Abnormal bone metabolism in Crohn's disease

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1. ABSTRACT

Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) have a major impact on the health of individuals and population. These diseases result from an inappropriate immune response, in genetically susceptible individuals, to microbial antigens of commensal microorganisms. This paper reviews the abnormal bone metabolism associated with CD, in order to elucidate the mechanism of bone loss.

2. INTRODUCTION

The incidence of Crohn's disease (CD) has sharply increased since the early 1950s in Europe, and has been characterized by a high incidence of CD and a low incidence of UC according to the first inquiry undertaken in the late 1980s. The annual incidence of CD increased from 5.2/100,000 inhabitants in 1988-1990 to 6.4 in 1997-1999 (1). In contrast, until the past decade, low prevalence and incidence rates have been reported from other parts of the

world including eastern Europe, south America, Asia and the Pacific region (2-5).

The prevalence of metabolic bone disease is significantly higher in patients with CD than in healthy individuals (6). Among metabolic bone diseases, osteopenia and osteoporosis (OS) are frequently observed in patients with CD, which can lead to increased risk of fractures (7, 8). Although several mechanisms may contribute to skeletal abnormalities in CD patients, inflammation and inflammatory mediators such as TNF, IL-1β, and IL-6 may be the most critical. It is not clear whether the changes in bone metabolism leading to decreased mineral density are the result of decreased bone formation, increased bone resorption, or both. This paper reviews the abnormal bone metabolism of CD, with the aim of elucidating the mechanism of bone loss.

3. RELATED INDICATORS IN BONE METABOLISM STUDIES

3.1. General indicators
Indicators of bone metabolism include Crohn's disease activity index (CDAI), body mass index (BMI), calcium and vitamin D (VitD), parathyroid hormone (PTH), 25-hydroxyvitamin D3 (25-OH D_3) and bone mineral density (BMD). BMD is measured by using dual-energy X-ray absorptiometry (DEXA) or dual photon absorptiometry scanning at the lumbar spine and femoral neck.

3.2. Bone turnover indicators
Bone turnover involves both bone formation and bone resorption. Biochemical markers which reflect bone formation are: osteocalcin (OC), bone-specific alkaline phosphatase (BAP), procollagen type I carboxy-terminal propeptide (PICP) and bone sialoprotein (BSP). In addition, biochemical markers which reflect bone resorption are: urine calcium, urine phosphorus, urine hydroxyproline (HOP), hydroxylysine glucoside (HOLG), tartrate-resistant acid phosphatase (TRAP), and degradation products of bone type I collagen including pyridinolines (Pyr), deoxypyridinolines (DPD), type I collagen cross-linked N-telopeptide (NTx) and carboxyterminal cross-linked telopeptides of type I collagen (ICTP or CTX). A marker representing osteoblast activity is osteoprotegerin (OPG), which is the inhibitor of receptor activator of nuclear factor kappa B (RANK) and RANK-ligand (RANKL) signaling.

3.3. Indicators of PBMC function and hormones evaluating bone turnover
IFN-γ and prostaglandin E2 (PGE2) represent the function of peripheral blood mononuclear cells (PBMCs). Hormones including estradiol (E2), testosterone (T), dihydrotestosterone (DHT) and sex hormone binding globulin (SHBG) also represent bone turnover.

4. FACTORS INFLUENCING ABNORMAL BONE METABOLISM

An imbalance in bone metabolism is one of the crucial factors leading to increased bone loss in CD parents.

Bischoff et al. (9) suggest several mechanisms that may be involved in IBD-associated bone disease: (1) high inflammatory activity directly induces bone degradation via yet unknown pathways, (2) treatment with corticosteroids may exert catabolic effects on bone, or (3) malabsorption and vitamin D deficiency may activate bone turnover. Schoon et al. (10) found that bone turnover in patients with long-standing CD in clinical remission is characterized by suppressed bone formation and normal bone resorption. Urine calcium excretion is reduced. Hence, interventions and therapy should be directed towards the improvement of bone formation.

Here we review the influential factors that may affect bone turnover, including common factors (sex, age, weight, diet, malnutrition, smoking), genetic predisposing factors, disease region, activity and duration, intestinal surgical ablation, corticosteroid therapy, disequilibrium of calcium, activation of inflammatory factors and hypogonadism.

4.1. Common factors affecting bone turnover
It has been demonstrated that various common factors, including sex, age, weight, diet, malnutrition and smoking, are risk factors for abnormal bone metabolism.

Reed's study indicated for the first time that diet played a role in the development of low bone density in premenopausal women with CD (11). Later, Andreassen et al. (12) identified gender, age, and body weight as the major determinants of BMD in patients with CD. As in healthy individuals, the combined effect of these factors accounted for up to 50% of the variability in BMD. Age was further demonstrated to be the most important predictor of bone loss by Habtezion et al. (13). They also found that disease activity, systemic inflammation, and hormonal and genetic factors may all be important determinants of bone loss in CD. Elevated BMI and C-reactive protein (CRP) and parathyroid hormone levels were predictive of vertebral fractures in the study of Siffledeen et al. (14). They demonstrated that vertebral fractures in CD patients occur with an equal frequency in those with low and those with normal BMD, regardless of corticosteroid use. The mean age of CD patients with vertebral fractures was much lower than that reported in the general population for these fractures.

In addition to age and low body weight, which are also risk factors for metabolic bone disease in the general population, a recent clinical study found that factors associated with chronic, ongoing, and long-lasting inflammation are probably major risk factors for metabolic bone disease (6). Therefore, common factors related to abnormal bone metabolism are complex. The precise mechanism of action of these factors, and the way how they interact with each other in abnormal bone metabolism, still need to be further studied.

4.2. Disease region and duration
In addition to the common factors associated with abnormal bone metabolism, CD itself is also a crucial factor. Many clinical studies have demonstrated that CD is

a risk factor for abnormal bone metabolism. The diseased region in CD and the disease duration are major factors influencing abnormal bone metabolism. Bouzaïdi *et al.* (15), in a prospective study, found that smoking, long disease duration and ileal site were all predictors of bone loss. Ben Hamida *et al.* (16) discovered, after adjusting for age and intestinal resection,the duration of evolution of more than 10 years persisted as a risk factor forOS. Orlic *et al.* (17) showed that duration of active disease was a statistically significant risk factor, while Thodis *et al.* (18) also found that disease duration made a significant contribution to bone loss.

In addition, the diseased region of the bone in CD patients has also been investigated. Staun *et al.* (19) found that the BMC of the spine and femoral neck was low in patients with CD. During the study significant bone loss was demonstrated only in the femoral neck. In that study, BMC or rate of change in BMC was not related to treatment with steroids or length of the resected small intestine. Ardizzone *et al. (*20) showed that IBD patients had a diffuse osteopenia, the degree of which did not differ between CD and UC; however, bone turnover was significantly higher in UC.And finally-, osteopenia was related to disease duration in CD, whilst it was related to male sex and glucocorticoid treatment in UC.

4.3. Corticosteroid therapy in CD
Corticosteroids, which play an important role in CD therapy, may be a single significant risk factor in abnormal bone metabolism for patients. Jahnsen *et al.* (21) studied patients with CD who had reduced BMD and found that this was associated with corticosteroid therapy. Robinson *et al.* (22) believed that both current steroid use and cumulative steroid dose were major determinants of BMD in CD patients. Bouzaïdi *et al.* (15) found that systematic corticotherapy was predictive of bone demineralization. Jahnsen *et al.* (23) found that corticosteroid therapy was involved in bone loss in CD patients in a 2-year study, though the multifactorial pathogenesis of bone loss in IBD made it difficult to assess the importance of each single contributing factor. Bartram *et al.* (24) studied 258 unselected patients (92 M, 166 F) with CD and found that increasing corticosteroid use was one of the independent risk factors forOS. However, less than half of the reduction in BMD could be attributed to risk factors such as corticosteroid use and low BMI and therefore the remainder was unexplained. De Silva *et al.* (25) also found that use of systemic steroids was independently associated with the occurrence of OS in patients with CD.

In contrast, some researchers believe that the reduction of BMD in CD patients is not associated with corticosteroid therapy. Ghosh *et al.* (26) found that low bone mineralization was a feature of CD but not of UC. Treatment with corticosteroids did not result in further bone loss in 1 year. Both Andreassen *et al.* (12) and Habtezion *et al.* (13) thought that steroid use was just a weaker predictor of bone loss. De Jong *et al.* (27) also found that low BMD was frequent in CD, but no decline in BMD over time was found, despite ongoing use of corticosteroids. Oshima *et al.*

(28) identified a decrease in BMD in 9 patients (30%). BMD did not correlate with total steroid consumption, but showed a negative correlation with CDAI, Glu-OC and serum NTx.

Uncertainty over whether corticosteroids cause bone loss in patients with CD may be related to their short-term, intermittent use, such as generally prescribed for budesonide, methylprednisolone and prednisolone.

D'Haens *et al. (*29) suggested that short-term methylprednisolone therapy impaired osteoblast activity in patients with CD whereas budesonide did not. Twenty-nine patients received either 9 mg of budesonide (controlled ileal release formulation) for 10 weeks, or 32 mg of methylprednisolone (equivalent to 40 mg prednisone) orally for 3 weeks with subsequent tapering. Patients who completed the trial with methylprednisolone (n = 8) had suppression of serum osteocalcin (30.2 +/- 2.6 to 20.4 +/- 2.0 ng/mL; $P < 0.01$), whereas no changes in this parameter of bone synthesis were observed during budesonide treatment (n = 11) (34.8 +/- 3.1 to 33.0 +/- 3.5 ng/mL). Urinary pyridinolines and DPD, highly sensitive markers of bone degradation, did not change in either group. Some years later, systemic glucocorticoid treatment in patients with active CD was investigated by Von *et al.* (30). In that study, lumbar spine and femoral neck bone mineral densitometry was performed at baseline and again after 3 months. Clinical examinations including evaluation of RANKL were performed prior to, and at 1, 2 and 12 weeks following steroid administration. A decrease in BMD in patients with CD appeared to result, at least in part, from a short-term effect of systemic glucocorticoids. Modulation of osteoclastogenesis by RANKL and decreased osteoblast function may be the underlying molecular basis. Although Tobias *et al.* (31) revealed that significant bone loss at the hip could be detected in patients receiving corticosteroid treatment for 2 months for active CD, it remained unclear whether this was because of disease activity or its treatment. This rapid bone loss may represent a risk factor for fracture and justify bone protective therapy.

While D'Haens *et al.* (29) found that short-term budesonide therapy did not injure bone, Schoon *et al.* (32) discovered that treatment with budesonide was associated with better preservation of bone mass compared with prednisolone, but only in corticosteroid-naïve patients with active ileocecal CD. In both the corticosteroid-free and corticosteroid-dependent groups, budesonide and prednisolone were equally effective for up to 2 years, but budesonide caused fewer corticosteroid side effects.

Since a significant proportion of steroid-naïve patients had osteopenia, mechanisms other than steroid use must also be involved in bone loss in CD. Therefore, control of disease activity is very important in CD patients, and periodic measurement of BMD in combination with bone mineral markers (Glu-OC and serum NTx) may be useful in predicting a decrease in BMD.

4.4. Disequilibrium of calcium and VitD
Calcium and VitD are both required in bone metabolism, and their dysregulation can cause abnormal

bone metabolism. Recently, a clinical study found that more than 70% of patients with quiescent CD were vitamin D-deficient or insufficient (33). Andreassen *et al.* (34) discovered that vitamin D deficiency (25-OHD < or = 10 pg/mL) was present in 44% of patients. Secondary hyperparathyroidism was present in 2% of unoperated patients and in 18% of patients subjected to bowel operations. They concluded that vitamin D deficiency is common in patients with CD, even when the disease is in remission and regardless of the location of the disease. Secondary hyperparathyroidism was most frequently seen in patients who had undergone intestinal resection. PTH correlated with BMD in a large group of unselected patients withCD; in contrast 25-OH D only correlated with BMD of the forearm. Gilman *et al.* (35) found that, relative to levels in their respective controls, CD patients had significantly higher levels of BAP and ICTP, and lower serum total OC and 25-OH D, while serum PTH levels were similar.

Since the lack of calcium and VitD are risk factors for abnormal bone metabolism, the usefulness of supplementation with calcium and VitD in CD patients needs to be investigated. Siffledeen *et al.* (36) thought that low BMD was frequently associated with CD. Supplementation with daily calcium and VitD was associated with increases in BMD. Kumari *et al.* (37) found that CD patients have a normal response to vitamin D in enhancing the efficacy of calcium absorption. Thus, supplementation with calcium and VitD seems to be a promising therapeutic method of preventing abnormal bone metabolism in CD patients.

4.5. Gene polymorphisms
Gene polymorphisms have been demonstrated to be a risk for abnormal bone metabolism in CD patients.

Lee *et al.* (38) found that both the TNF-alpha GT haplotype and the -857 CC genotype showed strong associations with BMD overall. This study identified a novel protective association between a TNF-alpha haplotype and BMD in CD. Polymorphisms in the genes encoding the inflammatory cytokine IL-6 and COL1A1 could influence BMD in patients with CD but the particular VDR gene polymorphisms studied did not have a major effect (39).

The association between vitamin D receptor gene polymorphisms and BMD of IBD patients was investigated by Bregenzer *et al.* (40). They found no association between the FokI polymorphism and BMD of the lumbar spine and femoral neck in patients with IBD.

4.6. Endocrine hormone level
Since deficiencies in hormone levels, especially E2, are risk factors for the incidence of OS in post-menopausal CD patients, some studies aimed to validate whether such deficiencies were also frequent in male CD patients. Robinson *et al.* (41) found that of 48 men with CD, eight (17%) men hadOS, and a further 14 (29%) had osteopenia. Three (6%) men had a low free androgen index and normal gonadotrophins consistent with secondary hypogonadism, two of whom had osteopenia of the hip and spine. The independent association between testosterone and the bone formation marker osteocalcin suggests that sex hormone status influences bone metabolism in men with CD. These results suggest that testosterone replacement might be an effective treatment in some men withOS and CD.

Klaus *et al.* (42) studied 111 male CD patients who underwent osteodensitometry (DXA) of the spine (L1–L4). Disease activity was estimated using CDAI. They found an altered hormonal status (i.e. E2 and, to a lesser extent, T deficiency) in male CD patients but failed to show any association with bone density or markers of bone turnover. The role of E2 in the negative skeletal balance in males with CD, analogous to E2 deficiency in postmenopausal females, deserves further attention. In addition, menopause could be associated independently with the occurrence of OS in CD patients (25). Therefore, hormone replacement may be an interesting method to relieve abnormal bone metabolism.

4.7. Skin-fold thickness (SFT)
Robinson *et al.* (43) discovered that hand skin-fold thickness (SFT) was independently associated with BMD in CD and was lower than in age-matched healthy subjects. Hand SFT in combination with other easily measurable confounding variables might therefore be useful in screening forOS in patients with CD.

4.8. Serum bone sialoprotein
There is increasing evidence to suggest that serum bone sialoprotein may also directly influence bone metabolism in these patients. Faust *et al.* (44) discovered that bone sialoprotein and urinary crosslinks were significantly increased only in patients with CD. According to these data, increased serum bone sialoprotein concentrations seem to be an additional valuable and sensitive marker of bone resorption in patients with CD.

4.9. Muscular mass and activity
Recently, it has been proposed that muscular mass and activity, rather than overall body weight, are important determinants of bone mass and, hence of bone strength in CD (45). Thus, the management of bone loss inIBD should address the effects of both nutrition and exercise on muscle mass. Lee *et al.* (46) further found that appendicular muscle mass (AMM) was an independent predictor of whole-body and regional BMD whereas lean mass was an independent predictor at the hip. Of the components of body composition, muscle mass was strongly associated with regional and whole-body BMD.

4.10. Complications or extra-intestinal involvement
Poturoglu *et al.* (47) proposed that complications or extra-intestinal involvement were a significant predictor of BMD in both groups. They studied a total of 142 patients with UC (n = 88) and CD (n = 54), and found that steroid use, disease activity, disease localization, disease duration, bowel surgery and gender had no influence on BMD.

5. TREATMENT OF ABNORMAL BONE METABOLISM

Since abnormal bone metabolism has a high incidence in patients with CD, more attention should be
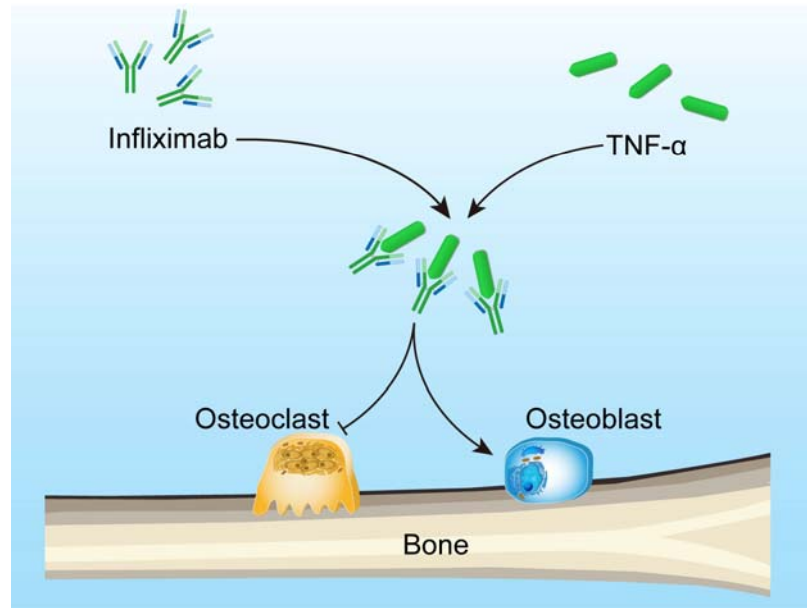
Figure 1. Abnormal bone metabolism therapy by anti-tumor necrosis factor alpha (TNF-alpha) antibody infliximab. Infliximab, the monoclonal antibody against TNF-alpha, works by binding to TNF-alpha to prevent TNF-alpha from binding to the receptor. It enhances bone formation and decreases bone resorption in bone metabolism in CD patient therapy.

paid to its treatment. Below we review the development of abnormal bone metabolism therapy in CD patients.

5.1. Anti-tumor necrosis factor-alpha antibody

Tumor necrosis factor alpha (TNF-alpha) plays a central role in the pathogenesis of CD inflammation. Disease activity and circulating proinflammatory cytokines are thought to play a role inOS. Turk *et al.* (48) discovered that bone disease accompanying CD at diagnosis suggests that bone metabolism is affected by the underlying inflammatory process, a finding which is probably confirmed by the central role of the proinflammatory cytokine TNF-alpha being strongly associated with the osteoclastogenic mediator RANKL, and inversely with bone density.

Infliximab, a chimeric anti-TNF-alpha antibody, is effective in the treatment of CD (49). Infliximab therapy in CD may rapidly influence bone metabolism by acting either on bone formation or bone resorption (50). This improvement seems to be independent of the clinical response to infliximab (51).

Ryan *et al.* (52) performed a prospective trial in which twenty-four patients with active CD were treated with infliximab (5 mg/kg). Infliximab therapy had a significant beneficial effect on bone metabolism in patients with active CD. These findings further support the theory that active ongoing inflammation and high levels of circulating cytokines play a pivotal role in the pathogenesis of bone loss in patients with CD. Furthermore, Bernstein *et al.* (53) found that maintenance treatment with infliximab improved BMD in patients with CD and this effect was independent of corticosteroid administration. The BMD response after infliximab therapy suggests that TNF-alpha

plays a role in the bone loss associated with CD. Miheller *et al.* (54,55) also found that Infliximab therapy in CD patients rapidly influenced bone metabolism by enhancing bone formation and decreasing bone resorption. In addition to its mucosal effect affecting bone homeostasis, this indicates a further rationale for usage of TNF-alpha blockade in the therapy of IBD.

Abreu *et al.* (56) observed 38 prospectively enrolled CD patients who received infliximab infusion for 4 weeks. CDAI and the IBD questionnaire (IBDQ) scores were significantly improved at week 4. Infliximab therapy was associated with an increase in BAP, a marker of bone formation, whereas NTX, a marker of bone resorption, was not increased. Among 22 patients who were taking glucocorticoids, mean glucocorticoid dose decreased 36%. Treatment with infliximab was thus associated with increased markers of bone formation (BAP) without increasing bone resorption (NTX). This effect may be due to a beneficial effect of TNF-alpha blockade on bone turnover, a beneficial effect on CD activity resulting in decreased glucocorticoid dose, or both. Studies of longer duration are needed to assess the effect of infliximab on BMD.

A retrospective study found that patients who were treated concurrently with infliximab and bisphosphonate exhibited a greater increase in BMD compared to those on bisphosphonates alone, although corticosteroids inhibited this effect (57). However, infliximab alone had no effect on BMD. Infliximab therapy was found to improve lumbar bone mass independently of nutritional status (58). This finding suggests that TNF-alpha plays a role in bone loss, but it may take a long time and more research to evaluate the role of infliximab on BMD (Figure 1).

5.2. Anti-resorptive agents

The observed CD-associated bone loss could be caused by reduced bone formation, possibly as a consequence of decreased osteocyte viability in the patients' past (59). Thus, anti-resorptive agents such as the bisphosphonates, risedronate and alendronate may be effective treatment forOS in CD patients. A previous study found that addition of oral etidronate did not further enhance BMD (36). For pediatric patients with CD, zoledronic acid has been demonstrated to result in a significant increase in lumbar spine BMD at 6 and 12 months following a well-tolerated infusion (60). Recently, a randomized controlled trial also found that a single dose of intravenous zoledronate can prevent glucocorticoid therapy-induced bone loss in patients with acute flares of CD (61). In addition, a 3.5 year study found that sodium-fluoride and intravenous ibandronate can improveOS in CD patients (62).

5.3. Altered function of PBMC

The function of PBMCs is related toOS in CD patients. Trebble *et al.* (63) found that raised CRP and erythrocyte sedimentation rate (ESR) in CD patients may indicate higher rates of bone loss, and this may be partly explained by altered production of interferon (IFN)-gamma by PBMCs. In that study, the influence of corticosteroids can be ignored, since no patients were receiving corticosteroid therapy. Thus, altering PBMC function may be an option for therapy.

In another study, Trebble *et al.* (64) proposed a strategy for altering PBMC function. They found that the availability of n-3 and n-6 polyunsaturated fatty acids (PUFAs) was altered in adult patients and thatIFN-gamma production by PBMC was lower. In adults with CD, high-dose fish oil (2.7 g EPA+DHA/d) in combination with antioxidants (vitamins A, C and E and Se) increased the EPA and DHA content of PBMC and decreased the production of IFN-gamma by PBMC, but was not associated with effects on bone turnover or nutritional status.

5.4. Granulocyte-macrophage colony-stimulating factor

Bernasconi *et al.* (65) showed that GM-CSF (granulocyte-macrophage colony-stimulating factor)-dependent stimulation of bone marrow-derived cells during dextran sulphate sodium (DSS)-induced colitis accelerated colonic tissue repair. These data provide a putative mechanism for the observed beneficial effects of GM-CSF therapy in CD.

5.5. Nutrition

In addition to medical therapy, nutritional therapy should also be paid attention by therapists. Whitten *et al.* (66) found that exclusive enteral nutritional therapy could normalize serum markers of bone turnover, suggesting an improvement in bone health.

6. Problems and prospection

Abnormal bone metabolism associated with gastrointestinal tract diseases has become a hot topic. The American Gastroenterological Association and the American College of Gastroenterology have instituted guidance for the treatment ofOS related to gastrointestinal tract diseases and IBD successively in 2002 and 2003. For the past several years, the incidence of CD has been increasing rapidly throughout the world, but research related toOS in these patients is lacking. There are many problems such as epidemiology of abnormal bone metabolism and identifying influential factors which deserve further study. Such studies could provide new non-traumatogenic diagnosis for gastrointestinal tract diseases from the viewpoint of bone metabolism, new ideas to illustrate the pathogenesis of CD, and new channels for CD therapy.

7. ACKNOWLEDGMENTS

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Abbreviations: IBD: Inflammatory bowel diseases; CD: Crohn's disease; UC: ulcerative colitis; CDAI: Crohn's disease activity index; BMI: body mass index; VitD: calcium and vitamin D; PTH: parathyroid hormone; 25-OH D_3: 25-hydroxyvitamin D3; BMD: bone mineral density; BAP: bone-specific alkaline phosphatase; PICP: procollagen type I carboxy-terminal propeptide; BSP: bone sialoprotein; HOLG: urine hydroxyproline hydroxylysine glucoside; TRAP: tartrate-resistant acid phosphatase; Pyr: pyridinolines; DPD: deoxypyridinolines; NTx: N-telopeptide; OPG: osteoprotegerin; RANKL: RANK-ligand; PGE2: prostaglandin E2; PBMCs: peripheral blood mononuclear cells; SHBG: sex hormone binding globulin; DXA: osteodensitometry; SFT: Skin-fold thickness; AMM: appendicular muscle mass; TNF-alpha: Tumor necrosis factor alpha; IBDQ: IBD questionnaire; NTX: bone resorption; PUFAs: polyunsaturated fatty acids; GM-CSF: granulocyte-macrophage colony-stimulating factor

Key Words: Inflammatory bowel diseases, Crohn's disease, Ulcerative Colitis**,** Calcium, vitamin D, Review

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