EDITORIAL

Clinical relevance of changes in bone metabolism in inflammatory bowel disease

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INTRODUCTION

Low bone mineral density (BMD) is an established complication in patients with inflammatory bowel disease (IBD). Data regarding IBD-related osteoporosis needs further clarification.

Epidemiological data of bone loss are very conflicting, due to different study methodologies, patient groups, geographical distribution, *etc*[1-3].

Fracture is the most important clinical outcome of low bone mass. However, estimation of fracture risk in IBD is difficult. Numerous risk factors need to be considered, and these factors should be weighed properly to obtain relevant answers to the questions of the clinicians. If possible, fractures should be prevented, but excessive drug use should be avoided. There are also national guidelines available on the screening, diagnosis, treatment and follow-up of bone loss in IBD patients. However, some of these protocols are based on results obtained from idiopathic and postmenopausal osteoporotic patients in the general population.

In this editorial, the authors aim to summarize the available epidemiological data, identify the appropriate patients for screening for low bone mass at diagnosis and during follow-up, and review the available therapy.

EPIDEMIOLOGICAL DATA

The prevalence of low bone mass in IBD shows a wide variation in the published literature for several reasons. Of note, even diagnostic criteria for osteoporosis and low bone mass were different in the early epidemiological studies.

Abstract

Low bone mineral density is an established, frequent, but often neglected complication in patients with inflammatory bowel disease (IBD). Data regarding the diagnosis, therapy and follow-up of low bone mass in IBD has been partially extrapolated from postmenopausal osteoporosis; however, the pathophysiology of bone loss is altered in young patients with IBD. Fracture, a disabling complication, is the most important clinical outcome of low bone mass. Estimation of fracture risk in IBD is difficult. Numerous risk factors have to be considered, and these factors should be weighed properly to help in the identification of the appropriate patients for screening. In this editorial, the authors aim to highlight the most important clinical aspects of the epidemiology, prevention, diagnosis and treatment of IBD-related bone loss.

The gold standard for the measurement of BMD is dual X-ray absorptiometry (DEXA). BMD values are expressed in relation to the young adult mean (T-score) or age-matched controls (Z-score). Low bone mass (or osteopenia) was defined by the World Health Organisation (WHO) in 1994[4] as the value of BMD more than 1 standard deviation below the young adult mean, but less than 2 standard deviations below this value (T-score < -1 and > -2.5). WHO defines osteoporosis as a value of BMD 2.5 standard deviations or more below the young adult mean (T-score < -2.5). Using the Z-score to define osteoporosis in IBD (Z-score of < -2) seems more logical in clinical practice, because most of the patients are diagnosed with IBD before reaching the peak bone mass. However, epidemiological studies performed more recently use the WHO definitions for evaluating the rate of osteoporosis and low bone mass in IBD.

The prevalence and pathogenesis is very different in the 2 main types of IBD [Crohn's disease (CD) and ulcerative colitis (UC)], but unfortunately, most of the early studies show cumulative epidemiological data[1-3,5]. Osteoporosis and low bone mass or a Z-score less than -2.0 has been found in as many as 30.6% of 75 unselected IBD cases[1]. Similarly, the rate of osteoporosis defined by a T-score below -2.5 was 15% in a very similar IBD population[5]. Further uncontrolled studies reported the incidence of osteoporosis in CD as low as 12%[6,7], but the incidence of osteoporosis was estimated to be as high as 18%-42%[8,9] in unselected cohorts.

Other studies showed that altered bone metabolism was more frequent in CD than in UC[10,11] at diagnosis. Jahnsen *et al*[10] reported that mean Z-scores were significantly lower in patients with CD compared to patients with UC or healthy subjects. Low BMD can be a feature of CD at the time of diagnosis[11], while the impact of steroid treatment leading to low BMD seems to be more significant in UC. The main limitation of both the early and recently performed epidemiological studies is the limited number of patients.

In addition, epidemiological data depend also on the site of BMD measurement. BMD was reported to be lower at the hip than at the spine in most studies[8,9,12]. Therefore, in contrast to postmenopausal and corticosteroid-induced osteoporosis, IBD-associated osteoporosis may be at least as common at the hip. Furthermore, osteoporosis has a north-to-south gradient in the normal population. Therefore, the geographical location of the referred population in the IBD-related bone studies should also be considered as a possible confounder, e.g. low bone mass was found to be 58% in a Dutch cohort[7], while it was 32.4% in a Turkish population[13].

Fracture risk in IBD

The clinical consequence of osteoporosis is increased risk of fractures. Osteoporosis is more predictive of bone fracture than is high cholesterol level in predicting myocardial infarction.

Studies performed in the general postmenopausal osteoporotic population indicate that the risk of fracture approximately doubles for each SD reduction in BMD. The increase in fracture risk for a specific change in BMD depends on the technique used, the site measured, and the fracture type. Measurements at the hip predict hip fracture with greater power than do measurements at the lumbar spine or forearm. An increase in this site-specific relative risk (RR) is estimated to be as high as 1.5 to 3.0 for each SD decrease in the general population[14], but age is also an important predictive factor[15]. Hip fractures have long been associated with an increased mortality rate in the general population but excessive mortality has also been shown to accompany non-hip fractures and low bone mass[16].

There are only a few population-based studies regarding the fracture risk in IBD populations. In a Canadian population-based study the incidence of fracture among persons with IBD has been shown to be 40% greater than in the general population[17] [RR: 1.41, 95% confidence interval (CI): 1.27-1.56]. The RR for hip and spine fractures was 1.47 (95% CI: 1.03-2.10) and 1.54 (95% CI: 1.04-2.3), respectively in CD and 1.69 (95% CI: 1.26-2.28) and 1.9 (95% CI: 1.36-2.65), respectively in UC. In another North American study from Olmsted County, the RR for an osteoporotic fracture was as high as 1.4 (95% CI: 0.7-2.7) in CD patients compared to matched controls[18]. The risk of spine fracture was shown to be even higher (RR: 2.2, 95% CI: 0.9-5.5).

A Danish population-based study[19] evaluated the fracture risk in IBD patients compared to age- and gender-matched controls. The RR of fractures requiring hospitalization was 1.19 (95% CI: 1.06-1.33) in CD patients, and 1.08 (95% CI: 0.97-1.20) in patients with UC. The risk of spine fracture was higher compared to the risk of hip fracture (1.87 *vs* 1.1). The main limitation of this study was that fractures which did not lead to hospitalization (e.g. of the radius) were not taken into account.

All the above-mentioned studies show that IBD patients are exposed to an increased risk of fracture over matched control populations, and the greatest increased risk is found in elderly patients with IBD. A smaller Danish study[20] found that female gender, postmenopausal status, a family history of fracture and current smoking have an impact on fracture risk with RR of 2.5, 1.87, 2.4 and 1.3, respectively. The hazard ratio (HR) increased by 1.3-fold (95% CI: 1.1-1.5) in the Olmsted County study per decade.

Vertebral fractures are frequently asymptomatic; occur spontaneously or after minimal trauma, for example coughing, bending or lifting. Their incidence may be underestimated in all populations. In the general population it is estimated that only one-third of spine fractures are diagnosed. Similarly, approximately 14% of all spine fractures in CD patients were asymptomatic in a European/Israeli study[21]. The fracture rate was very similar in patients with low bone mass compared to patients with normal BMD. The fracture rate correlated with age in females but not in males.

A minority, 4 out of 63 (6.3%) vertebral fractures caused clinical symptoms in a group of 156 CD patients with reduced BMD[22] and, in contrast to the above-mentioned European/Israeli study, lumbar BMD was significantly reduced in patients with fractures compared with those without any fractures, but BMD at the femoral neck did not show any correlation with fracture risk. Approximately one third of patients with fractures were younger than 30 years in this cohort, showing that this complication may affect young patients and deserves further clinical attention.

Another important risk factor is the medical therapy used, especially corticosteroids. There is evidence that even a low dose, e.g. 2-7.5 mg prednisolone daily results in increased fracture risk[23] in any indications. A prominent role of corticosteroid therapy regarding the risk of fractures was proved in a British study. The General Practice Research Database identified all the registered IBD patients ($n = 16\,550$) and created an age and gender matched group for evaluating the RR of fracture. The adjusted HR for hip fracture was 1.68 (95% CI: 1.01-2.78) and 1.41 (95% CI: 1.36-3.18) in CD and UC, respectively. Multivariate analysis identified both current and cumulative use of corticosteroids and the use of opioid analgesics as risk factors. This association was reported by Bernstein *et al*[24] in CD patients.

However, in a recent study of 224 CD patients, 36% had normal BMD, whereas osteopenia and osteoporosis occurred in 51% and 13%, respectively[25]. The same study demonstrated that vertebral fractures in CD patients occurred with an equal frequency in patients with low or normal BMD, regardless of corticosteroid use. Of note, the prevalence of osteoporosis in the general population is estimated to be as high as 15%. Finally, a change in the bone mass in IBD patients during short-term follow-up was shown to be low[26,27].

SCREENING

Screening for low bone mass at diagnosis is not recommended in all IBD patients. However, altered bone mineral metabolism can be observed at the diagnosis of IBD in a considerable proportion of patients, and fractures seem to correlate with BMD in the general population. Current guidelines of The American Gastroenterological Association[28] and the British Society of Gastroenterology[29] suggest determination of the risk of low bone mass and fracture individually to identify patients at risk before performing screening.

Advanced age was described to be one of the most important risk factors for IBD-associated osteoporosis, however some studies showed lower BMD at an earlier age[30,31]. Schoon *et al*[7] observed a greater risk of reduced BMD in patients with CD aged less than 18 years at diagnosis in comparison to those diagnosed at over 18 years, in their Z-score-based evaluation. Of note however, peak bone mass is achieved usually at the third decade of life.

Osteoporosis is more frequently in males with CD and UC as well. The incidence of male hypogonadism was observed to be as high as 6% (3 of 48 CD patients) in an early study[32] by measurement of serum testosterone and gonadotrophin hormone concentrations.

The duration of disease may have a valuable impact on bone metabolism in IBD for several reasons, including disease severity and drug therapy. It has been shown that cumulative steroid dose is associated with low BMD[6,26,30,33]. Corticosteroids are more often given to patients with frequent relapse of the disease, but an increased level of inflammatory cytokines seems to be an independent risk factor for accelerated bone loss[34,35]. Overall, duration, severity of disease, and corticosteroid use are difficult to separate as independent factors associated with reduced BMD.

The UK Consensus Group recommended DEXA in all patients taking 7.5 mg or more of prednisolone daily for 6 mo or more and suggested medical therapy with bisphosphonates if the T-score was < -1.5[36]. Steroid requirement is often unpredictable and bone loss associated with steroids may occur early, thus DEXA screening is recommended in all patients aged < 65 years when steroids are prescribed[29].

Of note, treatment with budesonide was associated with significantly higher BMD compared with prednisolone, in patients with active ileocecal CD[37].

Disease site (small bowel, ileum, colon) had no effect on BMD[6,11,38], and furthermore, the existence of low bone mass was observed in CD with fistulizing behavior[39].

Studies investigating the vitamin D status in patients with IBD reported conflicting results. The physiological concentration of 25(OH)-vitamin D was observed in some studies[11,40,41], while others reported reduced levels[42,43].

In summary, the guidelines suggest identifying at risk patient groups in whom DEXA screening is recommended. Screening densitometry should be performed in all IBD patients who are postmenopausal, male patients older than 50 years, in patients who receive corticosteroid therapy for more than 3 mo and in patients with a history of low trauma fracture or symptoms of hypogonadism[28]. Kornbluth *et al*[44] concluded that implementation of the guidelines led to the detection of low bone mass in a majority of patients who met the guidelines' criteria for DEXA screening.

PREVENTION AND TREATMENT

General and disease-specific risk factors may play a role in IBD-related low bone mass. Some can be modified[45], while others, such as age, genetics[46], and previous bowel resection[38] cannot be altered. Data indicate that CD-associated osteopenia can be correlated with the basic pathology of the disease itself rather than malabsorption or complications of steroid treatment[47]. Elevated local tumor necrosis factor-α (TNF-α) and other systemic inflammatory cytokine concentrations seem to be a common pathological pathway between CD- and IBD-associated osteoporosis[39,48].

Lifestyle changes can modify the BMD in IBD. Smoking cessation[49,50] and avoiding the consumption of excessive amounts of alcohol[51] are beneficial. Benefits of regular, low-impact exercise on bone mass have been proven in a randomized controlled trial[52].

Treatment should be offered if there is a reduced BMD, and other risk factors for fracture are present. However, specific treatment is licensed only for postmenopausal osteoporosis in most countries.

Adequate calcium intake has been suggested to be an important determinant of bone mass[53,54], however there was no correlation between the intake of calcium and BMD in CD patients[55,56].

Efficacy of vitamin D in the prevention of bone loss in IBD was investigated by Vogelsang *et al*[57]. There was no significant change in bone density in patients receiving 1000 IU/d vitamin D for 1 year, but significant bone loss was observed in the control group. Bernstein *et al*[58] analyzed the efficacy of this strategy in patients treated with glucocorticoids. Twenty-four patients were randomized to receive vitamin D and calcium (125 IU and 500 mg, respectively) or no treatment. There were no significant differences in BMD of the femoral neck and the vertebrae at 1 year. Calcium and vitamin D intake was not a predictor of bone status in premenopausal women; however their intake was less than the recommended dose[55]. In our study, calcium and active vitamin D supplementation was beneficial in changing markers of bone turnover (collagen crosslinks and osteocalcin) short-term in patients with active CD[59].

The active form of vitamin D is the hydroxylated 1,25(OH)$_2$-vitamin D. There are only limited data available regarding the presumable advantage of 1,25(OH)$_2$-vitamin D in CD-related osteoporosis. The efficacy of different forms of vitamin D was examined in a small cohort of CD patients in a Hungarian study[59]. The authors could show that 1,25(OH)$_2$-vitamin D had a prominent short-term beneficial effect on bone metabolism compared to 25(OH)-vitamin D.

In summary, editors of the guidelines recommend adequate calcium (1000-1500 mg/d) and vitamin D (400-800 IU/d) supplementation for IBD patients[28,29]. Efficacy of the substitution should be monitored by measuring serum calcium, 25(OH)-vitamin D and parathyroid hormone concentrations, even in CD with extensive small bowel involvement. In addition, the more frequent occurrence of kidney stones should be considered in IBD.

Earlier studies indicated that hormone replacement therapy in postmenopausal women with IBD may be favorable. Clements *et al*[60] showed a beneficial effect of hormone replacement therapy in 47 postmenopausal women with IBD, however 20 who received corticosteroids showed a smaller increase in BMD at the spine. Estrogen as monotherapy or in combination with progestin can be applied, but risk factors of myocardial infarction and stroke should be considered, as well as regular screening for breast cancer.

Bisphosphonates are the most potent anti-resorptive agents and are widely used for the treatment of osteoporosis and prevention of fractures in the general postmenopausal women population. They are also effective in the prevention of steroid-induced osteoporosis. Alendronate, risedronate and ibandronate are all proved to be effective in the therapy of IBD-associated osteoporosis[61-63]. The Royal College of Physicians guidelines[64] recommend that treatment with a bisphosphonate should be considered for all aged over 65 years on commencing steroids (or those under 65 who have already had a an osteoporotic fracture).

Administration of a TNF-α inhibitor was associated with improved BMD in CD. Long-term maintenance therapy improved BMD[65,66], and infliximab improved the bone metabolism in CD with inflammatory[35] and fistulizing behavior CD[39]. These data prove that TNF-α plays a fundamental role regarding CD-related bone loss. In the case of corticosteroid dependency, any corticosteroid-sparing agents (azathioprine, 6-mercaptopurine and methotrexate) may be of value, but a direct beneficial effect has only been proven with anti-TNF-α agents. However, bone loss itself is not an indication for anti-TNF therapy in IBD.

There is a lack of data regarding the therapeutic efficacy of calcitonin, strontium ranelate and recombinant parathyroid hormone administration in IBD patients, but there is no theoretical reason why these treatments would not be as effective as in postmenopausal women.

FOLLOW-UP

DEXA is not only the gold standard for the diagnosis of low bone mass, but it also seems to be the most appropriate method for follow-up. The most important limitation of this modality is that assessing small changes is difficult. The minimum relevant change is 3%-5% at the spine, and 4%-6% at the hip. In addition, the quality of the bone is also important and is not adequately measured by DEXA.

IBD patients who receive optimal calcium and vitamin D supplementation should undergo repeated DEXA measurements every 2 years. In the case of further bone loss despite appropriate supportive therapy, the initiation of antiresorptive therapy should be considered.

Corticosteroid-induced bone loss continues at a slower rate after the first year of therapy[67], therefore DEXA is suggested in each subsequent year of corticosteroid use or until the intervention threshold (e.g. T-score < -1.5) has been reached[29].

Serum osteocalcin, bone specific alkaline phosphatase and carboxyterminal polypeptide of type 1 collagen are used as markers of bone formation, whereas collagen degradation products such as urinary deoxypyridinoline, the carboxypeptidase of type 1 collagen and N-telopeptide cross-linked type 1 collagen are indicators of bone resorption.

Data regarding the usefulness and cost-effectiveness of these markers of bone metabolism in the diagnostic workup and the follow-up are controversial[68,69] because

of the heterogeneity in patients cohorts, methods and markers used in the different trials. Osteocalcin levels have been reported to be reduced by some authors[12,40], but normal concentrations were observed by others[9,70]. Type 1 collagen degradation products were shown to be increased[9,12] or normal[71] or elevated[70] as well. These conflicting data suggest that behavior of the disease, clinical status, medical therapy and some possible other factors may affect the bone turnover in IBD patients. It is possible that bone turnover is increased and resorption is predominant in patients with active disease, whereas low bone turnover is more prevalent in patients with quiescent disease.

None of the above-mentioned studies suggests the use of these serum or urinary markers in the diagnostic or follow-up workup in everyday practice.

The gastroenterologist should keep in mind that patients receiving any of the above-mentioned therapies should undergo appropriate screening examinations. Patients on calcium and vitamin D should be screened for kidney stones and nephrocalcinosis, but the interval of the screening is not well defined. All women receiving hormone replacement therapy should be followed up regularly for gynecological malignancies, and the risk-benefit ratio should also be considered and discussed.

CONCLUSION

Bone turnover is altered in patients with IBD. Many important risk factors (e.g. age, disease severity, medical therapy) have been identified, but a significant proportion of data regarding the diagnosis, therapy and follow-up of low bone mass in IBD have been extrapolated from post-menopausal osteoporosis. General and disease specific risk factors should be considered, particularly in patients with CD, and patients at risk of fractures should be identified and selected for diagnostic procedures. Lifestyle changes and adequate calcium and vitamin D supplementation should be introduced, and cessation of smoking is mandatory. Bisphosphonates should be considered in patients with existing osteoporosis, advanced age and long-term corticosteroid therapy. The vigilance of the physician, appropriate screening and follow-up, supportive therapy and specific control of the bone loss are all important for the optimal treatment of this complication in patients with IBD.

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