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Barbara Ryan

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Sundaram Ganesan Veerappan, Colm A. O'Morain, Jacqueline S. Daly, Barbara Ryan. Review article: Effects of anti-tumour necrosis factor- α on bone metabolism in inflammatory bowel disease.. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (12), pp.1261. 10.1111/j.1365-2036.2011.04667.x . hal-00635798

HAL Id: hal-00635798

<https://hal.science/hal-00635798>

Submitted on 26 Oct 2011

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Review article: Effects of anti-tumour necrosis factor- α on bone metabolism in inflammatory bowel disease.

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0627-2010.R2
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	05-Apr-2011
Complete List of Authors:	Veerappan, Sundaram; Adelaide&Meath Hospital, Tallaght, Department of Gastroenterology O'Morain, Colm; Adelaide&Meath Hospital, Tallaght, Department of Gastroenterology Daly, Jacqueline; Royal College of Surgeons in Ireland, Division of Biology, Department of Anatomy Ryan, Barbara; Adelaide & Meath Hospital, Dept of Gastroenterology
Keywords:	Inflammatory bowel disease < Disease-based, Bone disorders < Topics, Osteoporosis < Topics, X keyword = no topic

TITLE PAGE

Title: Review article: **Effects of anti-tumour necrosis factor- α on bone metabolism in inflammatory bowel disease.**

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

SUMMARY

Background

Patients with inflammatory bowel disease (IBD) are at increased risk of osteoporosis. A number of studies have emerged in recent years indicating that tumour necrosis factor (TNF) blockade appears to have a beneficial effect on bone mineral density (BMD) in IBD patients.

Aims

To provide a review of the available data regarding the effect of the currently licensed anti-TNF- α 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 (CD) patients in the short term. The longest study to date comprising 24 CD patients showed an overall improvement in two bone formation markers - b-alkaline phosphatase ($p=0.022$) and osteocalcin ($p=0.008$) at 4 months post treatment. Moreover, the largest study to date comprising 71 CD patients showed significant improvement in sCTx, a bone resorption marker ($p=0.04$) at week 8 post treatment. There is little data looking at the effect of anti-

1
2
3 TNF- α therapy on bone metabolism in ulcerative colitis. Moreover, the long term effects
4
5 of anti-TNF- α therapy on bone structure and fracture risk in IBD patients are currently
6
7 not known. The effect of cessation of anti-TNF- α therapy on bone metabolism is also
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9 unknown.
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12 13 14 15 **Conclusions**

16
17 Properly controlled long term trials are needed to fully evaluate the impact of TNF
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19 blockade on BMD.
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MAIN TEXT

INTRODUCTION

Bone demineralisation and osteoporosis in patients with inflammatory bowel disease (IBD) was first reported 35 years ago.¹ The largest risk was observed at the spine, with a 6.5 fold increase in fracture risk.² In a recent population based cohort study, the relative risk of hip fracture was 1.41 (0.94-2.11) for ulcerative colitis (UC) and 1.68 (1.01-2.78) for Crohn's disease (CD).³ This study also concluded that the risk of hip fracture is increased approximately 60% in IBD patients and that the majority of hip fracture risk in IBD patients cannot be attributed to steroid use.³ The pathogenesis of reduced bone mineral density (BMD) in IBD is multi-factorial. General risk factors as seen in the general population, such as age, gender, estrogen deficiency, alterations in calcium homeostasis, nutritional and dietary factors, smoking, alcohol and immobility are likely to play a role. Additional risk factors that have been shown to influence bone metabolism in some IBD patients includes Vitamin D deficiency,^{4,5} glucocorticoid treatment,⁶⁻⁹ hypogonadism,¹⁰ and Vitamin K deficiency.^{11,12} 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.^{6,13-15} Furthermore, newly diagnosed untreated IBD patients been reported to have reduced BMD.¹⁶

In IBD, use of corticosteroids as a therapy is a common. Approximately 70% of patients with CD are treated with corticosteroids and 35% become dependent on this therapy.^{17,18} The negative effects of corticosteroids on bone metabolism are well known;

1
2
3 they include both reduction of bone formation and concomitant increased bone
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6 resorption effects. Corticosteroids are also known to increase receptor activator of NF
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8
9 kappa ligand (RANKL) synthesis and inhibit osteoprotegerin (OPG) production which in
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11
12 turn results in net increase in the osteoclastogenesis. *In vitro*, addition of corticosteroids
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15 to osteoprogenitor cells increases their bone forming capacity while also increasing
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18 apoptosis of mature osteoblasts resulting in an overall reduction of bone formation
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21 capacity.¹⁹ Corticosteroids also cause vitamin D catabolism and inhibit calcium
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24 absorption in the gastrointestinal tract resulting in deficiency of these two crucial bone
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27 nutrients for bone maintenance.¹⁹

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30 Elevated pro-inflammatory cytokines and active inflammation have been implicated in
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33 the pathogenesis of bone loss in a variety of inflammatory models.²⁰⁻²⁵ Pro-inflammatory
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36 cytokine levels are elevated in IBD patients with active inflammation²⁶⁻²⁸ suggesting that
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39 disease activity could also play a role in IBD related bone disease. A rat model of colitis
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42 was associated with a dramatic 33% loss in trabecular bone and an even greater
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44
45 suppression in bone formation rate.²⁹ Healing of colitis was associated with an increased
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47
48 bone formation rate and a return of bone measurements to normal levels. Serum from
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51 children with CD affects bone mineralization in an organ culture model without altering
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53
54 bone resorption.¹² These observations suggest that mediators produced during intestinal
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57 inflammation may alter osteoblast function and bone formation, suggesting in turn that
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60 demineralisation in patients with IBD occurs primarily as a consequence of the intestinal
inflammation.

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3 TNF- α , IL -1 β and IL-6, are potent activators of bone resorption.^{23,30,31} These pro-
4
5 inflammatory cytokines cause net bone loss through a number of by mechanisms. These
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7 cytokines have been shown to stimulate osteoclast differentiation³²⁻³⁴, increase osteoclast
8
9 activation³⁵, inhibit osteoclast apoptosis³⁶ and inhibit osteoblast differentiation³⁷. They
10
11 also reduce bone formation in cultured osteoblasts in *in vitro*.^{31,38} Like, IL-1, TNF-
12
13 stimulated induction of osteoclast-like-cell formation in bone marrow culture³⁹ is
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15 mediated by increases in RANKL expression.⁴⁰ However, in addition to increasing
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17 RANKL expression, TNF also inhibits OPG in an osteoblastic model.⁴¹ Thus, pro-
18
19 inflammatory cytokines potentially cause bone loss by both increasing bone resorption
20
21 and inhibiting bone formation. In IBD patients, elevated TNF- α are noted not only in
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23 patients with active disease but even in patients with inactive disease who have
24
25 morphologically normal intestinal biopsies⁴² and recently is implicated as being an
26
27 important mediator of bone loss in this group of patients.^{43,44}

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34 Osteoblasts are also now known to express a surface ligand RANKL that can bind to
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36 osteoclast precursors (the RANK) or an osteoblast-derived soluble decoy receptor known
37
38 as OPG.⁴⁵ The binding of RANK to RANKL results in differentiation and maturation of
39
40 osteoclasts. OPG blocks this interaction, thereby inhibiting osteoclast formation. There is
41
42 emerging evidence that the RANKL–OPG system may be the final common pathway and
43
44 mediator of osteoclastic bone resorption. The discovery of the RANK ligand pathway and
45
46 its inhibition by OPG has had important implications for bone physiology. These
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48 interactions suggest that TNF- α blockade may have beneficial effect on bone generally.
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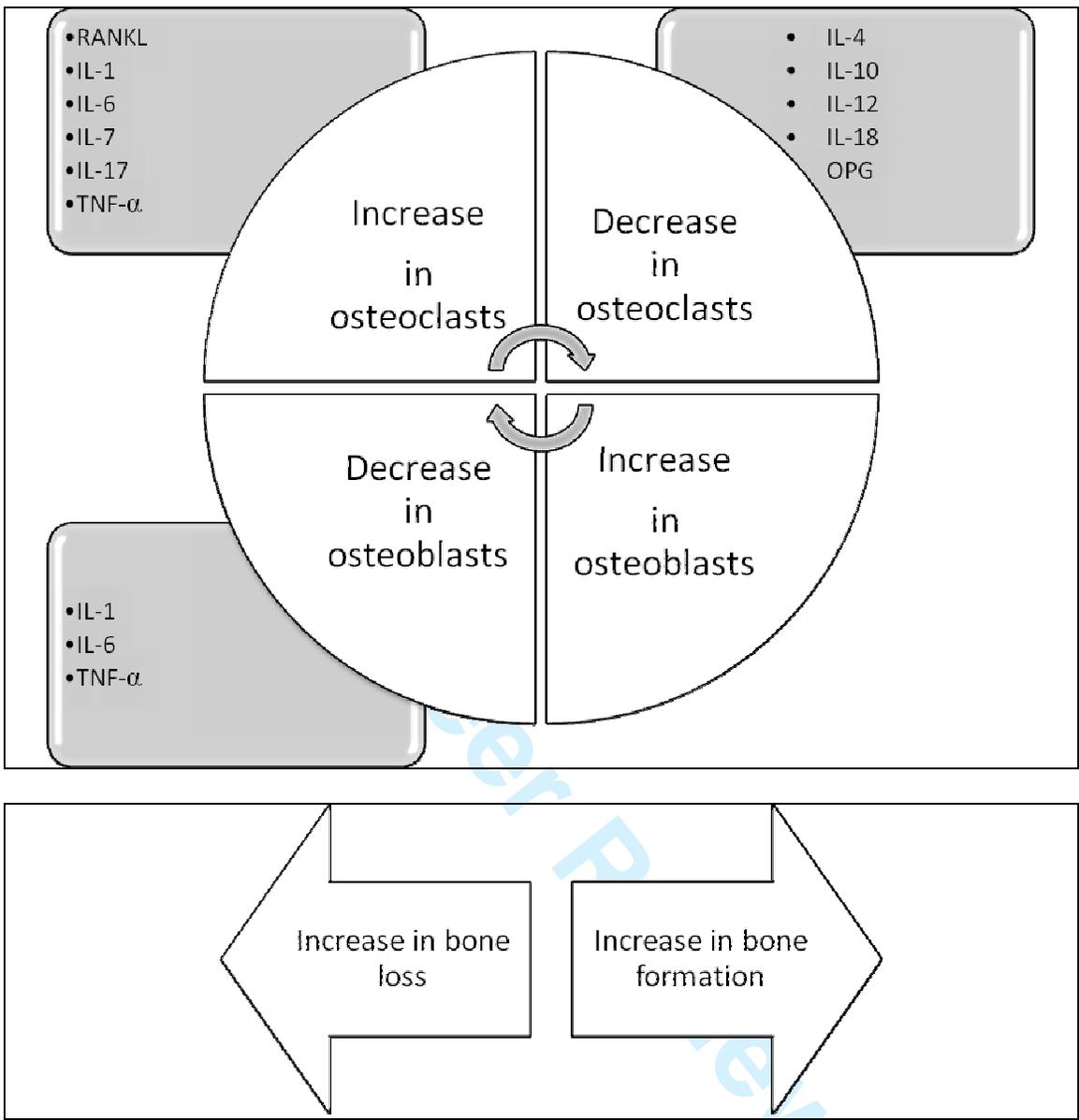


Figure 1: Effects of various cytokines on bone metabolism.

Unfortunately, data regarding the effect of TNF- α blockade on BMD and bone metabolism in IBD patients in the clinical setting are limited. In this review article, we aim to review the available data regarding the effect of anti-TNF- α therapy on bone metabolism and BMD in IBD patients.

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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- α . Infliximab neutralizes the biologic activity of TNF- α 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- α through apoptosis and/or other mechanisms.⁴⁶⁻⁵⁰ Infliximab has a half life of approximately 10 days. Infliximab is the first biologic agent to be licensed for use in IBD. 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 who have not responded well to other conventional therapies.^{51,52} 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 based upon the results of two randomized controlled trials.^{53,54} 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.⁵⁵ 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.⁵⁶ In clinical studies, infliximab treatment was associated with achievement of clinical response and clinical

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3 remission, mucosal healing and elimination of corticosteroid use. Despite its now
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5 widespread use in inflammatory disorders, only limited data exist on the role of
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8 infliximab on the bone metabolism in IBD. Furthermore most of the published data
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10 pertain to small cohorts of patients.
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14 15 **INFLIXIMAB AND BONE MARKERS** 16

17
18 The first studies to suggest that a beneficial effect was seen with TNF blockade on
19
20 bone metabolism in IBD patients were published in 2004. Franchimont *et al.*⁵⁷ studied 71
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22 infliximab naïve CD patients treated with infliximab (5mg/kg) for refractory CD and
23
24 compared their results to 68 matched healthy controls. The study included 21 fistulizing
25
26 refractory CD patients and 50 luminal refractory CD patients. Patients were treated with a
27
28 single infusion of 5mg/kg infliximab at baseline for refractory luminal disease and with
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30 three infusions of 5mg/kg infliximab at baseline, week 2 and week 6 for refractory
31
32 fistulizing disease. Serum bone formation markers - bone alkaline phosphatase (b-ALP),
33
34 osteocalcin (OC) and pro-collagen type 1 N propeptide (P1NP), and the serum
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36 carboxyterminal telopeptide (sCTX); a bone resorption marker were measured at baseline
37
38 and 8 weeks after completion of infliximab treatment (week 8 for refractory luminal CD
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40 and week 14 for refractory fistulizing CD). Clinical activity of the disease based of
41
42 Crohn's Disease Activity Index (CDAI) score and C-reactive protein (CRP) levels were
43
44 also measured in this study at baseline and 4 weeks after completion of therapy as a
45
46 marker of biological response. In this study, the authors observed that the serum
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48 concentration of the bone formation markers; (b-ALP, OC and P1NP) were lower in CD
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50 before infliximab treatment than in healthy controls while they return to normal levels
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3 after infliximab treatment at eight weeks. The authors reported that a relative
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5 improvement in bone formation (defined as an increase of at least 30% in the bone
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7 formation marker) was found after infliximab treatment in 29.7%, 60.8% and 46.5% of
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9 the patients when considering b-ALP, OC or PINP as marker, respectively. Serum
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11 concentration of sCTX was significantly increased in CD at baseline but no longer
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13 different from controls after infliximab treatment at eight weeks. Relative improvement
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15 in bone resorption (decrease of at least 30% in sCTX serum levels) was found after
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17 infliximab treatment in 38.2% of patients. The authors concluded that in their study
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19 infliximab showed a significant and rapid normalisation in the biochemical markers of
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21 bone turnover in CD patients and that this could probably be considered as clinically
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23 relevant in approximately 60% of the patients. This improvement didn't seem to be
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25 selectively associated with demographic or clinical characteristics of the patients,
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27 including clinical or biological response to infliximab or even steroid weaning. There was
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29 no significant difference when comparing median change in bone markers in luminal
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31 (treated with single infliximab infusion) and fistulizing CD (treated with three infliximab
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33 infusions).

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36 Ryan *et al.*⁵⁸ in a prospective trial studied 24 patients with active CD who were treated
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38 with infliximab (5mg/kg) for the first time. The majority of the patients had refractory
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40 luminal CD and only 2 patients had refractory luminal and fistulizing CD. There was no
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42 control group included in this study. Only one confounding factor which is the clinical
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44 response based on CDAI score was considered in this study. 42% of the patients were on
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46 steroids and 50% of the patients were on calcium/Vitamin D supplements at the start of
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48 the study. Five time points were assayed, namely; baseline, 1-2, 4-6, 8-10 and 12-18
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3 weeks post single infliximab infusion. In this study, infliximab infusion led to a
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5 significant increase in both markers of bone formation, b-ALP ($p=0.022$) and OC
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7 ($p=0.008$). Levels of both bone formation markers remained significantly increased even
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9 at 4 months post treatment. No significant change in serum N-telopeptide (sNTx) was
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11 observed although at 4 months post treatment, levels were lower than at baseline. Of
12
13 particular interest, the benefit seen on bone metabolism with infliximab treatment
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15 appeared to occur independently of the clinical response in terms of effect on CD
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17 activity; however the trend of increase in both bone formation markers and decrease in
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19 bone resorption marker was greater in responders compared with non-responders.
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21 Furthermore in this study, maximal reduction in CDAI was seen between 8 and 10 weeks,
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23 whereas bone formation markers continued to increase up to 16 weeks post treatment,
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25 suggesting that there might be a lag in the biological effect of the infliximab on bone
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27 metabolism.
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34 Following on this, Abreu *et al.*⁵⁹ in small, short prospective study involving 38
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36 refractory CD patients reported a significant increase in b-ALP ($p=0.010$) whereas serum
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38 NTx, was not increased ($p=0.801$) at week 4 compared to baseline post a single
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40 infliximab infusion. Again, this study did not compare its findings with an age matched
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42 control group and only two confounding factors, i.e. the effects of glucocorticoid use and
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44 the clinical response based on CDAI score on the changes seen were analysed in detail. In
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46 this study sera were also analyzed for immunoreactive parathyroid hormone (iPTH),
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48 calcium and pro-inflammatory cytokines (IL-1 α , IL-6, and TNF- α) at baseline and 4
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50 weeks following infliximab infusion. Overall, treatment with infliximab was associated
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52 with a statistically significant decrease in PTH levels ($p=0.008$) and statistically
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3 significant increase in serum calcium ($p=0.034$) at week 4. No significant changes in
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5 serum cytokine measurements from baseline to week 4 were noted. As mentioned
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7 previously, in this study the authors sub analyzed the data based on whether the patients
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9 were receiving glucocorticoids at the time of their initial infliximab infusion and whether
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11 patients were responders or non-responders. 22/38 (57.9%) patients were receiving
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13 glucocorticoids at their time of initial infliximab infusion. The increase in bone formation
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15 occurred in both glucocorticoid treated individuals and those not on glucocorticoid,
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17 concluding that glucocorticoid use is not the principal reason for osteoporosis in patients
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19 with CD. Importantly, in this study the effect was also seen in both infliximab responders
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21 and non-responders, again suggesting an independent effect of infliximab on bone
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23 metabolism.
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29 Miheller *et al.*⁶⁰ in a small study studied the effect of infliximab on bone formation and
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31 resorption marker in 27 fistulizing CD patients and compared the results with 54 patients
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33 with inactive CD who acted as controls and again the only confounding factor taken into
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35 account was based on clinical response to therapy defined by the decrease in the number
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37 of draining fistulas by half (responders) or no improvement in the number of draining
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39 fistulas post treatment (non-responders). Again, this was a short term study of just 42
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41 days, and in treated patients, there were significant difference in β -CrossLaps (bCL), a
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43 marker for bone resorption on days 0 and 14 ($p<0.01$) and days 0 and 42 ($p<0.05$). OC
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45 levels increased significantly between day 0 and 42 ($p<0.05$) corroborating the results
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47 from previous studies that infliximab has beneficial effects on bone turnover markers in
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49 CD. In this study, the beneficial effect of infliximab on bone markers was only noted to
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51 be significant in the responder group.
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INFLIXIMAB AND BONE MINERAL DENSITY

To date, few published studies have examined the effect of infliximab on actual bone loss in CD patients by measurement of BMD. A retrospective cohort analysis was performed by Pazianas *et al.*⁶¹ 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. A number of confounding factors which could affect the study outcome were analysed including sex, number of post menopausal women, number of women on hormone replacement therapy, follow up time, number of patients with recorded corticosteroid use during the study and number of infliximab infusions. After controlling for corticosteroid 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 was no control group.

In another retrospective study by Mauro *et al.*⁶² 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. Certain confounding factors such as age, sex, age at diagnosis, years of disease, final weight, weight change, bisphosphonate use, corticosteroids use and disease activity were analysed in this study. Patients in this study received infliximab (5m/kg) at intervals

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3 of four to eight weeks for a mean period of 18 months. The first and second DXA
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5 evaluations were 22.6 +/-11 months apart in the infliximab group and 20.4 +/- 8 months
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7 apart in the control group. The infliximab group had a significant increase in lumbar bone
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9 area, bone mineral content (BMC) and BMD between both evaluations compared to
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11 control (CD patients who had never received infliximab). The increase in BMC, i.e. the
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13 bone mass measurements in patients who had received infliximab treatment was
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15 significant when compared with control patients who had received glucocorticoids (n=8)
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17 or who had evidence of disease activity.
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22 Bernstein *et al.*⁶³ also found that maintenance treatment with infliximab (5mg/kg) at 6-
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24 8 weeks intervals for 1 year in 46 CD patients improved BMD after one year in the
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26 lumbar spine (2.4% increase, p=0.002), at the femoral trochanter (2.8% increase, p=0.03),
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28 and at the femoral neck (2.6% increase, p=0.001) and that this effect was independent of
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30 concurrent administration of glucocorticoids, calcium supplementation, or changes in C-
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32 reactive protein. Also BMD gain at the lumbar spine and the left femur between the
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34 groups without and with osteopenia were not different. However, whilst in confounding
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36 factors were analysed, there was no control group.
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43 **INFLIXIMAB AND OSTEOCLASTOGENESIS MARKERS**

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46 Only one study has evaluated changes in osteoclastogenesis markers (OPG and
47
48 RANKL) with infliximab therapy. Miheller *et al.*⁶⁴ studied 29 refractory CD patients who
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50 were treated with infliximab at week 0, 2 and 6. In 19 cases CD was associated with
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52 fistulas. There were no postmenopausal females in this cohort, and all of these patients
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54 were steroid free for at least 1 month before the first infliximab infusion. No patients in
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3 this study had been treated with bisphosphonates or vitamin D. Six patients were on
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5 calcium supplements. Serum OC as a bone formation marker, serum beta-crosslaps (bCL)
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7 as a marker of bone resorption, serum OPG, and serum RANKL were measured before
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9 each course of infliximab therapy. BMD measurements were also performed at baseline
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11 in all patients using a DXA scan. In this study, four of 29 patients had osteoporosis and
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13 14 of 29 had osteopenia. Serum levels of OC, the bone formation marker along with
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15 RANKL increased after infliximab therapy at week 6. Concentrations of bCL, the bone
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17 resorption marker along with OPG decreased at the same time. Femoral BMD correlated
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19 with baseline serum bCL and sRANKL concentrations (0.548; $p < 0.05$ and 0.532;
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21 $p < 0.05$). There were no significant correlations between bone remodeling markers (OC
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23 and bCL) and osteoclastogenesis markers (OPG and sRANKL) and lumbar BMD.
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25 Whilst at first viewing the results they seem a little paradoxical the authors concluded
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27 that elevated OPG in CD could be a counter-regulatory response to inflammatory
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29 cytokines or may reflect T-cell activation. No control groups were analysed but patient
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31 results were sub-analysed based on whether patients were considered to be responders or
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33 non-responders. Responders were defined as having a decrease in the number of fistulas
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35 by half, or a declining CDAI by 70 points. Significant changes were only seen in the
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37 responder group.
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48 **ADALIMUMAB**

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50 Adalimumab is a human IgG1 monoclonal antibody specific for human TNF. Unlike,
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52 infliximab which requires an intravenous infusion, adalimumab is administered by
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54 subcutaneous injection.⁶⁵ Adalimumab has been recently approved for the treatment of
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3 active CD. The clinical efficacy and safety of adalimumab in patients with moderate to
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5 severe CD has been demonstrated in four pivotal studies.⁶⁶⁻⁶⁹ All these studies have
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7 shown adalimumab to be superior to placebo for inducing and maintaining remission.
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9 Maintenance adalimumab therapy is administered as a subcutaneously every two weeks.
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11 The approved induction dosing of adalimumab in CD is 160 mg given subcutaneously
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13 initially at week zero, 80 mg at week two, followed by a maintenance dose of 40 mg
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15 every other week beginning at week four. The drug is available in a single-use prefilled
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17 pen (HUMIRA Pen) or in a single-use, prefilled glass syringe. At present time,
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19 adalimumab is only licensed for use in CD patients.
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27 **ADALIMUMAB AND BONE METABOLISM IN IBD**

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29 To the best of our knowledge, there are currently no published data investigating the
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31 effect of adalimumab on bone metabolism in IBD patients. However, one such report
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33 exists studying BMD in a population of RA patients treated for 1 year with
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35 adalimumab.⁷⁰ In this study, fifty patients with active RA (defined as having a 28-joint
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37 disease activity score (DAS28) of ≥ 3.2) who started adalimumab treatment (40 mg
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39 subcutaneously every other week) were included in an open label prospective study. The
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41 BMD of both the lumbar spine (L1-L4) and left femoral neck was measured before
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43 treatment and after one year by DXA. Both disease activity at baseline (DAS28) and
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45 disease duration were inversely correlated with femoral neck BMD and lumbar spine
46
47 BMD ($p < 0.05$). Mean BMD of both lumbar spine and femur neck remained unchanged
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49 after one year of adalimumab therapy (+0.3% and +0.3%, respectively). The authors
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51 concluded that their result shows that with adalimumab therapy, progression of bone loss
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3 is halted. However, measurements of bone turnover were not performed in this study and
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5 there was no control group.
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10 SUMMARY

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12 To date, the data, available examining the effect of infliximab on bone metabolism in
13 CD are limited. Moreover, there are **considerable** limitations with the studies which are in
14
15 print. Firstly, the existing studies are not randomised. Secondly, the sample numbers
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17 included are small; with the largest being 71 patients.⁵⁷ Therefore, meaningful analyses
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19 of various subgroups are restricted. Thirdly, the duration of follow up is by-and-large
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21 short, with longest being only for 14 weeks.⁵⁸ Hence the long term effect of infliximab
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23 maintenance therapy on bone markers - which most likely to correspond to a meaningful
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25 effect on bone density or even fracture rates – is not currently known, however tantalising
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27 it might be to extrapolate from existing short term studies. Fourthly, only few studies to
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29 date,^{57-60,64} have looked to some extent at differences in bone marker changes between
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31 responders and non-responders. The benefits on bone metabolism seen with anti-TNF
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33 therapy in those who respond (either clinically or biologically) compared to non-
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35 responder show no clear cut differences. Two studies failed to show any difference
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37 between the two groups.^{57,59} Another study,⁵⁸ showed a trend towards a greater increase
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39 in both bone formation markers and a greater decrease in bone resorption markers in
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41 responders compared with non-responders, but this did not reach statistical significance.
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43 In two of the remaining studies^{60,64} statistical significance was recorded only in the
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45 responder groups suggesting biological response may play a role. Hence the question
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47 arises - is it simply the neutralization of TNF- α that is critical if in fact these drugs have a
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3 role? Or is it that those whose disease activity improves secondary to suppression of
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5 TNF- α mediated inflammation are the ones whose bone markers improves? At the
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7 moment, the answer is not clear although the evidence leans towards the latter possibility.
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9 This is a crucial question as, if this latter is true, then it is likely that improvements in
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11 bone markers might be not specific to anti-TNF agents but rather are simply sequelae of
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13 reducing the inflammatory response and hence other medications such as thiopurines or
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15 methotrexate might well have similar effects. Finally, confounding factors that could
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17 affect the outcome of changes seen in bone markers such as the age, gender, current
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19 smoking, disease duration, disease location, current steroid treatment, number of
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21 infliximab infusions, and steroid weaning were only examined in a number of studies.
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29 Given the limitations outlined above, at most with the currently available data, one can
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31 conclude that infliximab appears to positively impact on bone metabolism in CD patients,
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33 but it is as yet unclear whether this is specific to the anti-TNF- α therapy alone or if it is
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35 secondary to reducing active inflammation and the associated pro-inflammatory
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37 cytokines. The beneficial effect does seem to be heterogeneous in aetiology and to vary
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39 from patient to patient. Primarily, the main beneficial effect appears to be related to an
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41 increase in bone formation although a decrease in bone resorption also appears to play a
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43 role in some patients. The effects seem to be independent on response or non-response to
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45 treatment based on clinical score, although in two studies^{60,64} the beneficial changes were
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47 only statistically significant in the responder groups. Furthermore, the beneficial effects
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49 on bone metabolism appear to be independent of steroid therapy. Case-control studies
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51 (which are few) indicated that CD patients in general had lower bone formation markers
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3 and higher bone resorption markers as compared to healthy subjects and that infliximab
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5 therapy reverses this balance. Patients who received infliximab have also been shown to
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7 increase BMD during therapy.
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10 It's likely that several different mechanisms play a role in this positive effect of
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12 infliximab on bone metabolism. Firstly, reduction of TNF- α , which has been shown to
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14 have a beneficial effect on bone metabolism *in vitro*, might also play a role *in vivo*.^{71,72}
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16 Secondly, reduction of other pro-inflammatory cytokines known to cause bone loss, such
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18 as IL-6 and IL-1 β ⁵⁰ by infliximab^{24,31} is likely to play a pivotal role. A third possible
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20 mechanism is that improvement in general well being and physical activity might also
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22 improve net bone formation. Fourthly, by reducing gut inflammation, infliximab might
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24 also improve bone metabolism indirectly by increasing absorption of crucial bone
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26 nutrients such as Vitamin D and calcium.
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Study	Number of patients	Underlying condition	Control group (No of patients)	Con-founding factors (Assessed)	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> ⁵⁷	71	CD (21 fistulizing, 50 luminal)	Healthy subjects (68)	Yes	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> ⁵⁸	24	CD (2 had fistulizing)	No	Responders vs. Non responders	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.

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Abreu <i>et al</i> ⁵⁹	38	CD	No	1. Steroid use 2. Responders vs. Non responders	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> ⁶⁰	27	CD (all fistulizing)	Yes (54-inactive CD)	Responders vs. Non responders	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> ⁶¹ (retrospective study)	61	CD	No	Yes	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> ⁶² (retrospective study)	15	CD	30 CD patients who had no infliximab treatment	Yes	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.

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5	Bernstein <i>et al</i> 63	46	CD	No	Yes	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.
19	Miheller <i>et al</i> 64	29	CD (19 fistulizing)	No	Responders vs. Non responders	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.

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

Bone metabolism is a dynamic, complex balance of bone formation and resorption, and disruptions to this homeostasis can result in bone loss, as seen in patients with IBD. The mechanisms involved are most likely varied and heterogeneous but currently available studies looking at the effect of infliximab on bone metabolism in CD would suggest the improvement seen with infliximab is likely secondary to various factors including reduced TNF- α levels,⁵⁹ and reduced disease activity.^{60,64} However, the beneficial effects seen with infliximab seem to be independent of steroid weaning.^{57,59,63}

To date, studies looking at the effects of anti-TNF- α therapy on bone metabolism in IBD are limited, and have only evaluated the role of infliximab on bone metabolism in CD patients. A number of major limitations exist, with published studies as outlined above, hence the apparent beneficial effects seen with infliximab on bone metabolism in these studies require further validation. No studies have yet evaluated the effects of adalimumab therapy on bone metabolism in IBD or the effect of anti-TNF α therapy in UC patients. Furthermore, currently available studies have only been carried out for a relatively short term, with the longest being for 14 weeks.⁵⁸ Hence the long term effect of maintenance therapy with anti-TNF- α on bone metabolism in IBD patients is not yet 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- α 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 BMD, to fully understand the mechanisms involved. Finally, what happens to the beneficial effects

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3 seen on bone metabolism in IBD patients following cessation of anti-TNF- α therapy is
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5 not known. Properly controlled long term trials are necessary to fully evaluate the effects
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7 of TNF blockers in this regard. Hence to conclude; larger, longer, randomized controlled
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9 trials are needed to address the most important question of all; i.e. "Does anti-TNF- α
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11 have a role in the treatment of osteoporosis?"
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17 **ACKNOWLEDGMENT**

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20 *Declaration of personal interest:* Prof. Colm O'Morain is on the international advisory
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22 board of Abbott, Schering Plough and Shire pharmaceutical companies.
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26 *Declaration of funding interests:* None.
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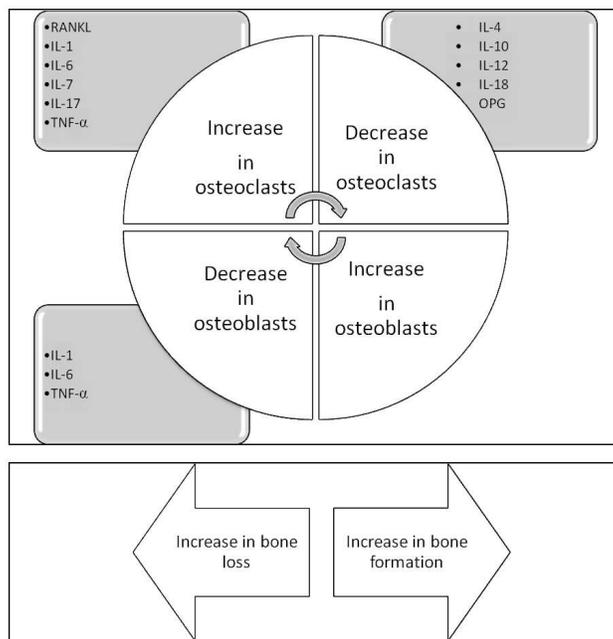
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