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Effects of Anti-Tumor Necrosis Factor α (anti-TNF) agents on Bone

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Abstract

Purpose of the review—TNF inhibitors are effective for achieving disease control in several inflammatory diseases. Although anti-TNF agents can inhibit bone loss *in vitro*, their role in the prevention of clinically relevant outcomes such as osteoporosis and fractures has not been clearly established.

Recent findings—There are many studies of the effects of TNF inhibitors on markers of bone turnover; however few have measured bone mineral density (BMD) or fractures. Most of these studies have small sample sizes and a minority had a placebo control group. Overall these studies suggest that the anti-resorptive effects of anti-TNF therapy are related to control of disease activity.

Summary—The antiresorptive effects of TNF inhibitors are likely related to their anti-inflammatory properties. Studies to date have not demonstrated any advantages of TNF inhibitors over traditional non biologic therapies in the prevention of bone loss and fractures.

Keywords

Anti-TNF; bone loss; rheumatoid arthritis; spondyloarthropathies

Introduction

It is established that patients with chronic inflammatory diseases have more bone loss and a higher risk of fractures compared to the general population [1–5]. Although the causes of bone loss in inflammatory disorders are multiple [6,7], several animal models of inflammation, along with clinical evidence, indicate that inflammatory mediators, including tumor necrosis factor alpha (TNF α), play a major role [8–11].

Numerous *in vivo* and *in vitro* experiments provide evidence that TNF α promotes bone resorption directly through activation of cells of the osteoclast lineage [12], and indirectly through the expression of osteoclast activators [13]. TNF α also suppresses bone formation

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via increased osteoblast apoptosis [14], and reduced differentiation [15] and proliferation [16] of osteoblasts and their progenitors. Thus, TNF α blockade holds the potential to inhibit or reverse bone loss [17–19]. In this regard, anti-TNF therapy has been proposed as a potential dual treatment to control inflammation and to prevent osteoporosis and associated fractures in inflammatory diseases. In this review only pathways that can potentially be targeted by anti-TNF agents are described. Extended reviews that include detailed information of the *in vitro* and *in vivo* experiments regarding the effect of different inflammatory cytokines on bone loss are available [20–22].

Bone remodeling

Bone remodeling is a physiological process that repairs microdamage, adapts bone strength to changes in mechanical load, and is critically involved in systemic calcium and phosphate homeostasis. The regulation of this process involves a complex network of multiple signaling pathways within and among the skeletal, immune, endocrine systems and the brain [23–25]. In the classical model, bone remodeling is initiated when osteoclasts resorb damaged or excess bone [26]. Under normal conditions the resorption is closely coupled to bone formation by osteoblasts that refill the resorption pit or Haversian canal. More recently, this model has been expanded to include the osteocyte [27]. Osteocytes embedded in the bone matrix sense and respond to changes in fluid flow and/or mechanical stretching arising from stress, strain or pressure created by mechanical loads on the bone [28, 29] and potentially local microdamage by releasing soluble signal molecules that control bone resorption and formation [30]. In this manner, the osteocyte is thought to orchestrate the processes of bone remodeling at the local level. Hence, perturbation of the delicate balance of coupled bone formation and resorption leads to osteopetrosis, or more commonly, osteoporosis.

Bone resorption requires the proliferation and differentiation of multipotent hemopoietic stem cells into macrophages, which fuse into multinucleated preosteoclasts and further differentiated into mature, active osteoclasts. Macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa beta ligand (RANKL), a member of the TNF superfamily, are considered the most critical signaling molecules for osteoclastogenesis [31, 32]. Interaction of M-CSF with its membrane receptor c-FMS is necessary for proliferation and survival of osteoclast precursors [33, 34], priming the bone microenvironment for osteoclast differentiation. Subsequently, RANKL must bond to its receptor RANK on osteoclast progenitors to activate the NF- κ and activator protein (AP)-1 pathways, which trigger fusion, differentiation, and activation of the mature osteoclasts [35]. RANK is expressed on the surface of osteoclast lineage cells; while M-CSF, RANKL, and osteoprotegerin (OPG), a soluble decoy receptor specific for RANKL, are all produced by osteoblastic cells [36]; the balance of the RANKL-RANK-OPG axis is a key regulator of bone resorption.

In healthy subjects bone formation is tightly coupled to bone resorption by a poorly understood mechanism that involves signaling directly between osteoblasts and osteoclasts via the Ephrin family of membrane bound ligands and receptors [37]. Regardless, osteoblast recruitment and differentiation are directly influenced by numerous hormones, cytokines, and growth factors including numerous members of the TGF β -superfamily, the WNT superfamily, and the TNF superfamily. These and other autocrine/paracrine signals influence the activation, commitment, and differentiation of mesenchymal stem cells and osteoblast progenitors into mature osteoblasts by regulating the expression and activity of several key transcription factors including runt-related transcription factor 2 (RUNX2) [38], the interaction of osterix-NFAT2 (nuclear factor for activated T cells), β -catenin [23, 25], and activating transcription factor 4 (ATF4). Though not entirely sufficient for

osteoblastogenesis, RUNX2 is generally considered the master regulator of osteoblast differentiation since it is required for the differentiation of mesenchymal cells into osteoblasts [39].

TNF α and osteoclastogenesis

Activation of the NF κ B pathway by RANK/RANKL signaling is a key driver of osteoclastogenesis and bone formation. Activation of NF κ B is also a hallmark of TNF α signaling via TNF receptor 1 (TNFR1) [40], which is expressed on macrophages and osteoclast precursors. Hence, it is not surprising that TNF α also promotes osteoclast formation and bone resorption. TNF α enhances osteoclast differentiation in the presence of minimal concentrations of RANKL [41] and induces the differentiation of pro-osteoclasts into mature osteoclasts in the absence of RANK signaling [42]. During inflammation, TNF α increases the expression of M-CSF and RANKL in several target cells including osteoblasts [43] which promotes osteoclast differentiation indirectly. Finally, TNF α has also been shown to inhibit osteoclast apoptosis through mTOR/S6 kinase [44]. Together, these mechanisms increase the number, and potentially, the lifespan of osteoclasts in pro-inflammatory environments resulting in elevated bone resorption (Figure)

TNF α and osteoblastogenesis

Although an increase in bone resorption, rather than a decrease in bone formation, is the main mechanism for bone loss during active inflammation [45], TNF α can disrupt the main pathways involved in osteoblast differentiation. A variety of *in vitro* and animal models have demonstrated that excess TNF α inhibits proliferation and differentiation and increases apoptosis of osteoblasts and their progenitors (Figure). These effects appear to be mediated primarily via TNFR1 activation of multiple downstream signaling pathways [46–50,51]. The best studied of these is the nuclear factor κ B (NF- κ B) pathway which suppresses osteoblast differentiation [40] and activity [35]. Traditional downstream targets of NF κ B, including p53 and p21 have also been implicated as important mediators of these effects [52,53]. Inhibited osteoblast differentiation may be mediated by reduced RUNX2 expression [54] through its ubiquitylation [48], and also through inactivation of pro-osteogenic mitogen-activated protein kinases (MAPK) pathways [25]. TNF α signaling also inhibits osterix expression, a critical regulator of the early stages of osteoblast differentiation, preventing the interaction of NFATc2 with osterix and the resulting activation of osteogenic target genes [55]. Others have demonstrated inhibition of the Wnt- β -catenin pathway through TNF α -induced upregulation of the Wnt inhibitors Dickkopf-related protein 1 (DKK1) [56] and sclerostin [57•].

Clinical studies on anti-TNF agents and

Clinical trials have shown equivalence or superiority of anti-TNF therapy compared to traditional non-biologic regimens in achieving disease control and preventing radiographic joint damage in different inflammatory diseases [58–61]. However, studies that examined the effect of these agents on bone health have primarily measured markers of bone turnover rather than clinically important endpoints. These studies of biochemical markers have not always yielded concordant results in different autoimmune diseases [62–66], but overall have shown modest and transitory increases in bone formation and decreases in bone resorption markers with anti-TNF therapy. These findings support the hypothesis that anti-TNF therapy has little effect on osteoblastogenesis, but primarily affects osteoclastogenesis, improving the bone formation/resorption ratio and thus slowing or arresting bone loss [63,64,67]. However, information about the comparative effects of long term anti-TNF therapy and conventional non biologic regimens on bone distant to sites of inflammatory damage are limited.

In this section we present evidence from clinical studies that examined the effect of anti-TNF therapy on preservation of bone mineral density (BMD) (including local and generalized bone loss) and on the occurrence of fractures compared to non biological treatments for rheumatoid arthritis (RA) and spondyloarthropathies (Table 1 & 2) [67–92].

Anti-TNF agents and bone loss in patients with rheumatoid arthritis (RA)

Most of the inflammatory diseases treated with anti-TNF therapy are associated with systemic bone loss. In RA, and to a lesser extent in psoriatic arthritis, periarticular bone loss (which occurs independently of direct contact with inflamed synovium) is often present in the small joints of the hands [93]. It appears that periarticular and generalized bone loss share similar mechanisms. Cytokines are released from the inflammatory pannus and delivered locally to the metacarpal bones, and systemically to the skeleton, activating osteoclastogenesis and bone resorption. Bone loss in the hands has been used as an outcome in some studies because it has been associated with generalized bone loss [94•] and osteoporotic fractures [95]. Progression of hand bone loss during anti-TNF therapy has been observed in several studies [69,77–80]. Dissociation in the anti-resorptive effect of these agents in the hands and in the spine or hip has been described, suggesting that metacarpal bone is more sensitive to inflammatory cytokines that are released from adjacent inflammatory tissue than bone in the hip and spine [69,70,77].

We found only two large randomized clinical trials (RCT) that examined the differences between anti-TNF therapy and other traditional disease modifying anti-rheumatic drugs (DMARDs) regimens on bone loss, the BeSt and the PREMIER trial. The BeSt trial examined the effect of four treatment regimens on bone loss using an intention to treat analysis: sequential monotherapy, step-up therapy, initial combination of synthetic DMARD + high dose of prednisone, and initial combination of synthetic DMARD + infliximab [81]. In this study, patients who received conventional therapy had higher bone loss in the hands than those who receive initial combination therapy with infliximab. This difference remained significant after adjusting for the use of antiresorptive treatments, but disappeared when change in disease activity was included in the analysis. Only radiographic disease progression, post-menopausal status, and inflammation were associated with hand bone loss after adjustment for various covariates [81]. A post-hoc analysis of the data grouping patients by therapeutic response instead of treatment regimen, found that gain in metacarpal bone occurred in association with clinical remission, regardless of the previous or current use of anti-TNF therapy [82•], supporting the hypothesis that anti-TNF therapy decreases bone loss through tight control of disease activity.

However a second well powered RCT, the PREMIER trial, reported in an exploratory analysis that combination of MTX with adalimumab resulted in less hand bone loss than either adalimumab or MTX monotherapies. In this trial, hand bone loss was associated with no use of adalimumab, increasing age and inflammation [78]. A sub-analysis of the data showed that patients in the MTX monotherapy group with high/moderate disease activity (DAS28>3.2) or high levels of C reactive protein (CRP ≥ 10 ng/ml) had greater bone loss in the hands compared to those in remission/low disease activity (DAS ≤ 3.2) or low levels of CRP (<10 ng/ml) [79]. In the group receiving both drugs, bone loss was similar regardless of the disease activity and inflammatory status, and was comparable to patients who had low disease activity with MTX only. These last findings suggest that the benefits of anti-TNF therapy may not be limited to control of inflammation, but also to the ability to block the direct effect of TNFα on osteoclast activation [79••].

Anti-TNF therapy also has been reported to arrest bone loss in the spine and hip in longitudinal studies [67–70,72–74]. However, comparative studies have shown conflicting

results [76,80]. For example, Marotte et al reported that hip and spine BMD declined in historical controls that received MTX only, but were preserved in patients treated with the combination of infliximab +MTX. In this study, changes in BMD were not associated with treatment response among patients treated with both drugs [75]. Haugeberg et al also observed that BMD loss at the femoral neck and hip was higher in patients who received MTX+ placebo compared to those who receive MTX+infliximab; but after adjustment for covariates, only measures of inflammation and radiographic damage were associated with bone loss [77]. Whereas in the BeSt trial, declines in hip and spine BMD were associated with progression of radiologic damage and less decline was observed with concomitant use of bisphosphonates but not with treatment regimen [81]. In many single arm studies with anti-TNF agents, arrest of bone loss was accompanied by improvement in disease activity [69,74] or a reduction in inflammation [73,74], which suggests that effective control of inflammation, rather than any specific drug therapy, is likely the mechanism that prevents further bone loss. A recent observational study performed in a commercially insured population in the US and Canada found that the risk of non vertebral fractures did not differ in patients receiving synthetic DMARDs (excluding MTX) compared to those receiving MTX (RR= 1.1, 95%CI [0.6–2.0]) or anti-TNF agents (RR=1.2, 95%CI [0.6–2.3]) [71•].

Anti-TNF agents and bone loss in patients with spondyloarthropathies

In addition to RA, spondyloarthropathies (SpA) constitute another group of chronic inflammatory diseases that is associated with systemic bone loss and is treated with anti-TNF agents. Table 2 summarizes the results of studies that have examined the effect of anti-TNF therapy on BMD in SpA. In most of the longitudinal single arm studies anti-TNF therapy has been associated with increased BMD at spine and hip, improved inflammation and disease activity [83,87,89], but results from comparative studies are inconsistent [84–86,88,91,92].

A small observational study [84], and a post-hoc analysis of a large randomized trial [92] reported that treatment with infliximab was associated with a gain in BMD at the spine and hip when compared to conventional treatment. Marzo-Ortega et al observed significant changes in hip, but not in the spine and femoral neck BMD, in patients treated with etanercept compared to those treated with conventional treatment [88]; however the same investigator did not replicate these findings in a small trial where infliximab+MTX was compared with MTX+placebo [91].

On the contrary, two studies suggested that biphosphonates but not anti-TNF therapy may improve BMD in SpA patients. Pazianas et al observed that use of biphosphonates was associated with gain in BMD at spine, and infliximab provided a marginal benefit only in those patients that were taking biphosphonates [85]. In agreement with these results, Kang et al found that BMD in spine was marginally higher in patients that received conventional therapy+biphosphonates compared to the other three regimens (conventional therapy, conventional therapy+anti-TNF and conventional therapy+ biphosphonates+anti-TNF); and BMD in the hip was higher in those patients receiving conventional therapy+biphosphonates +anti-TNF therapy compared to the other three regimens [86]. Studies that examined the effect of anti-TNF therapy on the occurrence of fractures in SpA are not available.

Conclusions and Future directions

It is not surprising that anti-TNF therapy has not shown a major benefit in bone loss and fracture prevention in inflammatory disease. There are multiple pathways independent of TNF α that activate osteoclasts, and inflammation generates many mediators that activate these pathways. Therefore studies that target these pathways are needed to determine their effects on clinically important outcomes.

In conclusion, most of the evidence suggests that anti-TNF therapy has indirect anti-resorptive effects on bone through control of inflammation. Currently, the evidence does not suggest that treatment with anti-TNF has any specific beneficial effect on prevention of osteoporosis or fractures beyond control of inflammation compared to conventional non biologic regimens. Many of the published studies have relatively short follow-up periods, limited statistical power, or lack proper controls. TNF α blockade may need longer and sustained disease control to show beneficial effects on bone. However, with the increased use of biphosphonates as concomitant therapy to prevent bone loss and fractures in patients with chronic inflammatory disease, it would be difficult to identify these effects.

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Key points

- There can be a dissociation in periarticular and systemic bone loss in rheumatoid arthritis
- The anti-resorptive effects of anti-TNF therapy are likely to be result of its anti-inflammatory properties.
- In Spondyloarthropathies, treatment with biphosphonates are more likely to prevent bone loss at spine compared to anti-TNF therapy.

Figure. Effects of Tumor Necrosis Factor α in Bone Cells

Tumor Necrosis Factor α (TNF α) causes bone resorption by the activation of osteoclastogenesis and the inhibition of osteoblastogenesis. TNF α enhances osteoclastogenesis through the following main pathways: 1) direct effect of TNF α on macrophages and pre-osteoclast cell proliferation or indirectly through the activation of IL6 and RANKL signaling; 2) direct activation of mature osteoclasts and 3) inhibition of osteoclast apoptosis. TNF α suppresses osteoblastogenesis by: 1) inhibition of the proliferation and differentiation of mesenchymal stem cells into osteoblastic cells; 2) inducing apoptosis of osteoblast lineage cells; and 3) suppressing osteoblast activity.

Table 1
Anti tumor necrosis factor (anti-TNF) therapy and bone mineral density in rheumatoid arthritis

Ref	Study	FU time	Treatment groups (n)	BMD Hands	BMD Spine	BMD Hip	Findings
[67]	Obs	1 year	T ₁ : INF (26)	ND	BMD increased (+3%, P<0.01)	BMD increased (12%, P<0.001)	Δ markers of bone turnover did not correlated with ΔBMD, but they changed in the expected direction.
[68]	Obs	1 year	T ₁ : INF (36)	ND	Stable BMD (+1.1%, P>0.05)	Stable BMD (-0.3%, P>0.05)	Disease activity improved but ΔBMD were not associated with disease activity, and use of prednisone or bisphosphonates
[69]	Obs	1 year	T ₁ : INF (102)	BMD loss (-0.8%, P<0.05) Response vs. non-response (-0.6% vs. -1.2%, P>0.05)	Stable BMD (+0.2%, P=0.05) Response vs. non-response (+0.7% vs. -0.6%, P>0.05)	Stable BMD (-0.20%, P>0.05) Response vs. non-response (+0.8% vs. -0.7%, P<0.001)	Osteocalcin increased at week 14 and then remained stable, β-CTx and RANKL decreased during follow-up; but OPG did not change. PDR use was not associated with ΔBMD
[70]	Obs	>2 years	T ₁ : INF (52)	BMD loss (-3.1%, P<0.05)	BMD increased (+2.6%, P<0.05) PDR users vs. no PDR users (+6.2% vs. 0.8%, P=0.002) RA 1 year vs. RA>10 years (+5.5% vs. -0.2%, P=0.009)	BMD stable (-0.1%, P>0.05)	ΔBMD in spine was associated with concurrent use of prednisone and RA duration
[71]	Obs	5285.2 py	T ₁ : anti-TNF T ₂ : MTX T ₃ : other DMARD	Risk of wrist fractures T ₁ ≈T ₂ ≈T ₃	ND	Risk of hip fractures T ₁ ≈T ₂ ≈T ₃	Risk of non-vertebral fracture was similar between treatment groups.
[72]	OL	6 – 12 months	T ₁ : INF (48)	ND	BMD stable	BMD stable	Markers of bone formation remained stable. Markers of bone resorption decreased the first 6 months of treatment but returned to baseline at 1 year
[73]	OL	1 year	T ₁ : INF/ADA (19)	ND	BMD stable	ND	Inflammatory markers and disease activity improved significantly.
[74]	OL	1 year	T ₁ : ADA(46)	ND	BMD stable +0.3% (P>0.05)	BMD stable +0.3% (P>0.05)	Disease activity significantly improved during follow-up. ΔBMD at hip were associated with concomitant use of PDR.
[75]	Cohort	1 year	T ₁ : INF + MTX (90) T ₂ : MTX (99 historical controls)	ND	BMD stable in T ₁ (-0.2%, P>0.05) BMD decrease in T ₂ (-3.9%, P<0.001)	BMD stable in T ₁ (+0.2%, P>0.05) BMD decrease in T ₂ (-2.5%, P<0.001)	Markers of bone turnover remained stable in both treatment groups. In the INF treated group, ΔBMD were not associated with treatment response.

Ref	Study	FU time	Treatment groups (n)	BMD Hands	BMD Spine	BMD Hip	Findings
[76]	RCT	6 months	T ₁ : INF + MTX + PDR (10) T ₂ : ETA + MTX + PDR (11) T ₃ : MTX + PDR (10)	BMD stable T ₁ & T ₂ (+1.3%, P=0.05) T ₃ (-4.6%, P>0.05)	BMD stable T ₁ & T ₂ (+0.2%, P>0.05) T ₃ (-0.8%, P>0.05)	BMD stable T ₁ & T ₂ (+0.1, P>0.05), T ₃ (-0.6%, P>0.05)	In the anti-TNF treated group, markers of bone formation increased while markers of bone resorption decreased. In the MTX + PDR treated group no changes in markers of bone turnover were observed
[77]	RCT	1 year	T ₁ : INF + MTX (10) T ₂ : MTX + placebo (10)	BMD loss (-2.4%, P=0.048) ΔBMD T ₁ ≈T ₂ (-2.1 vs. -2.8%, P=0.82)	BMD stable (+1.3%, P=0.36) ΔBMD T ₁ ≈T ₂ (-0.8% vs. -1.8%, P=0.71)	BMD femoral neck & hip stable -1.8%, P=0.07 & -1.4%, P=0.07 ΔBMD femoral neck T ₁ < T ₂ (-0.4% vs. -3.4%, P=0.01) ΔBMD total hip T ₁ < T ₂ (-0.2% vs. -2.6%, P=0.03)	BMD loss was lower INF compared to placebo in femoral neck and hip. Inflammation was associated with bone loss in hands and femoral neck. Radiographic damage was associated with bone loss at spine, femoral neck/hip.
[78]	RCT	26, 52, 104 weeks	T ₁ : ADA+MTX (261) T ₂ : ADA (261) T ₃ : MTX (246)	BMD loss T ₃ >T ₂ >T ₁	ND	ND	Bone loss was associated with age, inflammation and treatment regimen
[79•]	RCT	52, 104 weeks	T ₁ : ADA+MTX (214) T ₂ : MTX (188)	T ₂ : bone loss higher in those with high/moderate disease activity vs. low/remission T ₁ : bone loss similar in high/moderate disease activity and low/remission.	ND	ND	In MTX groups bone loss was higher non responders compared to responders, but no differences in the combination group. In the combination group BMD loss was comparable to MTX group on remission.
[80] [81]	RCT	1-2 years	T ₁ : Sequential monotherapy (81) T ₂ : Step-up combination (84) T ₃ : Combination + PDR (89) T ₄ : Combination + INF (88)	BMD loss at year 1 & 2 T ₃ & T ₄ <T ₁ & T ₂ (all P=0.05) BMD loss associated with disease severity	BMD loss T ₁ ≈T ₂ ≈T ₃ ≈T ₄	BMD loss T ₁ ≈T ₂ ≈T ₃ ≈T ₄	BMD loss higher in hand than hip & spine BMD loss associated with progression of radiographic destruction Biphosphonates associated with reduce BMD loss in spine and hip.
[82•]	RCT	1 year	T ₁ : Continuous remission T ₂ : Low disease T ₃ : High disease	BMD gain in T ₁ but not in T ₂ and T ₃	ND	ND	BMD was not associated with previous or current use of anti-TNF or prednisone.

Abbreviations: Ref, references; FU, follow-up; BMD, bone mineral density; ND, not done; Δ, changes; ≈, similar; Obs, observational; OL, open label; RCT, randomized clinical trial; INF, infliximab; ADA, adalimumab; MTX, methotrexate; PDR, prednisone; OPG, osteoprotegerin; β-CTx, beta carboxy-terminal cross-linking telopeptide of type I collagen; RANKL, receptor activator of nuclear factor kappa beta ligand; DMARD, disease modifying anti rheumatic drug; vs., versus.

Table 2
Anti-tumor necrosis factor (anti-TNF) therapy and bone mineral density in Spondyloarthritis

Ref	Study	FT time	Treatment groups (n)	Spine BMD	Hip BMD	Findings
[83]	Obs SpA	6 months	T ₁ : INF (29)	BMD increased (+3.6%, P=0.001)	BMD total hip increased (+2.2%, P=0.0012) BMD trochanter increased (+2.3%, P=0.00012) BMD total neck stable (+1.1%, P=0.19)	No changes in BMD with concomitant use of glucocorticoids. Osteocalcin increased at 6 weeks but no differences at 6 months.
[84]	Obs CD	Mean 23±11 months	T ₁ : INF (15) T ₂ : conventional treatment (30)	BMD increased T ₁ >>T ₂ (+8.1% vs. +1.0%, P<0.01)	BMD increased Left hip T ₁ ≈T ₂ (+2.7% vs. +1.3%, P>0.05) Right hip T ₁ >>T ₂ (+5.6% vs. -0.2%, P<0.05)	In the INF treated group, ΔBMD in spine was not associated with glucocorticoid use
[85]	Obs CD	Mean 2.2 ± 0.99 y	T ₁ : INF (23) T ₂ : conventional treatment (38)	No bisphosphonate, BMD loss T ₁ ≈T ₂ (-4.1% vs. -3.3%, P>0.05) Bisphosphonate, BMD loss T ₁ ≈T ₂ (+4.4% vs. +2.0%, P>0.068) Bisphosphonate users vs. non-users (+4.0% vs. -3.7%, P<0.001)	ND	Bisphosphonates was associated with spine BMD gain, but effect was partially inhibited by concomitant use of glucocorticoids. INF had a marginal effect in BMD only in those patients that used bisphosphonates
[86]	Obs AS	Mean range 13.5 to 15.6 months	T ₁ : conventional treatment (40) T ₂ : bisphosphonate (20) T ₃ : anti-TNF (19) T ₄ : anti-TNF+bisphosphonate (11)	BMD increased in all treatment, but marginally significant in T ₂ .	BMD remained stable in all treatment groups, but in T ₄ BMD increased at trochanter	ΔBMD at trochanter correlate with Δinflammatory markers. In patients without syndesmophytes, ΔBMD at spine and total hip was different between treatments, ΔBMD at femoral neck correlate with Δinflammatory markers.
[87]	OL CD	1 year	T ₁ : INF (46)	ΔBMD similar in all groups BMD increased (2.4%, P=0.002)	BMD increased at trochanter and femoral neck (+2.8%, P=0.03 and +2.6%, P=0.001 respectively)	ΔBMD at spine and femoral neck was independent of glucocorticoids use.
[88]	OL SpA	6 months	T ₁ : ETA (10) T ₂ : SSZ/NSAIDs (10)	ΔBMD T ₁ ≈T ₂ (+1.1% vs. -1.4%, P=0.19)	ΔBMD femoral neck T ₁ ≈T ₂ (+0.2% vs. -1.5%, P=0.34) ΔBMD total hip T ₁ >T ₂ (+1.6% vs. -1.3%, P=0.027)	Measures of disease activity improved in ETA treated group but not in controls.
[89] [90]	OL SpA	1 -2 years	T ₁ : INF/ETA (n=19) T ₂ : INF/ETA (n=106)	BMD increased	BMD hip increased	Markers of bone resorption decreased early and remained low during treatment, but markers of bone formation only increase temporarily (3 months) but return to baseline thereafter.
[91]	RCT AS	24 weeks	T ₁ : INF (201) T ₂ : placebo (78)	BMD increased T ₁ >>T ₂ (+2.5% vs. +0.5%, P<0.001)	BMD increased T ₁ >>T ₂ (0.5% vs. +0.2%, P=0.033)	In the INF treated group ΔBMD in spine was not associated with Δmarkers of bone turnover; but ΔBMD in hip was associated with

Ref	Study	FU time	Treatment groups (n)	Spine BMD	Hip BMD	Findings
[92]	RCT	30 weeks	T ₁ : MTX +INF (28) T ₂ : MTX+ Placebo (14)	Δ BMD T ₁ $\approx$ T ₂ (+3.6% vs. -1.3%, P=0.06)	Δ BMD total hip T ₁ $\approx$ T ₂ (+1.9% vs. +0.1%, P=0.14) Δ BMD femoral neck T ₁ $\approx$ T ₂ (+2.5% vs. -1.3%, P=0.09)	baseline osteocalcin and bone alkaline phosphatase, and inversely correlated with changes in carboxy -terminal collagen crosslinks BMD increased significantly in INF but not in the MTX monotherapy treated group, Δ BMD were similar in spine, hip and femoral neck

Abbreviations: Ref, references; FU, follow-up; BMD, bone mineral density; ND, not done; Δ , changes; $\approx$, similar; Obs, observational; OL, open label; RCT, randomized clinical trial; SpA, spondyloarthropathies; CD, Crohn's disease; AS, ankylosing spondylitis; INF, infliximab; ETA, etanercept; SSZ, sulfasalazine; NSAIDs, non steroidal anti-inflammatory drugs; MTX, methotrexate; Rx, treatment; vs., versus;