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Manipulating bone disease in inflammatory bowel disease patients

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Abstract

Diagnostic and therapeutic recommendations of the actual guidelines regarding inflammatory bowel disease (IBD)-associated bone loss are based on the experiences from the general osteoporotic population. Moreover, the fracture, as an end point of the bone loss has a different relationship to the bone mineral density in these patients compared to the general population. In this review we aimed to review the literature of the novel therapeutic possibilities regarding IBD-related bone loss. Dual-energy X-ray absorptiometry measurement should be performed in the presence of a risk factor such as age above 50, postmenopausal state, low trauma bone fracture in the history, corticosteroid therapy for more than 3 months or signs of hypogonadism. Serum Vitamin D and calcium levels should be measured in all patients. Supplementation is definitely needed in case of low serum calcium or Vitamin D concentrations and in patients under corticosteroid induction therapy. Short-term use of bisphosphonates in case of steroid induction was proved to be efficacious in preventing bone loss, but recent approvals do not include these indications. As fluorides and hormone replacement therapy have considerable side effects, their use in the young generation is also not acceptable.

Keywords Bone loss, inflammatory bowel disease, vitamin D, bisphosphonates, fluoride, hormone replacement therapy

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Introduction

Epidemiology and diagnostic debates

Inflammatory bowel disease (IBD) classically covers Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic systemic inflammatory diseases, affecting mainly the gut, but complicating extraintestinal manifestations (EIMs) are found in about 40% of the patients depending on the different populations studied [1-3]. The most widely known EIMs are skin lesions (pyoderma gangrenosum and erythema nodosum), articular manifestations (axial and peripheral arthropathies) and consequent liver diseases (primary sclerosing cholangitis and primary biliary cirrhosis), but there can be bronchopulmonary, cardiac and other systemic complications also.

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Despite the fact that gastroenterologists pay much more attention to scenic EIMs, the most frequent systemic complication of IBD seems to be bone loss. The incidence ratio of osteoporosis and osteopenia in IBD patients is 5-40% and 16-77%, respectively [4,5]. However, several facts should be taken into consideration while interpreting these data.

Some difficulties need to be pointed out regarding the calculation of the exact incidence and prevalence of IBD-associated bone diseases. WHO defined osteopenia and osteoporosis with the T-score, which is the multiple of the measured standard deviation of peak bone mass at the age of 30 [6] compared to healthy controls with a dual-x-ray absorptiometry (DEXA) method. Osteoporosis and osteopenia is defined by a T-score below -2.5, and between -1 and -2.5, respectively. As IBD has a peak incidence in young adults and 15% of the patients are in their childhood, most of the subjects have not reached their peak bone mass at the time of the diagnosis. Due to these anomalies, the rate of bone loss was described with a sex- and age-matched multiple of the standard deviation of the peak bone mass compared to healthy controls (Z-score) in early clinical studies [7-9] and recent studies included younger populations [10,11].

As recent guidelines do not advise to perform a DEXA scan for every IBD patient, the estimated incidence ratio may differ from the real one. Bone densitometry at the diagnosis of IBD is offered for patients having general and disease specific risk factors, like postmenopausal state, age more than 50 years,

corticosteroid therapy received for more than 3 months, or having symptoms of hypogonadism or a documented previous low trauma fracture in current guidelines of the American Gastroenterological Association (AGA) [12] and the British Society of Gastroenterology (BSG) [13].

DEXA measurement should be performed in all patients who are intended to be treated. As different DEXA devices use different type of x-ray beams, control DEXAs should be done with the same DEXA settings, moreover on the same instrument in ideal circumstances. Normal values should be validated on the local population, and validation process on anthropometric spine phantom should be performed one time at a week, at least, to eliminate the technical differences between measures.

As bone fracture is the final manifestation of bone loss, its risk should be estimated prior to the start of a specific therapy in a young IBD patient. The ratio of IBD-related hip fractures was reported to be up to 40-60% higher compared to matched controls in different populations [14,15]. An increase in the site-specific relative risk was estimated to be as high as 1.5 to 3.0 for one SD decrease in the general population [16].

The risk for hip and spine fractures was 1.47 (95%CI 1.03-2.1) and 1.54 (95%CI 1.04-2.3) in CD and 1.69 (95%CI 1.26-2.28) and 1.9 (95%CI 1.36-2.65) in UC, respectively [15]. The risk of vertebral fracture was double (RR 2.2, 95%CI 0.9-5.5) in another North American study [17], while the number of fracture related hospitalisations was observed to be higher in IBD patients compared to the general population (RR 1.19, 95%CI 1.06-1.33 for CD; and RR 1.08, 95%CI: 0.97-1.2 in UC) in a Danish cohort [18]. The risk of spine fracture was higher compared to risk of hip fracture in this latter study (1.87 vs. 1.1, respectively).

To complicate judging the significance of bone loss in the diagnostic workup further, one should keep in mind that a direct relationship between bone loss and fracture is not so obvious in IBD patients compared to the general population. The relationship between the risk of fracture and bone loss is comparable to the relationship between atherosclerosis and high cholesterol concentration in the general population, while risk of fracture was observed to be independent from bone mineral density (BMD) in some recent trials [19,20].

In this review we try to summarize the available literature on the therapy of IBD-related bone loss, while taking into consideration the aforementioned conflicting data on the epidemiological and diagnostic debates.

Eliminating the predisposing factors considering the pathogenesis of IBD-associated bone loss

There are some factors which might predispose IBD patients for bone loss. Genetic influence, cytokine mediated pathogenesis of IBD, low body mass index, hypogonadism, malabsorption, extensive intestinal surgery and corticosteroid therapy are the most important ones.

Some of them, like gender, age, and previous bowel resection [21] are not impressive. Proved metabolic bone disease at diagnosis of IBD [22] is suspicious for factors like genetics, which are also unimpressive factors. There are some experimental data highlighting the common pathogenic pathways of IBD and the related bone loss [23,24]. Increased cytokine load of the bones might potentiate bone resorption [25-27]. Efficacious anti-inflammatory treatment of the basic disease may decrease the amount of this pathogenic factor, however this is not a bone-specific therapeutic approach.

Different studies showed that systemic corticosteroid therapy is not the main cause of IBD-related bone loss [9,19]. Despite this observation, use of corticosteroids does influence the bone metabolism and increases fracture risk in IBD patients [28]. Taking the other well-known side-effects of steroid therapy into consideration, the elimination is essential for the prevention of bone loss. Moreover, budesonide can cause bone loss as well [29]. Patients on long-term budesonide therapy are regarded to be steroid dependent [30], and this condition needs further therapeutic consideration - in any case.

There are conflicting results in the literature on smoking as a risk factor for bone loss in IBD patients [26,31]. Due to its unfavorable effects on IBD itself, its cessation is mandatory, and might also lead to an improved bone metabolism in IBD patients.

Low body mass index (BMI) is a common consequence of osteopenia in the general population and in IBD also. Bernstein *et al* [32] observed that changes in body mass correlate with changes in BMD. Muscle mass was observed to be associated with regional and whole-body BMD in IBD patients in another study [33]. Based on these findings, it essential to optimize the nutritional status and preserve or augment muscle mass in IBD patients for the prevention of bone loss and fractures.

Benefits of regular, low-impact exercise on bone mass have been proven in the early randomized controlled trial of Robinson *et al* [34], as well. Moreover, low intensity exercise is beneficial from a general health perspective in patients with inactive or mild CD [35].

Therapeutic options

Calcium and Vitamin D

Calcium (Ca) and Vitamin D are essential for healthy bone metabolism. Vitamin D exists mainly in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is produced mainly in the skin from 7-dehydrocholesterol due to exposure to sunlight, but a small amount is obtained from the food, while vitamin D2 originates from plant sources. Vitamin D3 is transported to the liver, and hydrolyzed by the Vitamin D 25- hydroxylase enzyme. It is a substrate of another enzyme (1α-hydroxylase) located in the proximal tubule of the kidney, and Vitamin D3 is metabolized as $1,25\alpha(OH)_2$ Vitamin D3. Commercially, Vitamin D2 and Vitamin D3

are referred to as Vitamin D collectively, but the biologically active form is the $1,25(OH)_2$ Vitamin D3.

As Vitamin D3 can be produced endogenously, as long as the subject has access to adequate sunlight regularly, some authors state that it is not necessary to put this vitamin in the diet [36]. At the same time, extensive UV radiation exposure could have a role in the formation of skin cancer and melanoma, even in azathioprine treated IBD patients. Optimizing the balance between sun exposure and dietary vitamin D needs are discussed [37]. It is concluded that taking into consideration the relatively high recommended serum Vitamin D level and its proven beneficial effects on skeletal health and other suspected beneficial effects regarding diabetes [38], reduction in mortality from cancers [39] and prevention of autoimmune diseases [40], it is favorable to increase the daily dietary intake of Vitamin D.

Low serum Vitamin D concentration was documented in IBD patients in different [41-46] studies. Causes of Vitamin D hypovitaminosis in IBD are low dietary intake and bowel resection. The absorption was related to the extent of resected small-bowel segment in one study [47]. Intestinal absorption of 25-hydroxycholecalciferol was proved to be greater compared to absorption of cholecalciferol.

Despite the well-described malabsorption of Vitamin D in IBD, the increase of its supplementation seems to be doubtful. Vogelsang *et al* [48] could not observe any significant change in the bone density of patients receiving 1000 IU/d vitamin D for 1 year, however, significant bone loss was observed in the control group. Berstein *et al* [49] tested the benefits of Ca and Vitamin D supplementation (1000mg plus 250 IU) in 17 corticosteroid-dependent IBD patients and compared its efficacy to placebo. Supplementation therapy conferred no significant benefit to bone density at 1 year in those patients. Vitamin D (1000 IU) and Ca (1000 mg/day) supplementation combined with sodium fluoride (75 mg/day) was observed to be efficacious in improving bone density at the lumbar spine [50], but use of sodium fluoride is not recommended anymore in low bone mass due to the high prevalence of adverse events. In our previous study, Ca and active vitamin D supplementation had beneficial effects by changing short-term bone turnover markers in CD patients [51]. Leslie *et al* [52] observed that correlation between serum vitamin D levels and BMD at the lumbar spine and hip, and gain in total body BMD between baseline and approximately 2 years later was positively correlated to serum levels of vitamin D. The authors concluded that early optimization of vitamin D may play an important role in preventing IBD-related bone disease.

All the therapeutic recommendations regarding vitamin D supplementation originate from our experiences in the general population. Vitamin D and Ca supplementation reduces bone loss and incidence of non-vertebral fracture by 50% in men and women older than 65 years old [53].

Cranney *et al* [54] performed a meta-analysis regarding the efficacy and safety of vitamin D treatment related to bone loss. They concluded that further high quality studies are needed to answer this question even in the average population. This study observed some connection between 25(OH) Vitamin D concentrations and beneficial bone health outcomes, but an optimal threshold for serum Vitamin D concentration was not defined. Moreover, as Vitamin D and Ca were supplemented in parallel in most of the studies, their effect is not separable. A small beneficial effect was observed with Vitamin D intake in a dose as high as 700 IU/day with Ca supplementation.

A Cochrane Collaboration meta-analysis did not observe beneficial effects of Vitamin D with regards to fracture incidence (RR 1.01, 95%CI 0.93-1.09) in patients with involutional and postmenopausal osteoporosis [55]. Vitamin D and Ca reduced the risk of hip fracture incidence (RR 0.84, 95%CI 0.73-0.96), but did not affect non-vertebral fracture incidence (RR 0.95, 95%CI 0.9-1.0).

Finally, the guideline of the AGA [12], and the BSG [13] recommends to maintain normal Vitamin D serum levels, but there is no strict therapeutic guide in any of them.

The recent ECCO guideline offers Vitamin D and Ca supplementation to all patients receiving corticosteroid therapy for more than 12 weeks [56].

Beyond the bones, Vitamin D seems to have some other beneficial effects apart from preserving bone density. It has immunregulatory effects, and its clinical benefits have been widely studied recently and discussed elsewhere [57,58]. Taking into considerations these additional effects, normal serum Vitamin D concentrations seems to be a desireable aim to achieve in every IBD patient.

Bisphosphonates

Bisphosphonates are potent antiresorptive agents in postmenopausal osteoporosis and also have a fracture preventive effect in the general population.

The efficacy of this drug type has also been proved in different subsets of IBD patients. In the previous era when long-term corticosteroid therapy was still an acceptable option for patients with IBD, its efficacy was studied widely in this patient population. In early studies pamidronate and Ca therapy produced a 20% increment in lumbar spine bone density over a year [59].

Soo *et al* [60] compared the efficacy of Vitamin D (400 IU/day) and Ca (500 mg/day) supplementation and risedronate (35 mg/week) versus Ca and Vitamin D alone in a randomized controlled trial recently. Eighty eight CD patients were included in this study with BMD T-score < -1.0 calculated from the result of the DEXA measurement. DEXA control was performed 12 and 24 months later. Triple therapy was proved to be superior compared to Vitamin D and Ca supplementation alone regarding femoral trochanter and total hip bone mineral density at month 12, moreover, this trend was more pronounced at month 24. Efficacy of risedronate was observed to be more significant in non-smokers, those who had been on corticosteroid therapy in the previous year and current users of immunosuppressants.

A double-blind placebo controlled trial was designed to evaluate the efficacy of risedronate on bone mass in IBD in 2006 [61]. Patients with CD (n=31) and UC (n=30) with

low bone mass were recruited to this 12 month long study. Patients received 600 mg Ca with 5 mg of risedronate or placebo. Compared to the placebo group risedronate resulted in a 2.0% (95%CI 0.02-3.97) and 1.9% (95%CI 0.21-3.62) improvement in bone density at the spine and hip, respectively. Risedronate therapy was regarded as an effective therapy to improve bone mass in these patients. There was no difference between the placebo and risedronate treated group regarding the adverse events.

Efficacy of intravenous ibandronate was investigated in IBD-related bone loss also. Klaus *et al* [62] randomized 66 CD patients to receive Vitamin D (1000 IU/day) and Ca-citrate (800 mg/day) and intermittent sustained release sodium fluoride (50 mg) or intravenous ibandronate (1 mg/3 months). DEXA measurements were performed at the start of the study and 2.25 and 3.5 years later. Lumbar T-score increased in both therapeutic groups. The authors concluded that as bisphosphonates are the standard for care in osteoporosis, and this agent decreases fracture risk, data we do not have for sodium-fluoride; CD patients with osteoporosis can be treated safely with intravenous ibandronate. However, the same authors published another paper in the same year [63] showing that additional sodium fluoride or ibandronate had no benefit over Ca and cholecalciferol alone in managing reduced BMD in CD. 148 CD patients were randomized to receive Vitamin D (1000 IU/day) and Ca citrate (800 mg/day) alone or additional intravenous ibandronate (1 mg/3 months). Control DEXA was performed 1.0, 2.25 and 3.5 years later. During this period of time no treatment regimen was superior in any group or between-group analyses. None of the therapeutic regimens caused any remarkable side effects.

The same German group conducted a study with use of zoledronate in patients starting corticosteroid therapy [64]. Patients received 60 mg prednisolone per day as an induction therapy due to relapse of their disease and were randomized to receive 4 mg intravenous zoledronate or placebo. The BMD change under placebo and zoledronate (-0.26 ± 0.21 vs. +0.41 ± 0.19) differed significantly, meaning that zoledronate is effective in preventing glucocorticoid therapy-induced bone loss in patients with acute flare of CD. The authors offer to start this bisphosphonate therapy at the time of the steroid induction, but there is no suggestion regarding the offered duration. Further comparison should be performed regarding the actually recommended Vitamin D and Ca supplementation regime versus zoledronate to clarify this issue.

The benefit of aledronate therapy was also investigated in steroid dependant CD patients in a small Japanese study [65]. The mean cumulative steroid dose was 968 mg/year among the included 16 patients. Aledronate improved the BMD with 2.8% in the one year observational period. Thirty-two patients were randomized to receive 10 mg aledronate daily or placebo for 12 months in a Danish study [66]. Most of the patients had osteopenia, and the minority of them had osteoporosis. Mean BMD of the lumbar spine showed an increase of 4.6±1.2% in the alendronate group compared with a decrease of 0.9±1.0% in patients receiving placebo (P<0.01). BMD of the hip increased by 3.3±1.5% in the alendronate group compared with a smaller increase of 0.7±1.1% in the placebo group (P=0.08). Guidelines of the AGA and BSG could not take these novel results into consideration, and also experience with bisphosphonates was limited at the time of their introduction. However, actual ECCO guideline regarding IBD-related special situations offer bisphosphonate therapy for IBD patients with fractures [67].

Hormone replacement therapy (HRT)

Hypogonadism was showed to be as high as 6-37% in male IBD patients [68,69], which is significantly higher compared to the average population. As male hypogonadism and female postmenopausal state have major roles in the pathogenesis of bone loss, HRT is a reliable therapeutic approach both to prevent and treat osteopenia.

Malnutrition and chronic illness can cause menstrual dysfunction in women. Corticosteroid use has an impact on the normal gonadal function and showed to be associated with low testosterone production. However, Robinson *et al* [69] observed a correlation between total testosterone and osteocalcin (r=0.53, 95%CI 0.29-0.71, P=0.0001), independent of steroid use.

Only one trial was designed to evaluate the efficacy of HRT regarding bone loss in IBD patients. Clements *et al* [70] conducted a two-year prospective study with postmenopausal women suffering from CD or UC. The mean annual change in radial bone density was +1.42%/year (+0.58 to +2.26; P<0.005) and for spinal bone +2.60%/year (+1.06 to +4.15; P<0.005) with single photon absorptiometry. As all patients were postmenopausal women, this early study just proves the safety of HRT.

Due to the results of the Women's Health Initiative showing that risks from the HRT (more cardiovascular, thrombotic and breast cancer events) outweigh the benefits (decrease risk of colorectal cancer and hip fractures) the overall gain of this therapeutic approach is questionable. Moreover, use of HRT was showed to be hazardous in postmenopausal women for *de novo* IBD formation. Khalili *et al* [71] conducted a prospective cohort study in 108,844 postmenopausal women without a prior history of IBD. Compared with women who never used hormones, the multivariate-adjusted HR for UC was 1.71 (95%CI 1.07-2.74) among women who currently used hormones and 1.65 (95%CI 1.03-2.66) among past users, however the risk of CD was not increased. The risk of UC increased with longer duration of hormone use and decreased with time since discontinuation. The effect was independent of the type of the hormones (estrogen alone or combined with progestin).

Contrary to the results of the above mentioned Nurses' Health study, a beneficial effect of HRT to the activity of IBD was published in 2008 from the Mayo Clinic [72]. Data of sixty-five postmenopausal women receiving HRT were analyzed in this retrospective study. There was a significant protective effect on disease activity with postmenopausal HRT use (HR 0.18, 95%CI 0.04-0.72) and a dose-response effect was also noted in hormone replacement with longer duration of use.

However, risks of different types of HRT should be considered regarding prevention of bone loss. The use of estrogen therapy without progesterone (progestin) may be associated with an increased risk of endometrial cancer. Combined therapies (specifically oral conjugated equine estrogen plus medroxyprogesterne acetate) can increase the risk of stroke, invasive breast cancer, dementia, gallbladder disease, deep vein thrombosis and pulmonary embolism [73].

There is a lack of data in the literature regarding the influence of testosterone replacement in male IBD patients. Lower dehydroepiandrosterone sulfate (DHEAS) levels were present in 23 of 45 male IBD patients in a Hungarian cohort [74]. DHEAS and BMD were correlated at the lumbar spine and the femoral neck. No independent effect of testosterone deficiency was observed on bone parameters.

Based on the results of Klaus *et al,* [75] the rate of estrogen deficiency was 10 fold higher compared to testosterone deficiency (27% vs. 2.7%) in 111 male CD patients. Use of corticosteroids for 3 of 12 months was associated with lower estrogen levels ($P<0.05$). Authors concluded that estrogen deficiency might have a role in the pathogenesis of bone loss in male IBD patients, analogous to postmenopausal female subjects.

There is no current guideline regarding the hormone replacement in IBD patients, however the proper hormone substitution is essential in boys with IBD and delayed growth and puberty, and testosterone substitution is associated with an advance in pubertal status and an improvement in growth [76]. This strategy can also potentiate normal bone formation.

There is no data regarding effects of selective estrogen receptor modulators in IBD patients.

Other therapeutic modalities (fluoride, parathormone, calcitonine, osteoprotegerin)

In contrast to other agents used to treat bone loss, sodium fluoride ameliorates bone formation instead of decreasing bone resorption. Its efficacy was compared to Ca and Vitamin D therapy [50], and to parameters of bone density. Sodium fluoride was not protective against vertebral fractures and increased the number of non-vertebral fractures in postmenopausal women [77], so its use is not recommended [78].

Low parathormone levels were described in IBD patients in different studies [79-81]. Similarly to sodium fluoride, parathormone is a bone anabolic therapeutic agent. Parathyroid treatment was compared to HRT in corticosteroid-induced bone loss by Lane *et al* in a one-year long randomized controlled trial conducted in postmenopausal women [82]. Parathyroid therapy enhanced the BMD by 9.8% by DEXA within one year. The benefit of HRT was negligible in this setting. Although parathyroid therapy is an accepted part of the armamentarium against bone loss in the general osteoporotic population, there is no clinical data regarding its efficacy in IBD-related bone loss.

Calcitonin inhibits the functions of the bone resorting osteoclasts. Its efficacy was evaluated for preventing corticosteroid induced bone loss in patients with polymyalgia rheumatica [83] and asthma [59]. It was approved to treat, but not to prevent osteoporosis until March of 2013, when the FDA advised calcitonin not to be used in osteoporosis, except Paget's disease and for acute bone loss due to sudden immobilization; and also for excess Ca in the blood caused by cancer.

Osteoprotegerin is a member of the tumor necrosis factor α superfamily. It is produced by the osteoblasts, and plays a role in the regulation of osteoclast functions. Its concentration is secondarily elevated in IBD [24]. Its therapeutic applicability is widely studied in recent years, but there is no data regarding osteoprotegerin treatment in IBD.

Monitoring the efficacy of the therapy

Treatment for osteoporosis is prescribed for a minimum of 5 years in the general population.

After initiating a therapy for proven osteoporosis or because of the existence of a higher risk for fracture, changes of bone density should be controlled with DEXA measurement one year later. DEXA should be performed every one or two years as further follow up.

There are some biochemical parameters which can be measured before and few months after the initiation of the therapy. Osteocalcin is the most widely used marker for bone formation, and C-terminal crosslinking telopeptide of the type 1 collagen is the most important marker of bone resorption. However these markers are costly, not widely achievable and require justification of the key outcome of fracture reduction. Use of this kind of laboratory marker is not recommended in daily practice. Detailed information on the use of these markers is discussed elsewhere [84].

Controlling the serum and urine Ca concentrations is more important in IBD patients. As this population of patients has an increased tendency for formation of kidney stones and nephrocalcinosis, it is important to keep the serum and urinary Ca concentration within a normal range. Serum and urinary Ca levels should be measured every 3-6 months.

Conclusions

IBD is frequently complicated with bone loss. Inflammatory processes, malnutrition, Vitamin D deficiency and drugs can play a role in the enhanced bone loss, and general risk factors like age, postmenopausal state, body mass index have to be taken into consideration, as well.

The actual guidelines regarding IBD-associated bone loss are nearly 10 years old. New results with the old drugshave been published, and some new therapeutic modalities have been marketed in the last decade. However, most of them are approved exclusively to treat postmenopausal bone loss. We aimed to review the recent literature on the novel therapeutic possibilities regarding IBD-related bone loss.

First, we have to perceive that diagnostic recommendations are not clear regarding IBD-associated bone loss. As most patients are under the age of peak bone mass at diagnosis, it is reasonable to use the age- and gender-matched Z-score for the diagnosis, instead of the WHO-advised T-score. Most of the authors still use the T-score, because all of the recommendations are based on the WHO definitions.

Moreover, the fracture, as an endpoint of the bone loss has a different relationship to the BMD in IBD compared to the general osteoporotic population. Bone fractures occur without clinical signs more frequently in IBD compared to other populations, and fractures occur in patients with normal BMD more frequently. We need a much more accurate risk assessment system to predict fractures for proper therapy in this young population with a life-long chronic inflammatory disease.

What we can do without causing any harm is to prevent bone loss. Steroid sparing, Ca and Vitamin D supplementation, appropriate sun exposure and mild exercise could be advised to the patients. However, there is no evidence regarding the obvious benefits of these modalities.

As Ca and Vitamin D increase the serum Ca level, the higher tendency for formation of kidney stones and nephrocalcinosis should be taken into consideration. The doses of the optimal supplementation are not clear, moreover there is some discussion regarding the normal serum level of Vitamin D, and the method of Vitamin D measurement also. Supplementation which keeps the Vitamin D and Ca levels in the normal range, without marked elevation of urinary Ca excretion seems to be an acceptable strategy. Recent guidelines recommend administering Ca and Vitamin D parallel to corticosteroid induction therapy.

As the duration of bisphosphonate therapy is not fully elucidated even in postmenopausal women, its use in a young patient with IBD-associated osteoporosis is questionable. Short-term use of bisphosphonates in case of steroid induction was proved to be efficacious in preventing bone loss, but recent approvals do not include these indications. Although bisphosphonates are potent antiresorptive agents, their use in young males and females is not permitted in many countries of the world.

As fluorides and HRT have considerable side effects, such as-increasing the risk of hip fracture and cancer formation, their use in the young generation is also not acceptable. Moreover there is no clear evidence that supports their use in IBD-associated bone loss.

All in all to date we can give very little clear advice regarding the diagnosis and therapy of IBD-associated bone loss. DEXA measurement should be performed in the presence of a risk factor such as older age (above 50) or postmenopausal state, low trauma bone fracture in their history, corticosteroid therapy for more than 3 months or signs of hypogonadism. Serum Vitamin D and Ca levels should be measured in all IBD patients, regular urine Ca excretion also should be taken into consideration in patients who take Ca or Vitamin D. Other laboratory parameters do not have a place in the diagnosis or follow up of antiporotic therapy.

In our own clinical practice we perform DEXA scanning for almost all patients at the time of diagnosis or at least at the first visit to our institution least. Guidelines offer to perform DEXA in patients at risk for bone loss, however as our institution is a referral center for IBD, most of the referred patients have unfavorable disease course and multiple corticosteroid therapies in their history. At the same time, we check their Ca and Vitamin D levels. Based on these results and the clinical factors showing whether the patient has a risk for rapid bone loss we consider our therapeutic options. Due to local regulations, gastroenterologists are entitled to prescribe Ca and Vitamin D supplementation, but we have to refer our patients to an endocrinologist who indicates further therapies against bone loss.

Supplementation is definitely needed in case of low serum Ca or Vitamin D concentrations with an advised initial dose of 800 IU Vitamin D an 500 mg Ca daily.

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