

1-6-2011

# Review article: the effects of antitumour necrosis factor- $\alpha$ on bone metabolism in inflammatory bowel disease.

Sundaram G. Veerappan  
*Royal College of Surgeons in Ireland*

Colm A. O'Morain  
*Adelaide & Meath Hospital, Tallaght*

Jacqueline Daly  
*Royal College of Surgeons in Ireland, [jdaly@rcsi.ie](mailto:jdaly@rcsi.ie)*

Barbara N. Ryan  
*Adelaide & Meath Hospital, Dublin*

## Citation

Veerappan SG, O'Morain CA, Daly JS, Ryan BM. Review article: the effects of antitumour necrosis factor- $\alpha$  on bone metabolism in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2011;33(12):1261-72

This Article is brought to you for free and open access by the Department of Anatomy at [e-publications@RCSI](mailto:e-publications@RCSI). It has been accepted for inclusion in Anatomy Articles by an authorized administrator of [e-publications@RCSI](mailto:e-publications@RCSI). For more information, please contact [epubs@rcsi.ie](mailto:epubs@rcsi.ie).

---

— Use Licence —



This work is licensed under a [Creative Commons Attribution-Noncommercial-Share Alike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

---

*"This is the pre-peer reviewed version of the following article: Review article: the effects of antitumour necrosis factor- $\alpha$  on bone metabolism in inflammatory bowel disease. Aliment Pharmacol Ther. 2011 Jun;33(12):1261-72.. Epub 2011 Apr 26. which has been published in final form at DOI: 10.1111/j.1365-2036.2011.04667.x. This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).*

## TITLE PAGE

**Title:** Review article: Effect of biologic therapy on bone metabolism in inflammatory bowel disease patients.

**Authors:** Sundaram G. Veerappan<sup>1,2</sup>, Colm A. O'Morain<sup>1</sup>, Jacqueline S. Daly<sup>2</sup>, Barbara M. Ryan<sup>1</sup>.

### **Institutions:**

<sup>1</sup>Department of Gastroenterology, Adelaide & Meath Hospital, Tallaght, Dublin 24, Republic of Ireland.

<sup>2</sup>Divison of Biology, Department of Anatomy, Royal College of Surgeons in Ireland, Dublin 2, Republic of Ireland.

**Correspondence to:** Dr. Sundaram G. Veerappan, Department of Gastroenterology, Adelaide & Meath Hospital, Tallaght, Dublin 24, Republic of Ireland.

Tel: + 353 85 717 9737

E-mail: sveerappan@rcsi.ie

**Keywords:** Anti-TNF alpha, bone metabolism, inflammatory bowel disease.

## **SUMMARY**

### **Background**

Osteoporosis is a common clinical problem, and has been increasingly recognised to occur in patients with inflammatory bowel disease (IBD) in whom a reduction in bone mineral density (BMD) has been widely reported. A number of studies have emerged in recent years indicating that tumour necrosis factor (TNF) blockade appears to have a beneficial effect on BMD in IBD patients.

### **Aims**

To provide a review of the available data regarding the effect of the currently licensed anti-TNF- $\alpha$  therapies on bone metabolism and BMD in IBD patients.

### **Methods**

A Medline search was performed using the search terms 'infliximab', 'bone metabolism', 'IBD', 'BMD', 'bone markers', 'adalimumab', 'bone disease', 'Crohn's disease', and 'ulcerative colitis'.

### **Results**

Infliximab has a beneficial effect on bone turnover markers in Crohn's disease patient in short term. There is little data looking at the effect of anti-TNF- $\alpha$  therapy on bone metabolism in ulcerative colitis patients. Moreover, the long term effects of anti-TNF- $\alpha$  therapy on bone structure and fracture risk in IBD patients are currently not known. The effect of cessation of anti-TNF- $\alpha$  therapy on bone metabolism is also unknown.

### **Conclusions**

Properly controlled long term trials are needed to fully evaluate the effect of TNF blockade in this regard.

## **MAIN TEXT**

### **INTRODUCTION**

IBD comprises a group of disorders of the gastrointestinal tract characterized by chronic intestinal inflammation and a chronic relapsing course. IBD has traditionally been categorized as either ulcerative colitis (UC) or Crohn's disease (CD) on the basis of clinical, radiological, endoscopic and histological criteria. Both UC and CD are commonly characterized by a series of clinical exacerbations and remissions requiring long term use of medications, and not frequently, surgical interventions. CD may involve the entire gastrointestinal tract from mouth to perianal area, whereas in UC the inflammation is confined to the large bowel. Multiple other organ systems can be affected in IBD, including the bones and joints, skin, eyes, hepatobiliary system, lungs and kidneys. Collectively, these are called extra-intestinal manifestations of IBD, and they can occur prior to, in conjunction with, or subsequent to active bowel disease. The overall prevalence of any extra-intestinal manifestations in IBD patients ranges from 21%-40%.<sup>1-</sup>  
<sup>3</sup> In most large studies of IBD, the prevalence of extra-intestinal manifestations is higher in CD compared to UC.<sup>2-4</sup>

Bone demineralization and osteoporosis in patients with IBD was first reported about 30 years ago.<sup>5</sup> The largest risk was observed at the spine, particularly in women, with a 6.5 fold increase in fracture risk.<sup>6</sup> In a recent population based cohort study, the relative risk of hip fracture was 1.41 (0.94-2.11) for UC and 1.68 (1.01-2.78) for CD patients.<sup>7</sup> This study also concluded that the risk of hip fracture is increased approximately 60% in IBD patients and the majority of hip fracture risk in IBD patients cannot be attributed to steroid use.<sup>7</sup>

The pathogenesis of reduced bone mineral density (BMD) in IBD is multi-factorial. As seen in the general population, factors such as age, gender, estrogen deficiency, alterations in calcium homeostasis, nutritional and dietary factors, smoking, alcohol and immobility may play a role. Vitamin D deficiency,<sup>8,9</sup> glucocorticoid treatment,<sup>10-13</sup> hypogonadism,<sup>14</sup> and Vitamin K deficiency<sup>15,16</sup> also have been shown to cause bone loss in some IBD patients. However, emerging evidence suggests that these factors play a relatively weak role in the pathogenesis of BMD loss in IBD and are overshadowed by the effect of the IBD itself.<sup>10,17-19</sup> Newly diagnosed untreated IBD patients been reported to have reduced BMD.<sup>20</sup> Recently, active inflammation and elevated pro-inflammatory cytokines have been implicated in the pathogenesis of bone resorption in a variety of models.<sup>21-26</sup> Circulating pro-inflammatory cytokine levels are elevated in IBD patients with active inflammation<sup>27-29</sup> suggesting that disease activity and high cytokine levels could also play a role in IBD related bone disease. A rat model of colitis was associated with a dramatic 33% loss in trabecular bone and an even greater suppression in bone formation rate.<sup>30</sup> Healing of colitis was associated with an increased bone formation rate and a return of bone measurements to normal levels. Serum from children with CD

affects bone mineralization in an organ culture model without altering bone resorption.<sup>16</sup> These observations suggest that mediators produced during intestinal inflammation may alter osteoblast function and bone formation, and they are consistent with the observation that osteoporotic patients with IBD have higher serum interleukin (IL)-6 levels than non osteoporotic patients. There is a strong case for suggesting that demineralization in patients with IBD occurs primarily as a consequence of the intestinal inflammation.

TNF- $\alpha$ , IL -1 $\beta$  and IL-6, amongst others, are potent activators of bone resorption at low concentrations *in vitro*.<sup>24,31,32</sup> The mechanisms of actions are multiple, including stimulation of osteoclast differentiation<sup>33-35</sup> and activation<sup>36</sup> with concomitant inhibition of osteoclast apoptosis.<sup>37</sup> TNF- $\alpha$  also inhibits osteoblast differentiation<sup>38</sup> and TNF- $\alpha$ , IL-1 $\beta$  and IL-6 reduce bone formation in cultured osteoblasts.<sup>32,39</sup> Like, IL-1, TNF-stimulated induction of osteoclast like cells formation in bone marrow culture<sup>40</sup> is mediated by increases in receptor activator of NF kappa ligand (RANKL) expression.<sup>41</sup> However, in addition to increasing RANKL expression TNF also stimulates osteoprotegerin (OPG) in osteoblastic model.<sup>42</sup> Thus, pro-inflammatory cytokines potentially cause bone loss by both increasing bone resorption and inhibiting bone formation. In IBD patients, elevated TNF- $\alpha$  are noted not only in patients with active disease but even in patients with inactive disease who have morphologically normal intestinal biopsies<sup>43</sup> and recently is suspected of being an important mediator of bone loss in this group of patients.<sup>44,45</sup>

The signaling system that normally maintains coupled bone remodeling has not been well defined, although it is clear that excessive osteoclastic bone resorption or defective osteoblast synthesis creates a dysequilibrium, with a net loss in bone mass. The initial

step in the remodeling process involves osteoclastogenesis through a process of sequential proliferation, differentiation, and activation of mononuclear precursors. The recent discovery of an elegant receptor-based interaction between osteoblast and osteoclast precursors appears to provide this "missing link" and simultaneously integrates this system with the immune response. Osteoblasts express a surface ligand RANKL that can bind to osteoclast precursors (the RANK) or an osteoblast-derived soluble decoy receptor known as OPG.<sup>46</sup> The binding of RANK to RANKL induces a signaling and gene expression cascade that results in differentiation and maturation of osteoclasts. OPG blocks this interaction, thereby inhibiting osteoclast formation. RANKL is also a regulator of T cell–dendritic cell interaction in the immune system and is a crucial factor in early lymphocyte development and lymph node organogenesis.<sup>47</sup> The central importance of this system is seen in RANKL gene–deficient mice that are unable to support osteoclast differentiation, display severe osteopetrosis (even in the presence of bone-resorbing factors, such as vitamin D<sub>3</sub>, dexamethasone, and PGE<sub>2</sub>), show no evidence of bone remodeling, and simultaneously lack all lymph nodes.<sup>48</sup> There is emerging evidence that the RANKL–OPG system may be the final common pathway for many of the classical bone-active agents. The discovery of the RANK ligand pathway and its inhibition by OPG has had important implications for bone physiology as well as inflammation research. These interactions suggest that TNF- $\alpha$  blockade may have beneficial effect on bone generally. Unfortunately, data regarding the effect of TNF- $\alpha$  blockade on BMD and bone metabolism in IBD patients in clinical setting are limited. In this review article, we aim to review the available data regarding the effect of anti-TNF- $\alpha$  therapy on bone metabolism and BMD in IBD patients.

## **INFLIXIMAB**

Infliximab is a chimeric IgG1 monoclonal antibody comprised of 75% human and 25% murine sequences, which has a high specificity for and affinity to TNF- $\alpha$ . Infliximab neutralizes the biologic activity of TNF- $\alpha$  by inhibiting binding to its receptors. However, infliximab's mechanism of action most likely involves the destruction of activated effector cells bearing receptor bound TNF- $\alpha$  through apoptosis and/or other mechanisms.<sup>49-53</sup> Infliximab has a half life of approximately 10 days. Infliximab is the first biologic agent to be licensed for use in IBD patients. Besides its use in IBD, infliximab is also licensed for use in rheumatoid arthritis (RA), plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.

Infliximab is approved for the treatment of moderate to severe CD patients who have not responded well to other conventional therapies.<sup>54,55</sup> In clinical studies, infliximab has been shown to decrease histologic and endoscopic disease activity and to induce and maintain remission in patients with active CD. Infliximab is also approved for use in fistulizing CD patients based upon the results of two randomized controlled trials.<sup>56,57</sup> Accumulating evidence has suggested that scheduled, maintenance therapy with infliximab has substantial clinical benefits compared with episodic treatment in CD patients who achieved remission with initial infliximab induction therapy.<sup>58</sup> For this reason most centers have now moved to scheduled as opposed to episodic maintenance therapy.

Infliximab is the first and only biologic currently approved for the treatment of moderate to severe UC failing to respond to conventional therapies.<sup>59</sup> In clinical studies,

infliximab treatment was associated with achievement of clinical response and clinical remission, mucosal healing and elimination of corticosteroid use. Despite its now widespread use in inflammatory disorders, only limited data exist on the role of infliximab on the bone metabolism in IBD patients. Furthermore most of the published data pertain to small cohorts of patients.

### **INFLIXIMAB AND BONE MARKERS**

The first studies to suggest that a beneficial effect was seen with TNF blockade on bone metabolism in IBD patients were published in 2004. Franchimont *et al.*<sup>60</sup> studied 71 CD patients treated for the first time with infliximab (5mg/kg) for refractory CD and compared their results to 68 healthy control population matched for age and gender with this CD patients. The study included 21 fistulizing refractory CD patients and 50 luminal refractory CD patients. Patients were treated with a single infusion of 5mg/kg infliximab at baseline for refractory disease and with three infusions of 5mg/kg infliximab at baseline, week 2 and week 6 for fistulizing refractory disease. Serum samples for bone formation markers; bone alkaline phosphatase (b-ALP), osteocalcin (OC) and pro-collagen type 1 N propeptide (P1NP) and serum samples for bone resorption markers carboxyterminal telopeptide (sCTX) were measured at baseline and 8 weeks after completion of infliximab treatment (week 8 for refractory luminal CD and week 14 for refractory fistulizing CD). Clinical activity of the disease based of Crohn's Disease Activity Index (CDAI) score and C-reactive protein (CRP) levels were also measured in this study at baseline and 4 weeks after completion of therapy as a marker of biological response. In this study, the authors observed serum concentration of the bone formation

markers; b-ALP, OC and P1NP were lower in CD before infliximab treatment than in healthy controls while they return to normal levels after infliximab treatment at eight weeks. The authors reported that a relevant improvement in bone formation (defined as an increase of at least 30% in the bone formation marker) was found after infliximab treatment in 29.7%, 60.8% and 46.5% of the patients when considering b-ALP, OC or P1NP as marker, respectively. Serum concentration of sCTx was significantly increased in CD at baseline but no longer different from controls after infliximab treatment at eight weeks. Relevant improvement in bone resorption (decrease of at least 30% in sCTx serum levels) was found after infliximab treatment in 38.2% of patients. The authors concluded that in their study infliximab showed a significant and rapid normalization in the biochemical markers of bone turnover in CD treated patients and that this could probably be considered as clinically relevant in approximately 60% of the patients. This improvement didn't seem to be selectively associated with demographic or clinical characteristics of the patients, including clinical or biological response to infliximab or even steroid weaning. There was no significant difference when comparing median change in bone markers in luminal (treated with single infliximab infusion) and fistulizing CD (treated with three infliximab infusions).

Ryan *et al.*<sup>61</sup> in a prospective trial studied 24 patients with active CD who were treated with infliximab (5mg/kg) for the first time. The majority of the patients had refractory luminal CD and only 2 patients had refractory luminal and fistulizing CD. There was no control group included in this study. 42% of the patients were on steroids and 50% of the patients were on calcium/Vitamin D supplements at the start of the study. Five time points were assayed, namely; baseline, 1-2, 4-6, 8-10 and 12-18 weeks post single

infliximab infusion. In this study, infliximab infusion led to a significant increase in both markers of bone formation, b-ALP (p=0.022) and OC (p=0.008). Levels of both bone formation markers remained significantly increased even at 4 months post treatment. No significant change in serum N-telopeptide (sNTx) was observed although at 4 months post treatment, levels were lower than at baseline. Of particular interest, the benefit seen on bone metabolism with infliximab treatment appeared to occur independently of the clinical response in terms of effect on CD activity; however the trend of increase in both bone formation markers and decrease in bone resorption marker was greater in responders compared with non-responders. In this study as well, maximal reduction in CDAI was seen between 8 and 10 weeks, whereas bone formation markers continued to increase up to 16 weeks post treatment, suggesting that there might be a lag in the biological effect of the infliximab on bone metabolism.

Following on this, Abreu *et al.*<sup>62</sup> in small, short prospective study involving 38 refractory CD patients reported a significant increase in b-ALP (p=0.010) whereas serum NTx, was not increase (p=0.801) at week 4 compared to baseline post a single infliximab infusion. This study again did not compare its findings with an age matched control group. In this study sera were also analyzed for immunoreactive parathyroid hormone (iPTH), calcium and pro-inflammatory cytokines (IL-1 $\alpha$ , IL-6, and TNF- $\alpha$ ) at baseline and 4 weeks following infliximab infusion. Overall, treatment with infliximab was associated with a statistically significant decrease in PTH levels (p=0.008) and statistically significant increase in serum calcium (p=0.034) at week 4. No significant changes in serum cytokine measurements from baseline to week 4 were noted. In this study the authors also sub analyzed the data based on whether the patients were receiving

glucocorticoids at the time of their initial infliximab infusion and whether patients were responders or non-responders. 22/38 (57.9%) patients were receiving glucocorticoids at their time of initial infliximab infusion. The increase in bone formation occurred in both glucocorticoid treated individuals and those not on glucocorticoid, concluding that glucocorticoid use is not the principal reason for osteoporosis in patients with CD. Importantly, in this study the effect was also seen in both infliximab responders and non-responders, suggesting an independent effect of infliximab on bone metabolism.

Miheller *et al.*<sup>63</sup> in a small study studied the effect of infliximab on bone formation and resorption marker in 27 fistulizing CD patients and compared the results with 54 patients with inactive CD who acted as controls. Again, this was a short term study of just 42 days, and in treated patients, there were significant difference in  $\beta$ -CrossLaps (bCL), a marker for bone resorption on days 0 and 14 ( $p < 0.01$ ) and days 0 and 42 ( $p < 0.05$ ). OC levels increased significantly between day 0 and 42 ( $p < 0.05$ ) confirm the results from previous studies that infliximab has beneficial effects on bone turnover markers in CD patients.

## **INFLIXIMAB AND BONE MINERAL DENSITY**

To date, few published studies have examined the effect of infliximab on bone loss in CD patients by measuring BMD. A retrospective cohort analysis was performed by Pazianas *et al.*<sup>64</sup> on 61 patients with CD and low BMD as measured by DXA scans. 23 patients were on infliximab and 36 patients were on bisphosphonates. Mean duration between DXA scans was 2.2 +/- 0.99 years. After controlling for corticosteroids use, patients with concurrent infliximab and bisphosphonate treatment exhibited a greater

increase in BMD compared to those on bisphosphonate alone (+6.7%/year vs. +4.46%/year,  $p=0.045$ ); corticosteroids inhibited this effect ( $p=0.025$ ). However, infliximab alone had no effect on BMD. In this study, only lumbar spine BMD measurements were included for analysis and there were no control group.

In another retrospective study by Mauro *et al.*<sup>65</sup> data from 15 patients with CD who had received treatment with infliximab for the first time and who underwent DXA before and during infliximab treatment were compared with 30 CD patients who had never received treatment with infliximab and who had two DXA evaluations at least 12 months apart. Patients in this study received infliximab (5mg/kg) at intervals of four to eight weeks for a mean period of 18 months. The first and second DXA evaluations were 22.6 +/-11 months apart in the infliximab group and 20.4 +/- 8 months apart in the control group. The infliximab group had a significant increase in lumbar bone area, bone mineral content (BMC) and BMD between both evaluations compare to control (CD patients who had never received infliximab). The increase in BMC, i.e. the bone mass measurements in patients who had received infliximab treatment was significant when compared with control patients who had received glucocorticoids ( $n=8$ ) or who had evidence of disease activity.

Bernstein *et al.*<sup>66</sup> also found that maintenance treatment with infliximab (5mg/kg) at 6-8 weeks intervals for 1 year in 46 CD patients improved BMD after one year in the lumbar spine (2.4% increase,  $p=0.002$ ), at the femoral trochanter by (2.8% increase,  $p=0.03$ ), and at the femoral neck by (2.6% increase,  $p=0.001$ ) and that this effect was independent of concurrent administration of glucocorticoids, calcium supplementation, or changes in C-reactive protein. Also BMD gain at the lumbar spine

and the left femur between the groups without and with osteopenia were not different. However, this study did not have a control group to compare differences in the changes in BMD.

## **INFLIXIMAB AND OSTEOCLASTOGENESIS MARKERS**

Only one study has evaluated changes of osteoclastogenesis markers (OPG and RANKL) with infliximab therapy. Miheller *et al.*<sup>67</sup> studied 29 refractory CD patients who were treated with infliximab at week 0, 2 and 6. In 19 cases CD was associated with fistulas. There were no postmenopausal females in this cohort, and all of these patients were steroid free for at least 1 month before the first infliximab infusion. No patients in this study had been treated with bisphosphonates or vitamin D. Six patients were on calcium supplements. Serum OC as a bone formation marker, serum beta-crosslaps (bCL) as a marker of bone resorption, serum OPG, and serum RANKL were measured before each course of infliximab therapy. BMD measurements were also performed at baseline in all patients using a DXA scan. In this study, four of 29 patients had osteoporosis and 14 of 29 had osteopenia. Serum levels of bone formation marker (OC) and RANKL increased after infliximab therapy at week 6, while concentrations of bone resorption marker (bCL) and OPG decreased at the same time. Femoral BMD correlated with baseline serum bCL and sRANKL concentrations (0.548;  $p < 0.05$  and 0.532;  $p < 0.05$ ). There were no significant correlations between bone remodeling markers (OC and bCL) and osteoclastogenesis markers (OPG and sRANKL) and lumbar BMD. The authors concluded that elevated OPG in CD could be a counter-regulatory response to

inflammatory cytokines or may reflect T-cell activation.

## **ADALIMUMAB**

Adalimumab is a human IgG1 monoclonal antibody specific for human TNF. Unlike, infliximab which requires an intravenous infusion, adalimumab is administered by subcutaneous injection.<sup>68</sup> Adalimumab has been recently approved for the treatment of active CD. The clinical efficacy and safety of adalimumab in patients with moderate to severe CD has been demonstrated in four pivotal studies.<sup>69-72</sup> All these studies have shown adalimumab to be superior to placebo for inducing and maintaining remission. Maintenance adalimumab therapy is administered as a subcutaneously every two weeks. The approved induction dosing of adalimumab in CD is 160 mg given subcutaneously initially at week zero, 80 mg at week two, followed by a maintenance dose of 40 mg every other week beginning at week four. The drug is available in a single-use prefilled pen (HUMIRA Pen) or in a single-use, prefilled glass syringe. At present time, adalimumab is only licensed for use in CD patients.

## **ADALIMUMAB AND BONE METABOLISM IN IBD**

To the best of our knowledge, there are currently no published data investigating the effect of adalimumab on bone metabolism in IBD patients. However, one such report exists studying BMD in a population of RA patients treated for 1 year with adalimumab.<sup>73</sup> In this study, fifty patients with active RA (defined as having a 28-joint disease activity score (DAS28) of  $\geq 3.2$ ) who started adalimumab treatment (40 mg subcutaneously every other week) were included in an open label prospective study. The

BMD of both the lumbar spine (L1-L4) and left femoral neck was measured before treatment and after one year by DXA. Both disease activity at baseline (DAS28) and disease duration were inversely correlated with femoral neck BMD and lumbar spine BMD ( $p < 0.05$ ). Mean BMD of both lumbar spine and femur neck remained unchanged after one year of adalimumab therapy (+0.3% and +0.3%, respectively). The authors concluded that their result shows that with adalimumab therapy, progression of bone loss is halted. Measurements of bone turnover markers were not performed in this study though and there was no control group.

## **SUMMARY**

The data, albeit slightly limited, available to date strongly suggest that infliximab has beneficial effect on bone metabolism in CD patients. The beneficial effect does seem to be heterogeneous in aetiology and to vary from patient to patient. Primarily, the main beneficial effect appears to be related to an increase in bone formation although a decrease in bone resorption also appears to play a role in some patients. The effects seem to be independent of whether the response and non-response to treatment based on clinical score. Furthermore, the beneficial effects on bone metabolism appear to be independent of steroid therapy. Case-control studies (which are few) indicated that CD patients in general had lower bone formation markers and higher bone resorption markers as compared to healthy subjects and that infliximab therapy reverses this balance.

Patients who received infliximab have also been shown to increase BMD during therapy.

It's likely that several different mechanisms play a role in this positive effect of infliximab on bone metabolism. Firstly, neutralization of TNF- $\alpha$ , which has a beneficial

effect on bone metabolism in vitro, might also play a role in vivo.<sup>74,75</sup> Secondly, infliximab reduces elaboration of a host of other pro-inflammatory cytokines such as IL-6 and IL-1 $\beta$ <sup>53</sup> which also has a deleterious effect on bone metabolism<sup>25,32</sup> thus reduction of the inflammatory response in general is likely to play a pivotal role. A third possible mechanism is that improvement in general well being and physical activity might also improve net bone formation. Fourthly, by reducing gut inflammation, infliximab can improve bone metabolism indirectly by increase in resorption of the crucial bone nutrients required for bone formation.

Study	Number of patients	Underlying condition	Control group (No of patients)	Number of infliximab infusions	Bone formation markers measured	Bone resorption makers measured	Bone mineral density evaluated	Bone nutrients measured	OPG/RANKL measured	Time point measured	Major conclusion
Franchimont <i>et al</i> <sup>60</sup>	71	CD (21 fistulizing, 50 luminal)	Healthy subjects (68)	1 (for luminal disease); 3 (for fistulizing disease)	Yes (b-ALP, OC, PINP)	Yes (sCTX)	No	No	No	At baseline and 8 weeks post infliximab	↑ bone formation markers; ↓ bone resorption marker at 8 weeks post infliximab. Rapid normalization of formation and resorption markers noted to the level of controls with infliximab
Ryan <i>et al</i> <sup>61</sup>	24	CD (2 had fistulizing)	No	1	Yes (b-ALP, OC)	Yes (sNTx)	No	No	No	At baseline, 1-2, 4-6, 8-10, 12-18 weeks post infliximab	Significant ↑ in both markers of bone formation, b-ALP and OC. Levels remained significantly ↑ even at 4 months post treatment. No significant change in sNTx was observed although at 4 months post treatment, levels were lower than at baseline.

Abreu <i>et al</i> <sup>62</sup>	38	CD	No	1	Yes (b-ALP)	Yes (sNTx)	No	Yes (iPTH; Calcium)	No	At baseline and 4 weeks post infliximab	↓ in PTH and ↑ in calcium at week 4. ↑ in bone formation marker occurred in both glucocorticoid treated and those not on glucocorticoid patients
Miheller <i>et al</i> <sup>63</sup>	27	CD (all fistulizing)	Yes (54-inactive CD)	3	Yes (OC)	Yes (b-CL)	No	No	No	At baseline, week 2 and week 6 post infliximab	Significant ↑ in OC at week 6 noted, and significant difference noted of b-CL on days 0 and 14 and days 0 and 42
Pazianas <i>et al</i> <sup>64</sup> (retrospective study)	61	CD	No	Not mentioned	No	No	Yes	No	No	Mean duration between DEXA scans were 2.2 +/- 0.99 years	Patients on concurrent infliximab and bisphosphonates had increase in BMD compared to bisphosphonates alone. Infliximab alone had no effect on BMD
Mauro <i>et al</i> <sup>65</sup> (retrospective study)	15	CD	30 CD patients who had no infliximab treatment	Maintenance therapy every 4-8 weeks for a mean of 18 months	No	No	Yes	No	No	1st and 2nd DEXA were 22.6 +/- 11 months apart in the infliximab group and 20.4 +/- 8 months apart in the control group	The infliximab group had a significant increase in lumbar bone area, bone mineral content and BMD compared to control group.

Bernstein <i>et al</i> <sup>66</sup>	46	CD	No	Maintenance therapy every 6-8 weeks for 1 year	No	No	Yes	No	No	At baseline and 1 year post infliximab treatment	Improved BMD after 1 year in the lumbar spine (p=0.002), femoral trochanter (p=0.03) and at femoral neck (p=0.001) and this was independent of concurrent administration of glucocorticoids, calcium supplementation or changes in CRP.
Miheller <i>et al</i> <sup>67</sup>	29	CD (19 fistulizing)	No	3	Yes (OC)	Yes (b-CL)	Yes (only at baseline)	No	Yes	At baseline, week 2 and week 6 post infliximab	Serum levels of OC and RANKL increased, while bCL and OPG decreased at week 6. Femoral BMD correlated with basic serum bCL and sRANKL.

Table 1: Summary of published articles looking at the effect of infliximab on bone metabolism in IBD patients.

## **CONCLUSION**

To date, studies looking at the effects of anti-TNF- $\alpha$  therapy on bone metabolism in IBD patients are limited, and have only evaluated the role of infliximab on bone metabolism in CD patients. No studies have yet evaluated the effects of adalimumab therapy on bone metabolism in IBD patients or the effect of anti-TNF  $\alpha$  therapy in UC patients. Furthermore, currently available studies have only been carried out for short term, with the longest being for 14 weeks.<sup>61</sup> Hence the long term effect of maintenance therapy with anti-TNF- $\alpha$  on bone metabolism in IBD patients is not known. Moreover, the effects of these therapies on bone cells have not yet been studied. This is crucial to understanding the direct effect of anti-TNF- $\alpha$  on bone cells. Long term studies are also needed to compare changes in cytokines, osteoclastogenesis markers (OPG and RANKL), bone nutrients (PTH and vitamin D) and most importantly on BMD to fully understand the mechanisms involved. Finally, what happens to the beneficial effects seen on bone metabolism in IBD patients following cessation of anti-TNF- $\alpha$  therapy is not known. Properly controlled long term trials are necessary to fully evaluate the effects of TNF blockers in this regard.

## **ACKNOWLEDGMENT**

*Declaration of personal interest:* Prof. Colm O'Morain is on the international advisory board of Abbott, Schering Plough and Shire pharmaceutical companies.

*Declaration of funding interests:* None.

## REFERENCES

1. Ricart E, Panaccione R, Loftus EV Jr, *et al.* Autoimmune disorders and extra-intestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: A case control study. *Inflamm Bowel Dis* 2004; **10**: 207-14.
2. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease: A prospective study of 792 patients. *J Clin Gastroenterol* 1996; **23**: 29-34.
3. Lakatos L, Pandur T, David G, *et al.* Association of extra-intestinal manifestations of inflammatory bowel disease in a province or western Hungary with disease phenotype: Results of a 25-year follow-up study. *World J Gastroenterol* 2003; **9**: 2300-7.
4. Vind I, Riis L, Jess T, *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: A population-based study from the Danish Crohn Colitis Database. *Am J Gastroenterol* 2006; **101**: 1274-82.
5. Genant, HK, Mall, JC, Wagonfeld, JB, *et al.* Skeletal demineralization and growth retardation in inflammatory bowel disease. *Invest Radiol* 1976; Nov-Dec; **11(6)**: 541-9.
6. Vestergaard P, Mosekilde F. Fracture risk in patients with coeliac disease, Crohn's disease, and ulcerative colitis: A nationwide follow-up study of 16416 patients in Denmark. *Am J Epidemiol* 2002; **156**: 1-10.

7. Card T, West J, Hubbard R, *et al.* Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: A population based cohort study. *Gut* 2004; **53**: 251-5.
8. Silvennoinen JA. Relationship between vitamin D, parathyroid hormone and bone mineral density in inflammatory bowel disease. *J Int Med* 1996; **239**: 131-7.
9. Bischoff SC, Herrmann A, Goke M, *et al.* Altered bone metabolism in inflammatory bowel disease. *Am J Gastroenterol* 1997; **92**: 1157-63.
10. Silvennoinen JA, Karttunen TJ, Niemelia SE, *et al.* A controlled study of bone mineral density in patients with inflammatory bowel disease. *Gut* 1995; **37**: 71-6.
11. Bernstein CN, Seeger LL, Sayre JW, *et al.* Decreased bone mineral density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. *J Bone Miner Res* 1995; **10**: 250-6.
12. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med* 1983; **309**: 265-8.
13. Compston JE. Detection of osteoporosis in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1997; **9**: 931-3.
14. Robinson RJ, Iqbal SJ, Al-Azzani F, *et al.* Sex hormone status and bone metabolism in men with Crohn's disease. *Aliment Pharmacol Ther* 1998; **12**: 21-5.
15. Szulc P, Meunier PJ. Is vitamin-K deficiency a risk factor for osteoporosis in Crohn's disease? *Lancet* 2001; **357**: 1995-6.

16. Hyams JS, Wyzga N, Kreutzer DL, *et al.* Alterations in bone metabolism in children with inflammatory bowel disease: An in vitro study. *J Pediatr Gastroenterol Nutr* 1997; **24**: 289-95.
17. Abitol V, Roux C, Chaussade S *et al.* Metabolic bone assessment in patients with inflammatory bowel disease. *Gastroenterology* 1995; **108**: 417-22.
18. Jahnsen J, Falch JA, Aadland E, *et al.* Bone mineral density is reduced in patients with Crohn's disease but not in patients with ulcerative colitis. *Gut* 1997; **40**: 313-9.
19. Robinson RJ, Krzywicki T, Almond L *et al.* Effect of low-impact exercise program on bone mineral density in Crohn's disease. A randomized controlled study. *Gastroenterology* 1998; **115**: 36-41.
20. Lamb EJ, Wong T, Smith DJ, *et al.* Metabolic bone disease is present at diagnosis in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2002; **16**: 1895-1902.
21. Ammann P, Rizzoli R, Bonjour JP, *et al.* Transgenic mice expressing soluble tumor necrosis factor-receptor are protected against bone loss caused by estrogen deficiency. *J Clin Invest* 1997; **99**: 1699– 703.
22. Bickel M, Axtelius B, Solioz C, *et al.* Cytokine gene expression in chronic periodontitis. *J Clin Periodontol* 2001; **28**: 840– 7.
23. Udagawa N, Kotake S, Kamatani N, *et al.* The molecular mechanism of osteoclastogenesis in rheumatoid arthritis. *Arthritis Res* 2002; **4**: 281– 9.

24. Origuchi T, Migita K, Nakashima T, *et al.* IL-1-mediated expression of membrane type matrix-metalloproteinase in rheumatoid osteoblasts. *Clin Exp Rheumatol* 2000; **18**: 333– 9.
25. Oelzner P, Franke S, Muller A, *et al.* Relationship between soluble markers of immune activation and bone turnover in post-menopausal women with rheumatoid arthritis. *Rheumatology (Oxford)* 1999; **38**: 841– 7.
26. Matsuno H, Yudoh K, Katayama R, *et al.* The role of TNF-alpha in the pathogenesis of inflammation and joint destruction in rheumatoid arthritis (RA): a study using a human RA/SCID mouse chimera. *Rheumatology (Oxford)* 2002; **41**: 329– 37.
27. Murch SH, Lamkin VA, Savage MO, *et al.* Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. *Gut* 1991; **32**: 913– 7.
28. Komatsu M, Kobayashi D, Saito K, *et al.* Tumor necrosis factor-alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immuno-PCR. *Clin Chem* 2001; **47**: 1297– 301.
29. Lanfranchi GA, Tragnone A. Serum and faecal tumour necrosis factor-alpha as marker of intestinal inflammation. *Lancet* 1992; **339(8800)**: 1053.
30. Lin, CL, Moniz, C, Chambers, TJ, *et al.* Colitis causes bone loss in rats through suppression of bone formation. *Gastroenterology* 1996; **111**: 1263.
31. Kumar S, Votta BJ, Rieman DJ, *et al.* IL-1- and TNF-induced bone resorption is mediated by p38 mitogen activated protein kinase. *J Cell Physiol* 2001; **187**: 294– 303.

32. Sylvester FA, Wyzga N, Hyams JS, *et al.* Effect of Crohn's disease on bone metabolism in vitro: a role for interleukin-6. *J Bone Miner Res* 2002; **17**: 695–702.
33. Zhang YH, Heulsmann A, Tondravi MM, *et al.* Tumor necrosis factor-alpha (TNF) stimulates RANKL-induced osteoclastogenesis via coupling of TNF type 1 receptor and RANK signaling pathways. *J Biol Chem* 2001; **276**: 563–8.
34. Lam J, Takeshita S, Barker JE, *et al.* TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000; **106**: 1481–8.
35. Zou W, Hakim I, Tschöep K, *et al.* Tumor necrosis factor-alpha mediates RANK ligand stimulation of osteoclast differentiation by an autocrine mechanism. *J Cell Biochem* 2001; **83**: 70– 83.
36. Fuller K, Murphy C, Kirstein B, *et al.* TNF alpha potently activates osteoclasts, through a direct action independent of and strongly synergistic with RANKL. *Endocrinology* 2002; **143**: 1108–18.
37. Lee SE, Chung WJ, Kwak HB, *et al.* Tumor necrosis factor-alpha supports the survival of osteoclasts through the activation of Akt and ERK. *J Biol Chem* 2001; **276**: 49343–9.
38. Gilbert L, He X, Farmer P, *et al.* Inhibition of osteoblast differentiation by tumor necrosis factor-alpha. *Endocrinology* 2000; **141**: 3956–64.
39. Taichman RS, Hauschka PV. Effects of interleukin-1 beta and tumor necrosis factor-alpha on osteoblastic expression of osteocalcin and mineralized extracellular matrix in vitro. *Inflammation* 1992; **16**: 587–601.

40. Pfeilschifter J, Chenu C, Bird A, *et al.* Interleukin 1 and tumour necrosis factor stimulate the formation of human osteoclast like cells in vitro. *J Bone Miner Res* 1989; **4**: 113-18.
41. Hofbauer LC, Lacey DL, Dunstan CR, *et al.* Interleukin 1 beta and tumour necrosis factor  $\alpha$ , but not interleukin 6, stimulate osteoprotegerin ligand gene expression in human osteoblastic cells. *Bone* 1999; **25**: 255-59.
42. Hofbauer LC, Dunstan CR, Spelsberg TC, *et al.* Osteoprotegerin production by human osteoblast lineage cells is stimulated by vitamin D, bone morphogenetic protein-2, and cytokines. *Biochem Biophys Res Commun.* 1998; **250**: 776-81.
43. Reimund JM, Wittersheim C, Dumont S, *et al.* Increased production of tumour necrosis factor-alpha interleukin-1 beta, and interleukin-6 by morphologically normal intestinal biopsies from patients with Crohn's disease. *Gut* 1996; **39(5)**: 684-9.
44. Lichtenstein GR. Evaluation of bone mineral density in IBD: Current safety focus. *Am J Gastroenterol* 2003; **98(suppl 12)**: S24-30.
45. Nanes MS. TNF-alpha: Molecular and cellular mechanisms in skeletal pathology. *Gene* 2003; **321**: 1-15.
46. Aubin, JE, Bonnelye, E. Osteoprotegerin and its ligand: a new paradigm for regulation of osteoclastogenesis and bone resorption. *Osteoporos Int* 2000; **11(11)**: 905-13.
47. Kong, YY, Boyle, WJ, Penninger, JM. Osteoprotegerin ligand: a common link between osteoclastogenesis, lymph node formation and lymphocyte development. *Immunol Cell Biol* 1999; Apr; **77(2)**: 188-93.

48. Kong, YY, Feige, U, Sarosi, I, *et al.* Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999; Nov 18; **402(6759)**: 304-9.
49. Scallon BJ, Moore MA, Trinh H, *et al.* Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* 1995; **7(3)**: 251-9.
50. Su C, Salzberg BA, Lewis JD, *et al.* Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. *Am J Gastroenterol* 2002; **97(10)**: 2577-84.
51. Luger A, Schmidt M, Luger N, *et al.* Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. *Gastroenterology* 2001; **121(5)**: 1145-57.
52. Ten Hove T, van Montfrans C, Peppelenbosch MP, *et al.* Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut* 2002; **50(2)**: 206-11.
53. Van den Brande JM, Braat H, Van den Brink GR, *et al.* Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003; **124(7)**: 1774-85.
54. Targan SR, Hanauer SB, Van Deventer SJ, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337(15)**: 1029-35.
55. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359(9317)**: 1541-9.

56. Present DH, Rutgeerts P, Targan S, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340(18)**: 1398-405.
57. Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350(9)**: 876-85.
58. Rutgeerts P, Feagan BG, Lichtenstein GR, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126**: 402-13.
59. Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353(23)**: 2462-76.
60. Franchimont N, Putzeys V, Collette J, *et al.* Rapid improvement of bone metabolism after infliximab treatment in Crohn's disease. *Aliment Pharmacol Ther* 2004; **20**: 607-14.
61. Ryan BM, Russel MGVM, Schurgers L, *et al.* Effect of antitumour necrosis factor- $\alpha$  therapy on bone turnover in patients with active Crohn's disease: a prospective study. *Aliment Pharmacol Ther* 2004; **20**: 851-7.
62. Abreu MT, Geller JL, Vasiliauskas EA, *et al.* Treatment with infliximab is associated with increased markers of bone formation in patients with Crohn's disease. *J Clin Gastroenterol* 2006; **40(1)**: 55-63.
63. Miheller P, Muzes G, Zagoni T, *et al.* Infliximab therapy improves the bone metabolism in fistulizing Crohn's disease. *Dig Dis* 2006; **24(1-2)**: 201-6.
64. Pazianas M, Rhim AD, Weinberg AM, *et al.* The effect of anti-TNF-alpha therapy on spinal bone mineral density in patients with Crohn's disease. *Ann N Y Acad Sci* 2006; **1068**: 543-56.

65. Mauro M, Radovic V, Armstrong D. Improvement of lumbar bone mass after infliximab therapy in Crohn's disease patients. *Can J Gastroenterol* 2007; **21(10)**: 637-42.
66. Bernstein M, Irwin S, Greenberg GR. Maintenance infliximab treatment is associated with improved bone mineral density in Crohn's disease. *Am J Gastroenterol* 2005; **100(9)**: 2031-5.
67. Miheller P, Muzes G, Rácz K, *et al.* Changes of OPG and RANKL concentrations in Crohn's disease after infliximab therapy. *Inflamm Bowel Dis* 2007; **13(11)**: 1379-84.
68. Plosker G.L., Lyseng-Williamson K.A. Adalimumab; in Crohn's disease. *Biodrugs* 2007; **21(2)**: 125-32.
69. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130(2)**: 323-33.
70. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132(1)**: 52-65.
71. Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab. *Ann Intern Med* 2007; **146(12)**: 829-38.
72. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56(9)**: 1232-9.

73. Wijbrandts CA, Klaasen R, Dijkgraaf MG, *et al.* Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss? *Ann Rheum Dis* 2009; **68(30)**: 373-6.
74. Zou W, Hakim I, Tschoep K, *et al.* Tumour necrosis factor-alpha mediates RANK ligand stimulation of osteoclast differentiation by an autocrine mechanism. *J Cell Biochem* 2001; **83**: 70-83.
75. Abu-Amer Y, Erdmann J, Alexopoulou L, *et al.* Tumour necrosis factor receptors types 1 and 2 differentially regulate osteoclastogenesis. *J Biol Chem* 2000; **275**: 27307-10.