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TOPIC HIGHLIGHT

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Managing osteoporosis in ulcerative colitis: Something new?

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Abstract

The authors revise the latest evidence in the literature regarding managing of osteoporosis in ulcerative colitis (UC), paying particular attention to the latest tendency of the research concerning the management of bone damage in the patient affected by UC. It is wise to assess vitamin D status in ulcerative colitis patients to recognize who is predisposed to low levels of vitamin D, whose deficiency has to be treated with oral or parenteral vitamin D supplementation. An adequate dietary calcium intake or supplementation and physical activity, if possible, should be guaranteed. Osteoporotic risk factors, such as smoking and excessive alcohol intake, must be avoided. Steroid has to be prescribed at the lowest possible dosage and for the shortest possible time. Moreover, conditions favoring falling have to been minimized, like carpets, low illumination, sedatives assumption, vitamin D deficiency. It is advisable to assess the fracture risk in all UC patient by the fracture assessment risk tool (FRAX® tool), that calculates the ten years risk of fracture for the population aged from 40 to 90 years in many countries of the world. A high risk value could indicate the necessity of treatment, whereas a low risk value suggests a follow-up only. An intermediate risk supports the decision to prescribe bone mineral density (BMD) assessment and a subsequent patient revaluation for treatment. Dual energy X-ray absorptiometry bone densitometry can be used not only for BMD measurement, but also to collect data about bone quality by the means of trabecular bone score and hip structural analysis assessment. These two indices could represent a method of interesting perspectives in evaluating bone status in patients affected by diseases like UC, which may present an impairment of bone quality as well as of bone quantity. In literature there is no strong evidence for instituting pharmacological therapy of bone impairment in UC patients for clinical indications other than those that are also applied to the patients with osteoporosis. Therefore, a reasonable advice is to consider pharmacological treatment for osteoporosis in those UC patients who already present fragility fractures, which bring a high risk of subsequent fractures. Therapy has also to be considered in patients with a high risk of fracture even if it did not yet happen, and particularly when they had long periods of corticosteroid therapy or cumulative high dosages. In patients without fragility fractures or steroid treatment, a medical decision about treatment could be guided by the FRAX tool to determine the intervention threshold. Among drugs for osteoporosis treatment, the bisphosphonates are the most studied ones, with the best and longest evidence of efficacy and safety. Despite this, several questions are still open, such as the duration of treatment, the necessity to discontinue it, the indication of therapy in young patients, particularly in those without previous fractures. Further, it has to be mentioned that a long-term bisphosphonates use in primary osteoporosis has been associated with an increased incidence of dramatic side-effects, even if uncommon, like osteonecrosis of the jaw and atypical sub-trochanteric and

diaphyseal femoral fractures. UC is a long-lasting disease and the majority of patients is relatively young. In this scenario primary prevention of fragility fracture is the best cost-effective strategy. Vitamin D supplementation, adequate calcium intake, suitable physical activity (when possible), removing of risk factors for osteoporosis like smoking, and avoiding falling are the best medical acts.

Key words: Ulcerative colitis; Osteoporosis; Fragility fracture; Bone mineral density; Trabecular bone score; Hip structural analysis; Fracture assessment risk tool; Dual energy X-ray absorptiometry

Core tip: Diagnosis and treatment of osteoporosis in ulcerative colitis are discussed according to the latest evidence. Innovative applications of new programs derived from bone densitometry to evaluate bone quality and to predict fracture risk in patients affected by ulcerative colitis are described. Charts for ten years fracture risk may be utilized to refer patients to bone densitometry and/or to prescribe drugs against osteoporosis. Trabecular bone score and hip structural analysis may be considered to assess bone quality, that could be impaired by malabsorption and chronic inflammatory status. Advices for prevention and treatment of bone damage are given, also considering cost-effectiveness.

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INTRODUCTION

Osteoporosis is a well known extraintestinal manifestation of the inflammatory bowel diseases (IBD), more common in Crohn's disease (CD) than in ulcerative colitis (UC). Nowadays its management has been recognized as a relevant aspect in patients' follow up. As IBD is a chronic condition lasting the whole life of the patient, the effects of the disease and of its treatment, together with the ageing of the population, determine an increase in the prevalence and in the incidence of osteoporosis. The present article revises the latest evidences (2009-2014) in the literature regarding this theme, paying particular attention to the latest tendency of the research concerning the management of bone damage in the patient affected by UC. The authors have consulted PubMed, Embase, Cochrane Library, National Institute for Health and clinical excellence. In addition, the official positions of the gastroenterological societies and the leading guidelines for the management of osteoporosis have been examined.

ULCERATIVE COLITIS

UC is a chronic inflammatory disease of colon and rectum. The disease reaches from the anal verge to a variable proximal extension of the colon. The main peak incidence is between the second and the fourth decade, but the disease may also start later. Both men and women are affected with a similar frequency.

Aetiology is unknown. Regarding pathogenesis, the inflammation is probably caused by a pathologic immune response to an unknown environmental stimulus in the lumen of the colon in genetic susceptible people. A defective colonic epithelium may allow commensal bacteria to be sampled by dendritic cells of the mucosa and act as antigenic stimulus to induce an immune response, sustained by T-cells, leading to inflammation[1].

Symptoms are rectal blood and mucus, tenesmus, urgency and diarrhoea, depending on the extent and the severity of the disease. Usually UC is classified in mild, moderate and severe, depending on the clinical manifestations according to the Montreal criteria[2] (Table 1).

About one third of patients presents immune mediated inflammatory extra intestinal manifestations, which may affect liver and biliary system, joints and bone, skin, eyes.

The usual course of UC presents periods of acute inflammation and phases of remission of symptoms. In rare cases there is only one flare of disease, which can be very severe ("fulminant" colitis). The recurrences are variable in extent and severity and unpredictable in timing. Aim of the therapy is to induce the remission and to maintain it as long as possible.

Systemic and/or topical therapy is focused against pathologic immune response. Mainsteps of the pharmacological treatment are 5-aminosalicylic acid, glucocorticoids, azathioprine and its derivative 6-mercaptopurine, cyclosporine and biological agents such as infliximab and adalimumab.

Bone implication of UC is represented by osteoporosis, even if it is less frequent than in CD.

OSTEOPOROSIS

Osteoporosis is defined as a systemic disease characterized by low bone mass and micro-architectural deterioration of the bone tissue, with a consequent increase in bone fragility[3]. The compromised bone strength leads to an increased risk of fracture, as bone strength reflects the integration of bone mineral density (BMD) and bone quality[4]. The disease typically occurs in postmenopausal women and in the elderly people (primary osteoporosis) or in patients with diseases affecting bone mineral metabolism, like IBD (secondary osteoporosis). Also glucocorticoid treatment is a well-known factor leading to osteoporosis.

Common sites of osteoporotic fractures are the spine, the hip, the distal forearm and the proximal homerus. Osteoporotic fractures also occur at many other sites in-

Table 1 Montreal classification of extent and severity of ulcerative colitis

Extent	Anatomy	Severity	Definition
E1: Ulcerative proctitis	Limited to the rectum	S0: Clinical remission	Asymptomatic
E2: Left sided (distal) ulcerative colitis	Limited to a proportion of the colorectum distal to the splenic flexure	S1: Mild	⩽ 4 stools/d (with or without blood), absence of systemic illness, and normal inflammatory markers
E3: Extensive (pancolitis) ulcerative colitis	Extends proximally to the splenic flexure	S2: Moderate	> 4 stools/d but minimal signs of systemic toxicity
		S3: Severe	⩾ 6 bloody stools/day, pulse ⩾ 90 beats/min, temperature ⩾ 37.5 ℃, haemoglobin < 1.05 g/L, and erythrocyte sedimentation rate ⩾ 30 mm in the first hour

Adapted from: Ford *et al*[1].

Table 2 Effect on vertebral fracture rates (from randomized controlled trials)

	Osteopenia	Osteoporosis	Established
Raloxifene	•	■	■
Alendronate	NA	■	■
Risedronate	NA	•	■
Ibandronate	NA	■	■
Zoledronate	NA	■	■
Teriparatide	NA	NA	■
Strontium ranelate	•	■	■
Denosumab	NA	■	■

■ Denotes a preplanned analysis in the entire study population; •Denotes a post hoc analysis. NA: No evidence available. Adapted from: Body *et al*[12].

cluding pelvis, ribs and distal femur and tibia.

Osteoporotic fractures are associated with high rates of disability and mortality. Approximately 50% of fracture-related deaths in women are due to hip fractures, 28% to clinical vertebral fractures and 22% to other fractures[3]. In individuals who experience hip fractures, 20% die within the next year and 20% will require permanent nursing home care[4-6]. Vertebral fragility fractures are the most frequent fractures in osteoporotic patients, and even if this kind of injuries has less severe complications than hip fractures, they are associated with substantial disability due to impairment in spine dynamics and static biomechanics. Furthermore, the number and the severity of vertebral fractures are related to an exponential increase of subsequent fractures[7,8].

The gold standard method for the diagnosis of osteoporosis is the dual energy X-ray absorptiometry (DXA) which is a radiological tool based on the principle of photon absorptiometry developed in the sixties[9] that allows to quantify the BMD[10].

Bone densitometry scans for diagnostic classification and prediction of fracture risk are performed according to the international guidelines[11] on lumbar spine and proximal femur, which are the most important sites of fragility fractures. Absolute values of BMD are expressed as T-score and Z-score. T-score is calculated as standard deviation from the normal reference population, and Z-score is calculated as standard deviation from the sex and age matched population. Osteopenia is defined as a T-score between -1 and -2.5. Osteoporosis is defined as a T-score < -2.5[10]. Low BMD is directly correlated with an increase in fracture risk[3].

The goal of the pharmacological therapy of osteopenia and osteoporosis is to increase bone strength, in order to decrease the risk of fracture[3] mainly by increasing BMD. This can be achieved by decreasing bone resorption and/or increasing bone formation.

A lot of effective medications are approved for the prevention and the treatment of osteoporosis. Drugs can be divided into two categories: anti-resorptive (or anti-catabolic) and anabolic agents. Anti-resorptive agents, which include oestrogens, selective oestrogen receptor modulators (raloxifene), calcitonin, bisphosphonates (alendronate, risedronate, ibandronate, zoledronate) and denosumab, reduce osteoclast activity, preserving bone mineral density. The currently used anabolic agent is teriparatide (PTH 1-34) which stimulates osteoblast activity. Strontium ranelate is another agent that reduces fracture risk. It improves bone strength mainly through effects on bone formation and bone properties[3], even if it also has an anti-resorptive action.

The anti-fracture efficacy of the most frequent used drugs for osteoporosis is illustrated in Tables 2 and 3.

The effectiveness of drugs in primary and secondary prevention of fragility fracture is quite different. Regarding vertebral fractures, all the considered drugs are effective in preventing secondary osteoporotic fractures, whereas not all these drugs are also effective in primary prevention. No effectiveness is found in reduction of vertebral fracture rate in osteopenic patients. There are very few evidences regarding the prevention of hip and non-vertebral fractures: only few drugs seem to be useful, and among them only some of the bisphosphonates and denosumab[3,12].

In addition, to enhance the effectiveness of the pharmacological treatment, calcium and vitamin D supplements may be prescribed. In fact, vitamin D deficient patients do not show the same increase in bone mass and reduction in fracture rate as observed in vitamin D repleted patients[13].

Moreover, in order to improve bone mass, some changes in lifestyle are suggested, such as increasing physical activity, stop smoking, avoiding excessive alcoholic intake, maintaining an adequate body weight. Furthermore, in order to reduce fracture risk also the prevention of falling is important; so it is advisable to avoid inappropriate housing conditions (*e.g.*, carpets, low illumination), and the use

Table 3 Effect on nonvertebral/hip fracture rates (from randomized controlled trials)

	Nonvertebral		Hip	
	Osteoporosis (without prevalent vertebral fractures)	Established osteoporosis (with prevalent vertebral fractures)	Osteoporosis (without prevalent vertebral fractures)	Established osteoporosis (with prevalent vertebral fractures)
Raloxifene	NA	●	NA	NA
Alendronate	■	■	NA	■
Risedronate	NA	■	NA	■
Ibandronate	NA	●	NA	NA
Zoledronate	■	NA	■	NA
Teriparatide	NA	■	NA	NA
Strontium Ranelate	●	■	●	▲
Denosumab	■	NA	■	NA

■ Denotes a preplanned analysis in the entire study population; ▲ Denotes a preplanned analysis on a subset of the study population; ● Denotes a post hoc analysis. NA: No evidence available. Adapted from: Body *et al*[12].

of hypnotic and sedative drugs[12].

Patients should also be aware of the importance of the adherence to the treatment. In fact, it has been observed that only a low percentage (about 30%) of patients still follows therapy after one year[14].

ULCERATIVE COLITIS AND OSTEOPOROSIS

In literature it has been estimated that osteopenia in UC is found in about 35% of the patients, and osteoporosis in about 15%, based on DXA scans[15]. However, studies about the prevalence of osteopenic/osteoporotic fractures in patients with UC are scarce, with a small sample size and with a follow up that is not sufficiently prolonged to allow fracture detection[16]. Another bias is that investigated IBD patients' groups are not homogeneous regarding age, gender, severity and activity of disease, and type of treatment (steroids, supplementation of calcium and vitamin D). A recent retrospective ten years database analysis on UC male patients found a prevalence of fragility fractures of 7.9% in osteoporotic patients, 4.4% in osteopenic patients and 1.1% in patients with normal BMD[17]. Low bone mass in UC is also related to the severity of the disease, in so far mild and moderate UC seem not to represent a risk factor for osteoporosis[18]. Obviously, severe UC presents a higher level of inflammation and therefore the need of steroid administration, which are per se risk factors for bone loss and fracture.

Many factors have been suggested to be implicated in the pathogenesis of osteoporosis in UC. They are mainly classified in two groups: nutritional factors and inflammatory mechanisms.

In UC patients poor nutrition and malabsorption, particularly of calcium, vitamin D and K, can be caused by anorexia, insufficient diet, diarrhoea. On the other hand, IBD associated inflammatory cytokines [interleukin 1 (IL1) and 6 (IL6), tumour necrosis factor alfa (TNF-α)] have been shown to affect bone metabolism directly[19]. These cytokines are known to increase synthesis of receptor-activated nuclear factor K B ligand (RANKL), which is produced by osteoblasts and which activates proliferation and differentiation of osteoclasts, thereby inducing bone resorption[19]. In fact, the biological drugs inhibiting TNF alfa have been shown to increase BMD[19]. Moreover, recent studies in animals have indicated that these cytokines also negatively act on intestinal and renal absorption of minerals and vitamins[20]. Of course, the usual risk factors for osteoporosis may also be present in UC patients, such as low body mass index, older age, immobilization, smoking, prolonged use of corticosteroids, low peak of bone mass particularly in the case of paediatric onset of the disease.

Anyway, the two most important factors for developing OP in UC seem to be systemic inflammatory activity and the prolonged use of glucocorticoid. Corticosteroid treatment in UC patients is related to the inflammatory status, being cumulative doses of steroid directly related both to the severity of UC and the risk of low BMD[17].

Glucocorticoids act negatively on bone mineral metabolism inducing an impairment of bone cells coupling and activity, stimulating osteoclasts formation and activity, promoting osteoblasts apoptosis, inhibiting osteoblasts proliferation and synthesis of type I collagen and osteocalcin. In addition, they reduce intestinal absorption of calcium and increase urinary calcium excretion, leading to an increase in PTH secretion. Moreover, they reduce sex hormones production by inhibiting hypothalamic-pituitary-gonadal axis[21].

It has to be kept in mind that all these actions of glucocorticoid finally lead to a significant increase in bone loss and in vertebral and non-vertebral fracture risk. This effect is already observed in the first three-six months of steroid treatment, and it is already present with daily doses of 5 or more milligrams of prednisone equivalent[22].

SOMETHING NEW IN THE MANAGEMENT OF OSTEOPOROSIS IN ULCERATIVE COLITIS

The most cited scientific gastroenterological societies such as American Gastroenterological Association[23], American College of Gastroenterology[24], British Society of Gastroenterology[25], have dealt in their guidelines with

the management of osteoporosis in IBD patients. They give general recommendations regarding prevention and removing of fracture risk, indication of DXA test and prescription of specific pharmacological treatment of osteoporosis. These suggestions do not substantially differ from guidelines for prevention, diagnosis and treatment of primary and secondary osteoporosis in the general population[26-31].

In recent years, besides DXA test, another tool for assessing fracture risk has been proposed by the Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield (United Kingdom), and introduced in clinical practice.

Prediction of fracture risk

Fracture risk assessment tool (FRAX® tool - http://www.shef.ac.uk/FRAX/[32]) is based on the collection of the main anagraphic, anthropometric and anamnestic data regarding fracture risk factors, with or without BMD. This collection allows to compile a chart, available both for men and women aged 40 years or more, that predicts the 10-year probability of a hip fracture or of a major osteoporotic fracture, such as clinical spine, hip, forearm and humerus fractures. At the moment these charts are prepared for 59 countries worldwide.

Frax score is calculated by online compiling twelve fields of an algorithm: age; gender; height and weight; history of minimal trauma fractures; history of parental hip fractures; corticosteroid exposure (defined as oral glucocorticoids for more than 3 mo at a dose of prednisolone equivalent of 5 mg daily or more); concomitant rheumatoid arthritis; secondary strongly associated causes of osteoporosis, such as type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, malabsorption and chronic liver disease; more than three units of daily alcohol intake; smoking. Lastly, if available, BMD may be inserted, expressed as absolute value (g/cm^2) or T-score.

Entering these variables one can obtain a number, that quantifies the probability of having a major or a hip fracture in the subsequent ten years. This parameter helps the clinician in the decision whether to prescribe or not a pharmacological treatment for osteoporosis, according to a threshold of intervention. This threshold is not uniquely established and has not the same cut-off for all countries, depending on the clinical contest and health economic factors. The fracture risk varies markedly between the different countries, whereas the T-score varies only by a small amount. In addition, the clinical interpretation of a given T-score for fracture risk in women of every country depends on the age and on the presence of clinical risk factors. Intervention thresholds are also partly determined by the willingness to pay for health care in osteoporosis and by the access to DXA, which vary from country to country[29].

The use of FRAX tool in assessing fracture risk in UC patients was examined only in two retrospective studies[15,33]. Results are controversial, but encourage to explore the utility of this clinical tool in the management of IBD. The first[15] shows that the clinical FRAX score alone can accurately predict the risk of a osteoporotic fracture, reducing the need for DXA scans and for unnecessary pharmacological treatment for osteoporosis. As indicated in a position paper of the National Osteoporosis Guideline Group (NOGG)[34], if the patient results at low risk, no DXA scan is required. If the FRAX score, based only on clinical risk factors, is intermediate, patients should undergo DXA scanning and once the BMD is known, the FRAX score has to be recalculated to determine the need for specific anti-osteoporosis treatment.

The Authors of the first cited study[15] confirmed an increased prevalence of osteoporosis in their UC population and found that by using the FRAX score over 5 years they could have avoided 36% of DXA scans. They also found that patients who carry a high clinical risk of fracture are frequently not considered for treatment when this decision is based on T-score alone. Furthermore, considering NOGG guidelines[35], 8% of the patients examined in the study were over-treated with bisphosphonates. As illustrated by the Authors there are, however, some limitations in using FRAX tool in IBD patients. First, the FRAX algorithms are based on general population cohort studies undertaken in over 40 years old people, and have not been validated in IBD populations, where younger, under 40 years old people are frequently represented. In this condition FRAX tool calculates the risk for patients under the age of 40 using the data of individuals aged 40 years or more. It is likely, therefore, that the fracture risk in IBD subjects could be overestimated. It will be useful to collect specific data for patients under 40, particularly in IBD populations, but probably it will take several decades to complete a prospective cohort observation in young patients for the collection of an adequate number of fractures. Second, body mass index, a component of the FRAX score, in the general population does not fluctuate at the same rate as in IBD, where periods of active disease may cause substantial weight loss. Third, although the FRAX score includes corticosteroids use as a dichotomous risk factor (yes/no), it does not take into account the cumulative dose of steroids.

The other cited retrospective study[33] in IBD patients, raising from a population database of the province of Manitoba (Canada), examined the risk of major osteoporotic fractures (MOF) and of hip fractures after controlling for FRAX, independently from FRAX probability. The Authors did not find an increase in the risk of MOF in IBD patients after having controlled the FRAX probability, estimated both with and without BMD. The results for patients with CD and UC considered separately were similar. They found, conversely, an increase in the risk of developing a hip fracture, even after having controlled the FRAX probability, estimated both with and without

BMD. Due to the small number of events (hip fracture) it was not possible to compare UC and CD. The addition of the femoral neck BMD to calculate the risk did not significantly increase the estimated risk for hip fractures associated with IBD, suggesting, therefore, that IBD exerts a BMD independent effect on hip fracture risk. It may be useful that further studies confirm these results, differentiating UC from CD. It would be also desirable that IBD would be added as anamnestic dichotomous factor in FRAX risk calculation.

Assessment of bone structure

DXA represents the gold standard method for the diagnosis of osteoporosis[10]. However, while BMD is clearly one of the major determinants of bone strength[36], the assessment of fracture risk by BMD could lack sensitivity. In fact, many fragility fractures occur in osteopenic individuals (T-score between -2.5 and -1.0), not only in subjects with osteoporosis (T-score < -2.5)[37]. Other factors in addition to BMD account for bone strength and fracture risk, like bone geometry and bone microarchitecture, that concur to determine bone quality[38].

The best method for the direct assessment of bone micro-architecture is histomorphometry of the transiliac crest bone biopsy, but it is an invasive procedure and, moreover, it does not necessarily reflect microstructure at sites where the fragility fractures occur, like spine and femur. A number of techniques have been developed to assess bone geometry, as quantitative computed tomography (QCT)[39,40], high resolution peripheral quantitative computed tomography (HRpQCT)[41] and magnetic resonance imaging[42]. However, these techniques present more invasivity, higher costs, long time for their execution (long lasting scans). Alternatively, adaptation of X-ray based images, like plain radiographs, using gray-level textural features, have been tested, utilizing fractal dimension[43-45] and Fourier analysis[46-48]. An ideal solution, in terms of practicability, costs and risks, could be the adaptation of DXA-based images. DXA can be used to identify existing vertebral fractures[49-52], to evaluate hip geometry and to estimate femoral strength[53-55]. Moreover, a new DXA-based technique that considers bone mineral distribution in the proximal femur, instead of only bone mineral density, may be well-suited to enhance standard densitometric evaluation as a predictor of hip fracture risk[56]. The latest development is the trabecular bone score (TBS), a new gray-level textural measure that can be extracted from the 2-dimensional lumbar spine DXA image to estimate trabecular microstructure. TBS may provide skeletal informations that are not captured by the standard BMD measurement. Based on experimental variograms of the projected DXA image, TBS has the potential to discern differences in 3-dimensional (3D) micro-architecture between 2-D DXA measurements that are similar to each other[57,58]. An elevated TBS value correlates with better skeletal texture (a reflection of better microarchitecture); a low TBS value correlates with weaker skeletal texture (a reflection of degraded microarchitecture). The relationship between TBS texture parameters and 3D micro-architecture parameters has been documented by several ex vivo studies that have reported significant correlations between TBS and various micro-structural parameters of bone assessed by micro-computed tomography[57,59,60].

TBS is an imaging technique adapted directly from the DXA image of the lumbar spine. Thus, it is potentially readily and widely available. In recent years, a large number of studies have demonstrated that TBS is significantly associated with direct measurements of bone microarchitecture, and may be a useful adjunct to BMD for detection and prediction of fragility fractures in primary osteoporosis[58]. Thus, it promises potential utility also in secondary causes of osteoporosis[61]. In some conditions, like glucocorticoid-induced osteoporosis and in diabetes mellitus, the TBS appears to out-perform DXA. It also appears useful in numerous other diseases associated with diminished bone health, such as primary hyperparathyroidism, androgen-deficiency, hormone-receptor positive breast cancer treatment, chronic kidney disease, and autoimmune diseases like rheumatoid arthritis[61]. Further research is required to establish clearly the role of TBS in these and other disorders that adversely affect bone health, like CD and UC.

In adjunction to BMD measurement, TBS can be a useful tool also for monitoring treatment efficacy over time.

Assessment of hip geometry

Hip geometry, like BMD, has been shown to relate independently to hip fracture risk[62]. Loading forces on bone are distributed over the bone material in cross sections. The concentrations of loading forces, defined stresses, are a function of bending moments and cross sectional geometry. Based on the principle described by Martin and Burr[53,63] a specific program for bone densitometry has been developed, named hip structural analysis (HSA), that derives the cross sectional geometry from images acquired from a bone mineral scanner by the means of DXA. The main structural parameters are the surface area of the bone in the cross section (CSA) and the section modulus (Z), which are inversely related to maximum stresses due to axial and bending loads, respectively[64,65]. CSA is an index of bone resistance to axially directed loads. Z is computed from the cross sectional moment of inertia (CSMI) that weights the area in the cross section by the square of its distance from the centroid. CSMI reflects the flexural strength and is an index of structural rigidity. The maximum distance between the center of mass and outer cortex over the average cortical thickness provides a stability index of the cortex under compressive loads, bending included, the so called buckling ratio.

A few works have been published about HSA in primary and secondary osteoporosis[62,64,66-68] and to estimate bone quality variations after pharmacological treatment for osteoporosis[69]. A combination of BMD assessment

and geometric structural measurements may represent an additional and helpful mean in estimating bone strength and fracture risk. After therapy, particularly with new bone formation agents, changes in axial and bending strength and, for some drugs, in cortical thickness, are expected.

No data about these topics are available in UC patients and their investigation could be of considerable interest.

Treatment of osteoporosis in ulcerative colitis

Calcium and vitamin D represent a well-known non-pharmacological treatment for osteoporosis, which is usually employed in conjunction with drugs for primary and secondary fragility fracture prevention. Measurement of serum 25-OH-cholecalciferol is the standard method to assess vitamin D status. A recent point of view of the Institute of Medicine of the United States National Academies[70], considers at least 50 nmol/L (20 ng/mL) the sufficient level for the general healthy population and suggests a daily global intake of vitamin D of about 700-800 IU for the general population. However, this position is not overall accepted and other recommendations suggest higher doses of vitamin D intake for healthy adults[71].

Vitamin D insufficiency is a condition associated with rickets and osteomalacia, reduced muscle strength, reduced appendicular muscle mass, increase in muscle pain, increase in body sway and consequent risk of falls, and reduced response to osteoporosis treatment. For insufficiency [30-50 nmol/L (12-20 ng/mL)] or deficiency [< 30 nmol/L (12 ng/mL)] a greater amount of vitamin D supplementation is required, identified by IOM up to a maximum daily dose of 4.000 IU. In this case, a periodic check of the vitamin D status is necessary (every 1-3 mo), considering the extreme individual variability in the response, due to various clinical conditions such as malabsorption.

In UC vitamin D insufficiency and deficiency are common, ranging from 45% to 60% of patients[72,73]. Therefore, it appears advisable to routinely check 25OH-vitamin D in UC patients in order to identify and treat adequately the vitamin D pathological status. Vitamin D in association with calcium has been used in the treatment of osteoporosis in UC, without significant BMD improvement.

In the last decade vitamin D has gained a new surge of scientific interest for its extra-skeletal effects beyond its action on bone metabolism. The vitamin D receptor (VDR) has been isolated in tissues other than intestinal epithelium, distal renal tubules and osteocytes: adrenals, parathyroids, pituitary gland, mammary gland, ovary, testis, skin, heart, thymus, lymphocytes and promielocytes, hepatocytes, biliary epithelial cells and colon. Also 1alfa-hydroxylase, the vitamin D activating enzyme, is expressed in colonic cells[74,75]. A local production of 1,25(OH)2-vitamin D has been found in skin, lymph nodes, pancreas, brain, adrenal medulla, monocytes and macrophages, and colon[76]. A recent meta-analysis showed that higher blood 25OH vitamin D levels were associated with a reduced risk of colorectal cancer: pooled adjusted OR was 0.94 per 10 nmol/L increase in 25OH-vitamin D concentration[77]. All these experimental data indicate that vitamin D plays a role in the function of the cited tissues and organs. It is notable that in colonic biopsies' specimens of patients with UC both VDR expression and VDR protein are reduced respect to normal. Therefore it is hypothesised that vitamin D supplementation may be useful in UC patients not only for osteoporosis treatment purpose, but also for its extraskeletal actions.

Moreover, in UC patients various other actions of vitamin D might be useful, considering its involvement in inflammation and immune modulation: reduction of inflammatory cytokines[78,79], protective immune modulating properties[80,81], maintenance of integrity of the epithelial barrier of the colon[82].

Few original clinical trials regarding medical treatments for low bone mass in UC have been published in literature since the eighties. A recent systematic review and meta-analysis[83] has listed only nine works concerning anti-osteoporotic drugs in UC patients. However, populations considered in these studies are mainly not homogenous, including both CD and UC, male and female, pre- and post-menopausal women, active and non-active disease, different steroid exposure. Within the analyzed anti-osteoporotic treatments, there are variable concomitant medications, with different dosages of calcium and vitamin D supplementation. Seven of the cited nine studies have used anti-osteoporotic drugs and two non-pharmacological treatments (calcium and vitamin D supplementation). Among the seven using drugs, six utilized anti-resorptive agents (bisphosphonates and calcitonin) and one an agent stimulating bone formation (fluoride). Also the duration of the studies is quite different, ranging from few weeks to few years; this is important because the effect of osteoporosis treatment on bone mass and fracture risk is assessable in a reliable way only on a long period, lasting several years. Moreover, not all these studies are of outstanding quality.

For all these reasons it is difficult to draw firm conclusions, and consequently, definitive recommendations.

To our knowledge in the last five years only three clinical trials dealt with anti-osteoporotic drugs in UC[84-86]. These Authors have utilized bisphosphonates (alendronate, risedronate) and calcitonin. Kitazaki and Kriel used bisphosphonates to prevent glucocorticoid associated osteoporosis in active UC disease. Alendronate improved spine BMD after one year of treatment in a steroid treated UC population very heterogeneous for age (17-70 years, mean age 41 years)[84]. Kriel administered risedronate for a very short period (two months)[85]. Pappa prescribed calcitonin to study its short term efficacy on spine BMD in UC children and adolescents, without seeing significant clinical advance[86].

Amino-bisphosphonates, like alendronate and risedro-

nate, inhibit the enzyme farnesylpyrophosphate-synthase implicated in the biosynthesis of cholesterol. This action significantly reduces the prenylation of GTPase proteins, thus disrupting function of osteoclasts, leading to their apoptosis[87]. Experimental data in cell culture have shown that the described bisphosphonate action occurs also in various cancer cell lines[88]. GTPase proteins have been found to be involved in cancer of colon and rectum[89,90]. Being very poorly absorbed (less than 1%), oral bisphosphonates reach the colon and come in contact with the intestinal epithelium. Thus, they could lead colon cancer cells to apoptosis with the same mechanism[88]. Moreover, there are experimental evidences that bisphosphonates could hinder the growth of colon and rectum cancer inhibiting macrophages[91,92] and stimulating a subset of T-cells[93,94] involved in cancer developing. This potential therapeutic effect could be relevant in UC, where the risk of developing a colorectal cancer is notoriously increased.

FINAL CONSIDERATIONS ABOUT MANAGING OSTEOPOROSIS IN ULCERATIVE COLITIS

Osteoporosis in UC patients is a high prevalent and a high incident pathology, and fracture prevention is a mandatory question. On the other hand, there are scarce evidences about this issue, and therefore it appears not reasonable to give specific, population-based-approach recommendations about primary and secondary prevention of fragility fractures in UC patients. So it may be more advisable to suggest an individual-high-risk-approach, inspired by the consolidated guidelines for the diagnosis and treatment of post-menopausal osteoporosis.

First step

It is wise to assess vitamin D status in UC patients to recognize who is predisposed to low levels of vitamin D. Serum levels of 25OH-vitamin D could be measured in all patients and particularly in those who present well-known risk factors for deficiency: severe disease, elderly patients, reduced sun light exposure. Deficiency has to be treated, preferably with an oral daily cholecalciferol or calcifediol supplementation. Intermittent large doses, orally or parenterally, should be reserved in the case of reduced adherence to therapy. An adequate dietary calcium intake or supplementation and physical activity, if possible, should be guaranteed.

Osteoporotic risk factors such as smoking and excessive alcohol intake must be avoided. Steroid has to be prescribed at the lowest possible dosage and for the shortest possible time. Moreover, conditions favouring falling have to been minimized, like carpets, low illumination, sedatives assumption, vitamin D deficiency.

Secondly

It is advisable to predict the ten years fracture risk in all UC patient by the FRAX® tool, that calculates the risk for many countries of the world for the population aged from 40 to 90 years.

The use of FRAX in clinical practice demands a consideration about the fracture probability at which it is useful to intervene, both for treatment (intervention threshold) and for BMD testing (assessment threshold).

Assessing fracture probability could be useful to help physicians in deciding whether to treat or not for osteoporosis in order to prevent fragility fractures. A high risk value could indicate the necessity of treatment, whereas a low risk value suggests a follow-up only. An intermediate risk supports the decision to prescribe BMD assessment and a subsequent patient revaluation for treatment. The thresholds are variable, since they depend critically on local factors varying from country to country, like fracture incidence, willingness and capability to pay for access to BMD measurement and for health care in osteoporosis. Different scenarios are represented for example by The National Osteoporosis Foundation recommendation for the United States (www.nof.org) and by The National Osteoporosis Guideline Group (NOGG) for the UK (www.shef.ac.uk/NOGG/)[35].

Thirdly

Bone densitometry could be used not only for BMD measurement, but also to collect data about bone quality by the means of TBS and HSA assessment. These two indices could represent a method of interesting perspectives in evaluating bone status in patients affected by diseases like UC, in which there may be an impairment of bone quality as well as of bone quantity. Bone quantity accounts for most, but not for all, of the fragility fractures. No data are published about TBS and HSA in UC population, and this could be an interesting field for research.

Fourthly

In literature there is no strong evidence for instituting a pharmacological therapy in UC patients for clinical indications other than those that are applied to the patients with established osteoporosis.

Therefore, a reasonable advice is to prescribe pharmacological treatment for OP in those UC patients who present fragility fractures, that bring a high risk for subsequent fractures. Therapy has also to be considered in presence of a high risk of fracture, particularly when corticosteroid therapy is prolonged and with high cumulative doses. In patients without fragility fractures or steroid treatment, fracture risk assessment could support the medical decision about treatment, and in this case FRAX could be of relevant help.

Among drugs for osteoporosis the bisphosphonates are the most studied, with the best and longest evidence of efficacy and safety. Despite this, several questions are still open, such as the lasting of treatment, the necessity to discontinue it, the indication of therapy in young patients, particularly in those without previous fracture.

Further, a long-term bisphosphonates use in primary osteoporosis has been associated with an increased incidence of dramatic, even if uncommon, side effects, like osteonecrosis of the jaw and atypical sub-trochanteric and diaphyseal femoral fractures.

UC is a long-lasting disease and the majority of patients are relatively young. In this condition primary prevention of fragility fracture is the best cost-effective strategy. Vitamin D supplementation, adequate calcium intake, suitable physical activity (when possible), removing usual risk factors for osteoporosis (like smoking), and avoiding falling, are the best and the cheapest medical acts.

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