

Risk factors for osteoporosis in inflammatory bowel disease patients

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Author contributions: Lima CA performed most of the writing and prepared the table; Lyra AC coordinated the writing of the paper; Rocha R coordinated the writing of the paper; Santana GO designed the outline and coordinated the writing of the paper.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior authors or coauthors who contributed their efforts to this manuscript.

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Received: April 18, 2015

Peer-review started: April 18, 2015

First decision: June 18, 2015

Revised: August 22, 2015

Accepted: September 16, 2015

Article in press: September 18, 2015

Published online: November 15, 2015

Abstract

Inflammatory bowel disease (IBD) patients exhibit higher risk for bone loss than the general population. The chronic inflammation causes a reduction in bone mineral density (BMD), which leads to osteopenia and osteoporosis. This article reviewed each risk factor for osteoporosis in IBD patients. Inflammation is one of the factors that contribute to osteoporosis in IBD patients, and the main system that is involved in bone loss is likely RANK/RANKL/osteoprotegerin. Smoking is a risk factor for bone loss and fractures, and many mechanisms have been proposed to explain this loss. Body composition also interferes in bone metabolism and increasing muscle mass may positively affect BMD. IBD patients frequently use corticosteroids, which stimulates osteoclastogenesis. IBD patients are also associated with vitamin D deficiency, which contributes to bone loss. However, infliximab therapy is associated with improvements in bone metabolism, but it is not clear whether the effects are because of inflammation improvement or infliximab use. Ulcerative colitis patients with proctocolectomy and ileal pouches and Crohn's disease patients with ostomy are also at risk for bone loss, and these patients should be closely monitored.

Key words: Bone mineral density; Crohn's disease; Osteoporosis; Ulcerative colitis; Inflammatory bowel disease; Risk factors

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Core tip: Inflammatory bowel disease (IBD) is associated with bone loss. Some factors reduce bone mineral density and lead to osteopenia and osteoporosis. The major complication in osteoporosis is the increased risk of fracture, which may impact quality of life. This article reviews each risk factor for osteoporosis in IBD patients, like chronic inflammation, smoking, body composition, corticosteroid use, vitamin D deficiency, surgery, and

the effect of infliximab therapy.

Lima CA, Lyra AC, Rocha R, Santana GO. Risk factors for osteoporosis in inflammatory bowel disease patients. *World J Gastrointest Pathophysiol* 2015; 6(4): 210-218 Available from: URL: <http://www.wjgnet.com/2150-5330/full/v6/i4/210.htm> DOI: <http://dx.doi.org/10.4291/wjgp.v6.i4.210>

INTRODUCTION

Inflammatory bowel disease (IBD), which is primarily comprised of ulcerative colitis (UC) and Crohn's disease (CD), is associated with various systemic complications, such as extra-intestinal manifestations (EIMs)^[1]. These complications are found in approximately 40% of IBD patients. The most widely known EIMs are skin lesions (erythema nodosum and pyoderma gangrenosum), articular manifestations and liver diseases (primary sclerosing cholangitis and primary biliary cirrhosis)^[2,3].

IBD patients exhibit a higher risk for bone loss than the general population. Chronic inflammation causes a reduction in bone mineral density (BMD), which leads to osteopenia and osteoporosis. Cross-sectional studies reported a highly variable prevalence of low BMD in IBD patients. The prevalence of osteopenia and osteoporosis varies significantly depending on the study population, location, and design, but it ranges from 22%-77% and 17%-41%, respectively^[4].

The incidence of inflammatory bowel disease seems stable in Western countries, but this disease has become more prevalent in Eastern countries, including Asia and Eastern Europe^[5]. Extra-intestinal manifestations are also present in IBD patients in Eastern countries. Some studies demonstrated that these patients are at risk for bone loss and osteoporosis^[6].

Dual-energy X-ray absorptiometry (DXA) is the current gold standard technique for the measurement of bone mass. Measurements are generally obtained at the femoral neck and lumbar spine. DXA results are typically expressed as the number of standard deviations (SD) above or below the expected mean for individuals of the same age, ethnicity and gender (Z score) or the mean of peak bone mass in young adults (T score)^[7-9]. The World Health Organization reported formulated diagnostic ranges for osteoporosis based on T scores. Osteoporosis and osteopenia are defined by a T score below -2.5, and between -1 and -2.5, respectively. These recommendations were derived from postmenopausal Caucasian females. Therefore, caution must be exercised when extrapolating these data to other groups^[9,10]. The current guidelines recommend DXA screening in IBD patients with one or more of the following risk factors: History of vertebral fractures, postmenopausal, male > 50 years of age, chronic corticosteroid therapy, or hypogonadism^[9-11].

The major complication of bone loss and osteoporosis

is the increased risk of fracture, especially non-traumatic fractures^[12,13]. Bernstein *et al.*^[14] demonstrated that the incidence of fracture in persons with IBD is 40% greater than the general population. Other authors also reported similar findings^[15-17]. Whether differences between IBD type (CD or UC) and BMD exist are not known. A cross-sectional population based study by Jahnsen *et al.*^[18] found that CD patients exhibited significantly reduced BMD compared to UC patients and healthy controls. A cohort of 3141 IBD patients in Taiwan also demonstrated a higher risk of osteoporosis in CD patients than UC patients^[6]. However, these results are not consistent with other reports.

Whether gender interferes with BMD in IBD patients is not known. Arizzzone *et al.*^[19] demonstrated that spine and femur BMD Z and T scores were significantly lower in men than women UC patients, but this difference was not demonstrated in CD patients. A case control cross-sectional study of 113 CD patients found that female patients exhibited significantly decreased BMD of the femoral neck and the trochanteric region, but BMD was not significantly different from healthy controls in men^[20].

Other risk factors associated to IBD or the general population are also related to the loss of bone mass with older age, postmenopausal status, smoking, malnutrition, physical inactivity, corticosteroid use for more than three months and vitamin D deficiency^[21].

This review describes the specific risk factors for osteoporosis in IBD patients.

INFLAMMATION

Many factors exert important effects on bone metabolism, but there is increasing evidence that inflammation per se contributes to osteoporosis in IBD. Some studies in patients with newly diagnosed IBD demonstrated a reduction of BMD, even without the use of medications, such as corticosteroids^[22,23].

Several chronic inflammatory disorders are associated with osteoporosis and an increased number of fractures. Inflammation is characterized by the production of cytokines, which is associated with increased bone resorption and reduced bone formation. The main system involved in the development of osteoporosis in IBD and other inflammatory diseases is likely the RANK/RANKL/osteoprotegerin^[24].

The receptor activator of nuclear factor- κ B (RANK) is a transmembrane protein that is expressed on the surface of cells of hematopoietic origin that belongs to the TNF receptor family. RANK is the primary cytokine receptor in the development of osteoclastogenesis^[25-28]. The ligand for RANK receptor (RANKL) is expressed on the surface of osteoblasts, mesenchymal cells and other cells, such as T and B lymphocytes. The binding of RANKL to RANK induces the differentiation of osteoclast precursors. RANKL also increases the resorptive activity of osteoclasts and prolongs their survival by suppressing

apoptosis^[25-28].

Osteoblasts produce osteoprotegerin (OPG) as a control to maintain balance. OPG is a decoy receptor molecule that naturally binds RANKL to inhibit osteoclast activation and protect against bone loss^[25-28]. Chronic inflammatory states mediated by T cell-produced cytokines affect osteoblasts and osteoclasts. Activated T cells produce RANKL and its soluble form, which directly triggers bone loss *via* the induction and activation of osteoclasts by RANK^[29].

Several pro-inflammatory cytokines are involved in the activation of osteoclasts, such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), IL-6, IL-11, IL-15 and IL-17^[30]. IL-6 plays an important role in the mediation of inflammatory osteoporosis, and it may also be involved in the pathways that lead to osteoporosis but are not elicited by inflammation^[31].

Turk *et al.*^[32] demonstrated that patients with newly diagnosed and untreated CD exhibited elevated pro-inflammatory cytokines levels (IL-6, TNF- α , and IL-1) and increased free RANKL and OPG activity. These authors also observed a positive correlation between TNF- α and sRANK.

Disease activity interferes with bone metabolism. Some studies demonstrated that patients with disease in remission exhibit an increase in BMD. Reffitt *et al.*^[33] analyzed 137 IBD patients and demonstrated that patients with longer disease remission exhibited higher BMD.

SMOKING

Smoking has been recognized as a risk factor for bone loss and fractures for many years. Several mechanisms were proposed to explain the differences in BMD between smokers and non-smokers. However, the pathophysiological mechanisms underlying osteoporosis in cigarette smokers have not been fully explored^[34,35].

Some studies demonstrated that the dose and duration of smoking may influence the effect of smoking on bone^[35,36]. Smoking seems related to a vitamin D deficiency, and one possible explanation is that smoking alters the hepatic metabolism of vitamin D by influencing 25 hydroxylase in the liver, which lowers serum 25-hydroxyvitamin D^[34,35]. There is also evidence that smoking alters gastrointestinal calcium absorption. Smokers lead an unhealthy lifestyle that includes low calcium/vitamin D intake, lack of exercise and alcohol ingestion, which affects bone health^[34,35].

Whether smoking is associated with estradiol levels is controversial, but some studies demonstrated that smoking alters estrogen production and metabolism. There are some possible mechanisms. Nicotine may reduce estrogen production, and smoking enhances the hepatic metabolism of estradiol. Smokers exhibit higher serum sex-hormone binding globulin levels, which reduces free estradiol concentrations^[34,35].

Few studies investigated the relationship between smoking and the RANK-RANKL-OPG system. Some

reports demonstrated that smokers exhibit lower OPG levels without a difference in RANKL levels^[36]. A cross-sectional study of 126 UC and 39 CD Iranian IBD patients demonstrated that femoral neck T scores were predicted by age, body mass index (BMI), smoking, and corticosteroid use. However, the association between smoking and BMD was not observed in the lumbar spine in this study^[37]. Silvennoinen *et al.*^[38] evaluated the effect of smoking on BMD in 152 IBD patients (67 UC, 78 CD, 7 indeterminate colitis) and 73 controls and found that female IBD patients who currently smoked or with a previous history of smoking exhibited lower Z scores for the lumbar spine and femoral neck than female patients who had never smoked.

Smoking is also associated with relapses and disease activity (especially CD) and the need for steroids, which also negatively interferes with bone metabolism. The suspension of smoking is associated with more flare-ups in UC patients. However, smoking cessation should be encouraged in all IBD patients because it reduces other complications, such as cardiovascular disease, lung cancer and changes in bone health^[39].

BODY COMPOSITION

Low BMI is a well-documented risk factor for low BMD and fracture^[40]. Azzopardi *et al.*^[41] analyzed the risk factors for osteoporosis in 83 CD patients and found a significant association between BMI and BMD.

Many others studies also identified a positive association between BMD and BMI^[42-44]. Atreya *et al.*^[45] also considered BMI a strong risk factor for altered bone metabolism and a way to identify osteoporotic patients who are missed by current guidelines. Leslie *et al.*^[46] studied 388 IBD patients and found that greater weight, height, and body mass measurements positively correlated with bone density at all sites. Fat and lean tissues exhibited positive relationships with BMD in this study, but lean tissue exhibited a much stronger correlation than fat tissue, especially for the total hip.

Low BMI is a risk factor for fractures, but whether obesity is a protective factor is not clear because obesity increases the risk of some osteoporotic fractures^[47,48]. Johansson *et al.*^[49] published a recent meta-analysis of the association of fracture risk and BMI in women and concluded that there is a slight increase in osteoporotic fracture risk with increasing BMI after adjustment for BMD. Therefore, body composition appears more important than BMI in bone metabolism.

Mechanical loading of the muscles that act on the bone produce an anabolic effect, which results in osteogenesis^[50,51]. Many IBD patients have reduced muscle (lean mass) because of nutritional factors, a sedentary lifestyle or medications, and these factors may lead to a reduced bone mass that is secondary to the decrease in mechanical stimulation of the skeleton^[52].

A Canadian study analyzed the bone mass (bone mineral content) and muscle mass (lean mass) of 65 CD patients. Multiple regression analysis demonstrated

that only total lean mass was independently associated with lumbar bone mineral content (BMC), BMC in both hips and total BMC^[52]. Lee *et al.*^[53] demonstrated a similar effect in a cohort of 61 CD patients. This study found that lean mass and muscle strength, but not fat mass, significantly correlated with regional and whole body BMD, but lean mass was the only independent predictor of hip BMD after multiple regression analysis. These authors concluded that maintaining or increasing muscle mass may positively affect BMD and prevent the development of osteopenia and osteoporosis.

GLUCOCORTICOID USE

Glucocorticoids (GCs) are frequently used in the treatment of inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, asthma and IBD. GC exposure is common in IBD patients, and over 50% of patients are exposed to systemic GCs within 5 years of diagnosis, and 20% have used at least 3 g of prednisone in any 1-year period^[54].

Many studies consistently identified systemic GC use as a risk factor for osteoporosis and bone mineral loss in IBD patients^[54,55]. Abraham *et al.*^[56] studied 166 IBD patients and demonstrated that the risk of osteoporosis was twice as high in patients who used corticosteroids [OR = 2.4 (1.5-3.4), $P = 0.001$].

Osteoporosis attributed to GC exposure is the most common etiology of drug-induced osteoporosis. Approximately 50% of patients receiving chronic GC therapy will develop osteopenia and fractures, and 17% of these patients will develop fractures within the first year of GC therapy^[57].

Some risk factors for the development of fractures after steroid exposure were identified: Age older than 65 years, cumulative steroid dose (high GC dose and duration of treatment > 3 mo), positive family history of osteoporosis, low calcium intake, female sex, low bodyweight (BMI < 24 kg/m²) and low BMD^[57,58].

The mechanism of this loss is not fully understood. GC exposure alters the balance between osteoclast and osteoblast activity in bone metabolism. One important mechanism for the effects of GC on bone is osteoblastic dysfunction. GC inhibits stem cell differentiation into osteoblasts and induces osteoblast apoptosis, which decreases the secretion of osteoid matrix and new bone formation^[57,59].

GCs increase the expression of RANKL and decrease the expression of its soluble decoy receptor OPG in stromal and osteoblastic cells. These alterations caused a greater differentiation of precursors into osteoclasts, which increases their resorptive activity and enhances bone reabsorption. There is also evidence that GCs directly prolong the lifespan of mature osteoclasts^[57,59,60]. The increase in RANKL is only transient. Therefore, the failure of bone formation, rather than increased bone resorption, is likely the main mechanism underlying glucocorticoid-associated bone loss^[58].

GCs also exhibit a negative effect on sex hormones

status because GCs reduce estrogen and testosterone production. This negative effect of oral GCs on gonadal function may increase bone resorption^[52,54].

GCs reduce intestinal calcium absorption and inhibit calcium reabsorption in the kidney, which indirectly leads to a negative net calcium balance and stimulates an increase in parathyroid hormone. These changes further increase the number of osteoclasts and stimulate bone resorption^[57,58].

ROLE OF VITAMIN D

The role of vitamin D in IBD was not investigated in recent years. This vitamin primarily increases serum calcium and phosphate levels and promotes bone mineralization.

Vitamin D is available in two forms: Vitamin D3 (cholecalciferol), which is produced in the skin by exposure to sun light and obtained from animal sources, and vitamin D2 (ergocalciferol), which is obtained from plant sources. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D [25-(OH) D], which circulates in the blood plasma and is stored in fat tissue and muscles. Metabolites of vitamin D are transported bound to albumin binding protein or vitamin D. This protein regulates the effects of the metabolites in target organs^[61].

A study of 49 healthy young men demonstrated that free and bioavailable 25-(OH) D positively correlated with BMD, which suggests a possible benefit of vitamin D supplementation during deficiencies^[62].

Vitamin D exerts its biological effects through the vitamin D receptor^[61]. Multiple tissues and immune cells express this receptor, and these cells contain the enzyme that converts vitamin D into its active metabolite. Therefore, vitamin D appears to influence the innate immune response by inhibiting the maturation of dendritic cells and IL-12 and the adaptive immune response by inhibiting the production of IFN- γ , IL-17 and IL-21^[63,64].

Several studies demonstrated a high prevalence of vitamin D deficiency in IBD patients. Many factors are attributed to this deficiency, and some of these factors are common to the general population, such as low sun exposure, inadequate intake, inactivity and other factors related to inflammatory disease, such as terminal ileum resection and low absorption due to the inflammatory process^[64]. Disease activity is also associated with low levels of vitamin D in CD and UC patients^[65,66].

Vitamin D deficiency leads to reduced calcium and secondary hyperparathyroidism, which stimulates osteoclastogenesis, increases bone resorption, and results in osteopenia and osteoporosis^[64].

IS ANTI-TNF A PROTECTIVE FACTOR?

Elevated TNF- α concentration may play a role in dysfunctional bone metabolism in IBD. TNF- α is a major factor in the inactivation of osteoclasts. This cytokine induces osteoclast differentiation, increases osteoclast

Table 1 Infliximab effects on bone mineral density in Crohn's disease

Ref.	Study design ¹	Participants number	Endpoints	Results
Miheller <i>et al</i> ^[69]	Prospective	29 CD patients	Determine the effects of IFX on bone metabolism in CD patients	IFX improves bone metabolism in CD independently from the behavior of the disease
Abreu <i>et al</i> ^[70]	Prospective	38 CD patients	Assess the ability of IFX to increase bone formation measured by markers of bone turnover in active CD patients	Treatment with IFX was associated with increased markers of bone formation
Franchimont <i>et al</i> ^[71]	Prospective	71 CD patients, 68 controls	Assess the evolution of markers of bone turnover after IFX treatment for active CD	IFX induces improvement in biochemical markers of bone turnover
Mauro <i>et al</i> ^[72]	Retrospective	15 CD patients, 30 controls	Assess whether treatment with IFX had a beneficial effect on lumbar bone mass	Treatment with IFX was associated with significant increases in lumbar bone area, BMC and BMD in CD patients
Pazianas <i>et al</i> ^[73]	Retrospective	61 CD patients	Evaluate the effects of IFX administration on BMD in CD patients	IFX may work in synergy with bisphosphonates to provide additional increases in BMD in CD patients

¹All were cohort study. CD: Crohn disease; IFX: Infliximab; BMC: Bone mineral content; BMD: Bone mineral density.

bone resorption, and protects these cells against apoptosis, which sensitizes osteoblasts to apoptosis and diminishes bone formation^[67].

Infliximab (IFX) is a monoclonal antibody that exhibits high affinity and specificity for TNF- α . Anti-TNF therapy is an important IBD treatment because it allows for remission induction, relapse prevention and a decrease in corticosteroid use^[68]. Some studies demonstrated the benefits of IFX use on BMD (Table 1). However, the exact mechanism of action of this anti-TNF in bone metabolism is not clear.

Miheller *et al*^[69] investigated the effects of IFX on bone metabolism by measuring biochemical parameters in 29 CD patients and found that IFX increased osteocalcin levels (marker of bone formation) and reduced beta-Cross Laps levels (marker of bone resorption).

Abreu *et al*^[70] observed increased bone alkaline phosphatase (bone formation marker) in 38 CD patients treated with IFX and no significant change in the dose of N-telopeptide of type I collagen (NTX-marker of bone resorption). Franchimont *et al*^[71] also examined the evolution of biochemical markers of bone metabolism after the first treatment with IFX in 71 CD patients. The authors of this study detected a normalization of bone markers after 8 wk of IFX treatment, with a median increase in formation markers of 14%-51%, according to the marker, and an approximately 10% reduction in bone resorption^[71].

A retrospective study by Mauro *et al*^[72] in 15 CD patients treated with IFX demonstrated significant increases in BMC and BMD in the lumbar spine compared to the control group.

The benefit of using IFX in BMD was also demonstrated with its associated use with bisphosphonates, as noted by Pazianas *et al*^[73] in a retrospective cohort. They studied 61 CD patients, and patients who used bisphosphonates plus IFX experienced a greater increase in BMD than patients who used only bisphosphonate (6.7%/year vs 4.46%/year, $P < 0.05$).

The mechanism of action of IFX on bone metabolism is not well established, but its benefits in BMD may

occur *via* the alteration of bone markers, the reduction of GC utilization and the induction of clinical and endoscopic remission.

Adalimumab is a human monoclonal IgG1 antibody that is specific for human TNF. It is also used in the treatment of IBD and other inflammatory diseases, such as rheumatoid arthritis and spondyloarthritis^[74]. Studies demonstrated benefits in BMD in some patients using this therapy. Durnez *et al*^[75] studied 59 patients with spondylo arthropathy treated with anti-TNF (infliximab, adalimumab or etanercept) during a follow up of 6.5 years and found an increase in BMD of 11.8% in the lumbar spine and 3.6% in the trochanter.

Wijbrandts *et al*^[76] conducted a prospective, open-label study of 50 rheumatoid arthritis patients. They analyzed the mineral density of the lumbar spine and femoral neck before and 1 year after adalimumab treatment. The authors observed no significant changes in BMD in lumbar spine (0.3%) or femoral neck (0.3%) and concluded that therapy with this anti-TNF does not increase BMD, but it can stop bone loss.

Another study by Krieckaert *et al*^[77] evaluated the effect of long-term adalimumab use on BMD of the lumbar spine, hip and hands of rheumatoid arthritis patients. A total of 184 patients were studied, and hip and lumbar spine BMD remained stable after 1 year of treatment, but BMD in the hands decreased significantly by 1.41%. The mean BMD change per year was -0.58% and 0.07% for hip and lumbar spine, respectively, after a mean follow-up of 4.0 years (overall P value of hip was < 0.0001 and spine was 0.67). The authors considered that the BMD changes were associated to disease activity.

However, there are currently no published data investigating the effect of adalimumab on bone metabolism in IBD patients. There are also no data with certolizumab pegol.

EFFECT OF SURGERY

Proctocolectomy with ileal pouch-anal anastomosis

(IPAA) is the procedure of choice for the treatment of most patients with refractory UC, UC with dysplasia and familial adenomatous polyposis^[78-80]. Some studies demonstrated an increase in long-term BMD after total colectomy with IPAA^[79]. This surgery may improve BMD in UC patients, possibly due to the discontinuation of corticosteroids, improvement in nutritional status and a decreased production of cytokines by the diseased colon^[78,79].

However, it is unclear whether total colectomy with ileal pouch provides benefits or detriments to BMD. In a study of 327 UC patients who underwent this surgery, 32% had low BMD 4 years after surgery, which suggests that bone loss continues after colectomy^[78].

Possible risk factors and mechanisms of bone loss are considered. An ileal pouch changes the anatomy and function of the small intestine by reducing the absorption of bile salts, which contributes to the reduced absorption of vitamin D. The stasis of stool in the ileum in UC patients with IPAA promotes bacterial overgrowth, which causes deconjugation of bile salts and leads to the malabsorption of vitamin D^[79]. Another mechanism is inflammation of the ileal pouch, which increases inflammatory cytokines levels, such as IL-1, IL-6 and TNF- α , and stimulates osteoclast activity and promotes bone loss^[79].

Navaneethan *et al.*^[81] also found a lower BMD in UC patients undergoing total proctocolectomy and ileal pouch compared to the control group (31.1% vs 15.1%, $P < 0.001$). They also found that BMD was already low before surgery in 13 patients, and 7 (53.8%) of these patients exhibited an increase in BMD after surgery. Some studies demonstrated a higher incidence of fractures in UC patients with IPAA, ranging from 7%-15%^[78,81].

IBD patients, particularly CD, are at increased risk of surgery based on disease severity and duration. The most common surgery for CD patients involves removal of the terminal ileum, which is associated to a vitamin D deficiency and the consequent secondary hyperparathyroidism, which promotes bone mass reduction. However, the relationship of these factors with osteoporosis in CD is not well defined^[54].

Gupta *et al.*^[82] analyzed 126 patients with ostomy, and 95% of these patients had CD and ileostomy. This study also demonstrated a high frequency of fractures (9.5%) in CD patients after ostomy, with significantly higher rates in patients with low BMD. IBD patients with ostomy and low BMD also exhibited low BMI. Fractures were also five times more frequent in IBD patients with ostomy and low BMD.

IBD patients with ostomy are at higher risk for bone loss, and these patients should be monitored closely, especially patients with risk factors, such as low BMI and a previous history of fractures.

CONCLUSION

IBD is associated with bone loss, and patients are at

increased risk of developing fractures. Many risk factors are associated with reductions in BMD in this population, including inflammation, smoking, body composition, glucocorticoid use, vitamin D deficiency and surgery. Infliximab seems to increase BMD, but the exact mechanism is not well established. More studies are needed to analyze the effect of other anti-TNF therapies in BMD.

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P- Reviewer: Chow WK, Rajendran VM

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