 response.

Adverse effects of dopamine agonists

The most frequent adverse effects of dopamine agonist therapy are nausea, constipation, headache, mood disturbance, nasal stuffiness and dizziness.\(^{1,25}\) Studies in patients treated with dopamine agonists for prolactinomas have shown less frequent adverse effects with cabergoline than with bromocriptine.\(^{7,11}\) Indeed, in the largest study of cabergoline in patients with acromegaly,\(^{7,11}\) only 3% of patients had adverse effects that required drug withdrawal (despite relatively high doses).

In the past 5 years, cabergoline and pergolide (which has been removed from the US market) have been associated with an increased risk of cardiac valvular dysfunction in patients receiving high-dose therapy for Parkinson disease.\(^{7,11}\) However, patients receiving dopamine agonist therapy for endocrine indications differ from the Parkinson disease cohorts in a number of key respects, including cumulative dose exposure and age. Since these findings were published, a number of studies have assessed the risk of clinically relevant valvular lesions in patients receiving dopamine agonist therapy for hyperprolactinemia.\(^{7,11}\) The majority of which show reassuring results. One study did, however, report increased levels of tricuspid regurgitation.\(^{7,11}\) Another key issue in the assessment of this concern in patients with acromegaly is that they often have clinically relevant cardiac abnormalities (myocardial, valvular and conduction system abnormalities) as a result of acromegaly and its co-morbidities (hypertension, left ventricular hyperplasia and type 2 diabetes mellitus).\(^{7,11}\) More data are required regarding the safety of dopamine agonist therapy for patients with prolactinomas and acromegaly to assess if there is a similar risk in these patients as for those with Parkinson disease.

Tumor shrinkage on dopamine agonist therapy

Very little data are available regarding tumor shrinkage in patients with acromegaly who are receiving dopamine agonist therapy. Combined results from a number of studies revealed that 29% of patients had some tumor shrinkage and the majority of patients who had tumor shrinkage were also hyperprolactinemic.\(^{7,11}\) In the study by Abs et al,\(^{7,11}\) 12 of 48 patients (nine with macroadenomas) had radiographically obvious GH-secreting tumors prior to treatment with cabergoline and five of these nine patients had tumor shrinkage (but it was <50%). In one series involving treatment with quinagolide, two of 16 patients had tumor shrinkage.\(^{7,11}\) Whether these findings represent a real effect of dopamine agonist therapy or an effect related to prior exposure to radiotherapy is difficult to assess from findings that relate to such small numbers of patients and patients who have heterogeneous characteristics.

Pegvisomant

Pegvisomant is an injectable, genetically engineered, pegylated analogue of human GH that blocks the action of GH at the site of its cognate receptor. Amino acid substitutions in the GH molecule result in structural changes that enable enhanced binding of pegvisomant to the GH receptor, but also prevent the secondary rotational changes of the receptor that are needed for downstream signaling and function.\(^{82}\) The addition of pegylated glycol units to the molecule (pegylation) extends the half-life of pegvisomant by reducing renal clearance and also decreases immunogenicity of the molecule.

Unlike other medical therapies for acromegaly, pegvisomant acts at the GH receptor rather than at the level of the pituitary adenoma, which make it an important additional agent in the treatment of acromegaly, particularly when other agents have failed. In terms of cost, pegvisomant is more expensive than dopamine agonist or SRL therapy and as such it is often used as a second-line agent, or in combination with other agents once other treatment options have failed or are poorly tolerated.\(^{12}\) Pegvisomant therapy results in a reduction in levels of IGF-1 and, as a result, the negative feedback loop to the hypothalamus and pituitary gland is altered and GH levels paradoxically rise. For patients with acromegaly who are treated with pegvisomant, therefore, GH measurements cannot be used to monitor disease activity and IGF-1 becomes the key biomarker, along with clinical signs and symptoms. As IGF-1 is the sole marker of disease activity in response to pegvisomant, knowledge of the limitations and performance of local IGF-1 assays and reference ranges is essential.\(^{82}\)

Efficacy of pegvisomant

The first clinical study to assess the efficacy of pegvisomant in acromegaly showed a rapid and sustained benefit following 12 weeks of treatment.\(^{83}\) In this randomized, double-blind, prospective trial, the effect of three different doses of pegvisomant (10, 15 and 20 mg per day) were compared to that of placebo in 112 participants. Significant dose-dependent reductions in IGF-1 levels were observed for the treated groups compared with the placebo group; specifically, 38%, 75% and 89% of patients receiving pegvisomant 10, 15 and 20 mg, respectively, achieved IGF-1 levels within the normal reference range. The reduction in IGF-1 concentrations occurred within the first 2 weeks of treatment (note, however, that patients were loaded with 80 mg of pegvisomant at the start of the study) in 75% of patients and was sustained for the remaining 12-week study period.\(^{83}\) In keeping with the biochemical response, the clinical response was also impressive with symptoms
of acromegaly being reduced in patients from all three pegvisomant groups. Clinically relevant reductions in soft-tissue swelling, excessive perspiration and fatigue were observed in patients receiving the 20 mg per day dose. Subsequently, Van der Lely et al. performed a study that assessed patients with acromegaly treated with pegvisomant over a longer period (6–18 months). In this study, patients started on 10 mg of pegvisomant daily and the dose was titrated every 2 weeks using normal age-adjusted IGF-1 as a target. The maximum dose of pegvisomant used was 40 mg per day. Normal IGF-1 levels were achieved in 97% (87 of 90) of patients receiving pegvisomant for 12 months or more. A dose reduction was required in 11 of 90 patients, as IGF-1 levels fell below their age and sex-matched reference range, thus rendering these patients GH-deficient. Furthermore, many patients with IGF-1 in the normal reference range may be rendered GH-deficient on pegvisomant; this concept has been discussed by Mukherjee et al. From a metabolic perspective, pegvisomant therapy also reduced insulin and fasting glucose levels, but no change in HbA1c occurred despite GH levels increasing as IGF-1 levels decreased or normalized.

Use in SRL-treatment resistance
A number of small studies have assessed the use of pegvisomant in patients whose disease is resistant to SRL therapy. Bonert et al. first described six patients who were somatostatin-resistant and in whom normal IGF-1 levels were achieved with pegvisomant treatment. Colao et al. reported on 16 patients with acromegaly whose disease was suboptimally controlled on long-acting SRL therapy. All 16 patients had undergone surgery and two had also received radiotherapy. The patients had received the maximum monthly dose of octreotide or lanreotide for at least 24 months prior to enrollment but did not have adequately suppressed GH or IGF-1 levels. Daily pegvisomant was administered and adjusted every 6 weeks to achieve an IGF-1 level within the reference range. Four of the patients were withdrawn from the study owing to poor compliance or protocol violation. After 12 months of treatment with pegvisomant, nine of the 12 remaining patients had normal IGF-1 levels. In the three patients with elevated IGF-1 levels, a >50% decrease from their baseline IGF-1 level had occurred.

Long-term post-marketing surveillance
ACROSTUDY, an international, pharmacally-sponsored, surveillance registry, was set up to monitor safety and efficacy of pegvisomant treatment in patients with acromegaly. Data were collected between 2004 and 2009 in 10 countries and included a total of 792 patients. The patient cohort was heterogeneous—387 patients had undergone surgery alone, 19 had received radiotherapy alone and 241 had received surgery and radiotherapy. At enrollment, 83% of patients had already been receiving pegvisomant. The mean duration of pegvisomant therapy was 3.3 years, with 90% of patients receiving pegvisomant as once-daily therapy and 67% receiving pegvisomant monotherapy; specifically, 6% received pegvisomant and a dopamine agonist, 23% received pegvisomant and an SRL, and 4% received pegvisomant, an SRL and a dopamine agonist.

In this observational study, 62% of patients achieved an IGF-1 level within the age-related reference range after 1 year of pegvisomant treatment and this level remained constant thereafter. The authors conclude that this low rate of IGF-1 normalization was probably due to under-dosing of pegvisomant, as many patients with raised IGF-1 levels remained on a modest dose of pegvisomant. While it is impossible to be sure of the exact reasons for the lack of dose escalation of pegvisomant, some possibilities include adverse effects of the drug, economic limitations and dosing limitations. The mean weekly dose was 106 mg for patients who responded to treatment with normalization of IGF-1 levels, whereas those with an elevated IGF-1 level were on a mean dose of 113 mg per week. Rates of IGF-1 normalization were similar between the monotherapy group and the groups that received combination therapy with either dopamine agonists or SRLs. The data from this observational study probably more closely reflect the response rates and experience with pegvisomant observed in actual clinical practice than that reported from clinical trials, which have greater clinical investigator input and patient contact.

Tumor growth while taking pegvisomant
Concern exists that pegvisomant may cause tumor growth because it decreases negative feedback by IGF-1 on the pituitary gland and hypothalamus and increases GH levels. Buhk et al. published the results of a 24-month prospective trial that assessed tumor volume in 61 patients treated with pegvisomant monotherapy. All patients had received SRL therapy previously, 34.0% had received radiotherapy and 86.9% had undergone surgery. The study participants commenced daily pegvisomant treatment and this agent was adjusted as necessary throughout the trial, with mean dose being about 10 mg and a maximum dose of 30 mg per day. Patients had pituitary MRI scans at 6, 12 and 24 months of therapy. Over the 24-month study period, no statistically significant change in tumor volume occurred in 45 of the 61 patients who completed the study. However, clinically significant tumor growth occurred in three patients within 12 months of commencing pegvisomant; it should be noted that none of these patients had received prior radiotherapy.

Jimenez et al. reviewed the imaging of 43 patients treated with long-term pegvisomant therapy (>18 months) in various clinical trials and also separately looked at the nine patients from a total of 304 patients within clinical trials in whom tumor growth was noted within 12 months of starting pegvisomant. In all, 29 of the 43 patients whose imaging was reviewed had received radiotherapy; 24 patients had a significant clinical reduction in tumor volume and of these, 22 had received radiotherapy previously. Importantly, the nine patients who experienced tumor growth within 12 months of starting pegvisomant had not received prior radiotherapy. Six patients had progressive tumor growth prior to commencing pegvisomant and two had probable rebound tumor expansion after stopping SRL therapy, as the expansion occurred within a short
period of commencing pegvisomant and stopping SRL therapy. In these two cases, the patients have remained on pegvisomant and the tumor has remained stable in size.\textsuperscript{52} In summary, a small risk of clinically significant tumor growth occurs while on pegvisomant therapy and such growth appears to be particularly prevalent in patients who have not received prior radiotherapy. Whether this potential increased risk of tumor growth is related to pegvisomant therapy per se or to the natural history of these pituitary adenomas needs further assessment.

**Combination of pegvisomant and other agents**

Pegvisomant has been evaluated in combination therapy with the more traditional medical therapies such as octreotide and lanreotide. Feenstra \textit{et al.}\textsuperscript{19} looked at the addition of once-weekly pegvisomant to long-acting SRL therapy. This trial had an open-label, 42 week design and involved 26 patients with acromegaly in whom disease activity had not been controlled with maximum doses of long-acting SRLs for at least 6 months. The patients had received 30 mg long-acting octreotide or 120 mg lanreotide autogel\textsuperscript{R} before enrolment and continued to take these medications throughout the study period. The starting dose of pegvisomant was 25 mg per week, titrated towards achieving IGF-1 levels within the age-adjusted reference range. After 18 and 42 weeks of therapy, 81\% and 95\% of patients, respectively, had achieved an IGF-1 level within the age-adjusted reference range. The median weekly dose required was 60 mg (range 40–80 mg). No tumor expansion was observed on MRI scans and 10\% of patients experienced mild non-progressive liver function test abnormalities. The authors concluded that combined treatment with monthly, high-dose, long-acting SRL therapy and weekly pegvisomant is as effective as daily pegvisomant. They also reasoned that this regimen may have cost benefits for some patients, especially if they do not need large doses of pegvisomant (i.e. >60 mg) and that compliance might improve with weekly versus daily injections of this drug.

Neggers \textit{et al.}\textsuperscript{20} studied 32 patients who had been treated with a maximum dose of long-acting SRL therapy and were then started on combination therapy with pegvisomant. The initial weekly dose of pegvisomant was 40 mg, which was adjusted until patients achieved an IGF-1 level within the age-adjusted reference range. All 32 patients attained the IGF-1 target with a median dose of pegvisomant of 60 mg (range 40–160 mg). No difference in the dose needed was observed between those participants who had undergone surgery and those who were on primary medical therapy. For patients with type 2 diabetes mellitus, metabolic control improved, with HbA\textsubscript{1c} reductions detected over 6–18 months. A total of 11 patients (34\%) experienced transient elevated liver function tests; this adverse effect occurred particularly in patients who also had co-existing type 2 diabetes mellitus (odds ratio 5.1). No increase in tumor size was detected and four patients had a >25\% decrease in tumor size.

**Once-daily versus once-weekly pegvisomant**

Pegvisomant is licensed as a once-daily injection; however, given the long half-life of this drug (~100 h), it has been suggested that less frequent dosing might be adequate. Early phase II trials assessed weekly dosing regimens, but phase III trials of the agent used once-daily dosing.

In a study of 10 patients performed by Lehe \textit{et al.}\textsuperscript{21} five patients could be treated successfully with less than daily dosing with pegvisomant. These authors initially administered pegvisomant once daily; their aim was to titrate the dose to achieve an IGF-1 level in the 90\% quartile of the reference range for age and sex. If the IGF-1 level fell below the target range, pegvisomant was administered every second day and then twice-weekly; thereafter, if tolerated. Over a mean follow-up period of 15.3 months, 50\% of patients tolerated a regimen of less than daily dosing. The authors concluded that daily dosing of pegvisomant was not essential in all patients and treatment could be tailored in some cases. A subsequent study by Higham \textit{et al.}\textsuperscript{22} assessed the use of once-weekly administration of pegvisomant. In this study, five patients who had stable disease for 3 months on daily pegvisomant were converted initially to a bi-weekly regimen and then to a once-weekly dose. This approach was successful in keeping patients' IGF-1 levels within the age-adjusted reference range and all patients elected to stay on this weekly dose at the end of the study period. Once-weekly dosing of pegvisomant may, therefore, be a therapeutic option and could increase patient compliance with treatment.

**Adverse effects of pegvisomant**

Pegvisomant is generally well tolerated; adverse effects include mild, self-limiting skin reactions and lipoatrophy at injection sites. Deranged liver transaminase levels have also been reported, but it can be difficult to separate other biliary causes from abnormal liver function tests and it must be remembered that prior SRL therapy can cause cholestasis. Elevations in liver transaminase levels resolve fully on cessation of pegvisomant without any further sequelae and seem to be idiosyncratic.\textsuperscript{35} If clinically indicated, a second course of pegvisomant can be considered and some patients have successfully re-started therapy after normalization of liver transaminase levels.\textsuperscript{36} Initial pretreatment and subsequent 6-monthly liver function tests are recommended when using pegvisomant. Antibodies to pegvisomant may also be present, although they do not seem to interfere with therapeutic response to pegvisomant or cause adverse effects.

**Novel agents**

**Pasireotide**

Pasireotide is a synthetic multireceptor targeting SRL; the drug has high affinity for SSTR1, SSTR2, SSTR3 and SSTR5. Somatotroph tumors express SSTR1, SSTR2, SSTR3 and SSTR5,\textsuperscript{14} and in particular they have a greater abundance of SSTR2 and SSTR5. The SSTR targeting of pasireotide may, therefore, be superior to that of conventional SRLs such as lanreotide and octreotide that primarily target SSTR2.\textsuperscript{16–18} A proof-of-concept trial published in 2004 compared a single dose of pasireotide (100 μg or 250 μg) with subcutaneous octreotide. All three interventions significantly reduced GH levels and there was a marked dose-dependant reduction in GH levels between the
low and higher-dose pasireotide groups. The authors reported three types of response to pasireotide. The first response involved a reduction in GH levels for both octreotide and pasireotide treatment, presumably mediated by SS2R. In the second type of response, pasireotide was more efficacious than octreotide, presumably because of SS5R overexpression. In the last response, octreotide was better than pasireotide, which was presumed to occur as a consequence of high SS2R and low SS5R expression.

A phase II, multicenter, open-label, randomized, crossover trial of pasireotide was then conducted, in which 60 patients with active acromegaly were initially given octreotide for 28 days to assess response to standard treatment. Thereafter, the patients were randomly assigned to 200, 400 or 600μg pasireotide per day. The primary end point was a binary response based on circulating GH and IGF-1 levels and secondary end points included symptoms, signs and MRI findings. After 1 month of treatment, 11 (19%) of 58 patients achieved a full response. The full response rate was as follows for the different doses of pasireotide: 200 μg (14%), 400 μg (12%) and 600 μg (30%). Appreciably more people on the 600 μg dose achieved GH levels <2.5 μg/l when compared with the other doses. After 3 months of treatment, 27% of patients on pasireotide achieved a full biochemical response: 49% had GH levels <2.5 μg/l and 38% achieved a normal IGF-1 level.

No significant increase in tumor size occurred with treatment and 20 patients (39%) experienced clinically significant decreases in pituitary tumor volume. A number of mild to moderate gastrointestinal disturbances were reported, with patients developing nausea (25%), diarrhea (22%), abdominal pain (12%) and flatulence (10%). Other adverse events included increased blood glucose levels (7%) and increased HbA1c levels (5%), which led to the development of diabetes mellitus (5%).

The authors conclude that after 3 months of treatment with 200–600 μg pasireotide, one-third of patients achieved full biochemical control and 39% had a reduction in tumor size. Larger phase III trials are awaited to further assess the efficacy of this drug.

Chimeric molecules
A number of in vitro studies have assessed the efficacy of various compounds, which have affinity for multiple SSRs and dopamine receptors. In one study, patients with GH-secreting tumors that partially responded to octreotide therapy were treated in vitro with different chimeric compounds; the result was a greater reduction in GH secretion than reported with octreotide alone. Future in vitro and clinical studies will determine if these compounds have a role in the management of patients with acromegaly.

Conclusions
Medical therapy has an increasingly important role in the management of acromegaly, both as a primary and secondary therapy. SRL therapy leads to normalization of GH and IGF-1 levels in 48–52% and 42–68%, respectively, of patients and may also lead to clinically significant tumor shrinkage. Dopamine agonist therapy might be useful in patients with mild disease and may also be of benefit in some patients who are not hyperprolactinemic, but further data is needed regarding long-term safety in relation to cardiac valve dysfunction. Pegvissomat normalizes IGF-1 levels in the majority of cases but does not lead to tumor shrinkage. In summary, the currently available medical therapies, administered as monotherapy or in combination, are effective in a proportion of patients; however, there are still subsets of patients who do not respond to existing medical therapy and the ongoing development of newer medical therapies is essential.

Review criteria
Articles were selected after searching PubMed for articles published between 1990 and 2010, using the search terms "acromegaly," "medical, therapy," "dopamine agonist," "octreotide," "lanreotide," "somatostatin analogues," "somatostatin receptor ligands," "pegvisomant," "pasireotide." Full text articles in the English language were used, when possible. Reference lists of identified papers were reviewed for further leads.

As there was a word limit for this review not all papers were included, rather the ones felt to be most pertinent.


Author contributions
M. Sherlock, C. Weeds and M. C. Sheppard wrote the article. The research data for the article, provided a substantial contribution to discussion of the content and reviewed/edited the manuscript before submission.