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Mini Review

Review: Epidemiology and Pathophysiology of Osteoporosis in Inflammatory Bowel Disease

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Abstract

Osteoporosis is a common clinical pathology encountered in everyday medicine and while the foremost population that comes to mind is elderly postmenopausal women, it may affect varied age-groups and indeed, has several causative factors. One such interesting association is between gastrointestinal illnesses like IBD and osteoporosis. Osteoporosis is important to diagnose because it increases the likelihood of fractures and in IBD patients, this should be especially noted because they are often on glucocorticoid therapy, which on its own is responsible for an increase in fragility fractures. With age and decrease in estrogen, the loss of bone mineral density increases. As a result, patients are at an increased risk of developing osteoporosis and subsequent fractures. In IBD subjects, paramount aspect is the early onset of osteopenia and osteoporosis. Hence, guiding us towards the understanding that in addition to age, genetics, and lifestyle, there are a number of factors operating at a molecular and nutritional status level that lead to osteoporosis. This review article discusses the epidemiology and pathophysiology of osteoporosis in IBD patients to help garner an in-depth view of the imbalance in the several factors that play a role in the pathogenesis and provide a composite view of this common association.

Keywords: *Inflammatory Bowel Disease (IBD); Crohn's Disease (CD); Ulcerative Colitis (UC); Osteoporosis*

Abbreviations

BMD: Bone Mineral Density; CD: Crohn's Disease; DEXA: Dual-Energy X-Ray Absorptiometry; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; GI: Gastrointestinal; GM-SF: Granulocyte/ Macrophage Colony-Stimulating Factor; IBD: Inflammatory Bowel Disease; IFNγ: Interferon Gamma; IL: Interleukin; NFκB: Nuclear Factor Kappa B; OPG: Osteoprotegerin; PTH: Parathyroid Hormone; RANK: Receptor Activator of Nuclear Factor κ B; RANKL: Receptor Activator of Nuclear Factor κ B Ligand; SERM: Selective Estrogen Receptor Modulator; TNFα: Tumor Necrosis Factor Alpha; UC: Ulcerative Colitis

Introduction

Inflammatory Bowel Disease (IBD), as the name suggests, involves recurrent inflammation of the alimentary tract. IBD is a hypernym that includes Crohn's disease (CD) and Ulcerative colitis (UC). While CD can involve any segment of the gastrointestinal (GI) tract pathognomonic skip lesions, UC involves continuous lesion from rectum to the small intestine. Pancolitis in patients with UC, generally indicates a more severe form of the disease. In addition to clinical features, endoscopy, histopathology and radiology aid in differentiating the two. However, both Crohn's and UC can involve manifestations outside the GI tract as well [1]. An often ignored extraintestinal manifestation of IBD is osteoporosis, which can be detrimental as it increases the risk of fractures in this subset [2].

Osteoporosis has been defined by the WHO based on Dual-Energy X-Ray Absorptiometry (DEXA) scan measurements of bone mineral density (BMD). BMD that is equal or more than 2.5 standard deviations (SD) below the young adult mean value is considered the cut-off for osteoporosis. Meanwhile, a BMD between 1 and 2.5 SD below the young adult mean value qualifies as low bone mass, also known as

osteopenia. If the patient's BMD is more than 2.5 SD below the young adult mean value and one or more fragility fractures are present, they are said to have severe/established osteoporosis [3,4]. Clinically, osteoporosis may be diagnosed in a patient who develops a typical fracture (fracture of the vertebra, hip, rib, Colle's fracture of distal radius), in presence of no or minimal trauma. These are known as fragility fractures [5,6].

Bone mineral content is the mass of mineral per unit length of bone. Value of the BMD, that is mass of mineral per unit volume, represents the size of the bone and its mineralisation. Studies show that variation in BMD can account for 75% of the variation in tensile stress and 80% of the variation in compressive stress. This exemplifies that BMD determines the bone strength [7,8].

Osteoporosis is a significant issue that is usually associated with being elderly, particularly in women of postmenopausal age-group. However, several drugs and pathological conditions can also lead to osteoporosis, even in younger patients. IBD is one of those conditions and it is important to understand that the loss in BMD is multifactorial, with genetics, malnutrition, cytokine interaction, and treatment with glucocorticoids contributing to it [9]. In fact, osteoporosis is commonly seen in GI illnesses that result in malabsorption, like Celiac disease, short bowel syndrome, post-gastrectomy and pancreatic insufficiency [2,10]. In IBD, apart from the malabsorptive state, systemic inflammation and glucocorticoid therapy also contribute to osteoporosis. Thus, GI diseases lead to an increase in the likelihood of fragility fractures and must be considered as a possible causative factor when patients are being evaluated for low BMD [6].

Discussion

Epidemiology

IBD patients often have low BMD, with milder forms of bone loss occurring in up to 70% of the cohort [6,11]. The overall prevalence of low BMD is 15% in the IBD population [9]. However, there are inconsistencies in the data for BMD seen in IBD patients [12]. For osteopenia, the prevalence rates vary from 40-50%, while osteoporosis is seen in 2 - 30% of the IBD patients [13-15]. While the incidence of osteopenia has been found to be 22% in males and 59% in females, for osteoporosis the incidence rates are 5% in men and 41% in women [2]. Studies show that patients with IBD have about a 40 % higher incidence of fractures as compared to the general population [15]. In IBD itself, the risk of fracture in CD patients is 1.3 - 14 times more than in patients with UC [10].

Pathophysiology

Bone remodelling is a constant process through life, involving the osteoblasts and osteoclasts. While osteoclasts are multinucleated cells with monocytic predecessor, osteoblasts are derived from the mesenchymal stem cells. Osteoclasts release acids and enzymes that resorb the bone and osteoblasts have an opposing role of laying down unmineralized bone matrix known as osteoid. At a molecular level, the interplay between a receptor on osteoclast precursor, RANK - the receptor-activator of Nuclear factor kappa B (NFκB) and ligand on the surface of osteoblasts, RANKL - receptor-activator of NFκB ligand, determines the maturation of the osteoclasts into multinucleated cells that carry out the resorptive process. The RANKL can also bind to osteoprotegerin (OPG), a soluble decoy receptor that is derived from osteoblasts. OPG prevents RANKL from interacting with RANK preventing the osteoclast differentiation and hence, inhibiting the reabsorption process. Studies in mice without OPG demonstrated early development of osteoporosis [16]. Thus, RANKL is a key regulator of bone metabolism and inhibition of RANKL by OPG can prevent bone resorption as well as cartilage destruction. Monoclonal antibody known as Denosumab works similarly to OPG. Denosumab blocks the interaction of RANKL with RANK on osteoclasts and therefore, finds use in treatment of osteoporosis. As it prevents cartilage destruction, Denosumab is also utilized in treatment of patients with osteoporosis and Rheumatoid Arthritis (RA) as well as can be explored as a treatment option in RA patients that cannot tolerate DMARDs [17-19].

In addition, RANKL also plays a regulatory role in interaction of T-cells and dendritic cells in the immune system. This contributes significantly to initial lymphocyte development and lymph node formation [20]. In fact, studies indicate that RANKL deficient mice devel-

oped osteopetrosis, owing to the excess bone deposition without adequate resorption, and lacked lymph nodes [21,22]. It has also been found that activated T-cells express surface and soluble forms of RANKL, which is functionally active and can lead to osteoclast differentiation. Activated T-cell derived RANKL plays a critical role in development of osteoclasts, with monocytes and/or T-cell derived cytokines (IL-1, IL-3, IL-6, IL-7, IL-17, TNF-α, IFN-γ and GM-CSF) playing a lesser significant role in the process by inducing RANKL expression in stromal cells. These cytokines are released as a result of the ongoing systemic inflammatory process in the bowel mucosa [22-29]. Besides stimulating the osteoclast development, T-cell derived RANKL also contributes to the stimulation of dendritic cells and monocytic lineage cells that express RANK. This leads to an increase in bone resorption by stimulation of osteoclast development through RANK-RANKL pathway [24,25,30].

These interactions point towards the intricate relation between the immune system and the bone metabolism.

Another contributing factor of osteoporosis in IBD is the calcium imbalance attributed to the malabsorption along with subsequent deficiency of vitamin D (1,25-dihydroxyvitamin D3). This is especially prevalent in CD pts who undergo small-bowel resections. Vitamin D is required for absorption of calcium from the gut. Fat malabsorption leads to deficiency of fat soluble vitamins like A, D, E and K. Vitamin D deficiency further leads to increased Parathyroid (PTH) hormone which in turn leads to bone resorption. Hence, secondary hyperparathyroidism may be present in IBD patients, and it is prudent to recognize this and start treatment early. Further, use of corticosteroids in IBD leads to decrease in serum calcium levels by decreasing calcium absorption from intestine, increasing excretion of calcium in urine and inhibiting bone formation. This in turn contributes to the secondary hyperparathyroidism and increase in bone resorption [31,32]. Vitamin D, PTH, glucocorticoids as well as PGE_2 increase RANKL expression and downregulates OPG production, which leads to an increase in RANK-RANKL interaction, thereby leading to osteoclastogenesis and increase in activity of osteoclasts [8,20]. PGE_2 is increased in inflammatory processes due cytokine IL-1 production and in turn promotes osteoclastic bone resorption through above-mentioned action [28]. In contrast, upregulation of OPG by calcium ions, TGF-β (cytokine that inhibits the inflammatory process) and estradiol, inhibits the RANK-RANKL interaction and thus, leads to decrease in osteoclastic activity [8,33]. Studies indicate that loss of estrogen also leads to an increase in production of IL-6 - plays a role in osteoclast development, thus, leading to an increase in bone resorption [9,34].

Understanding the role of these hormones and inflammatory mediators at a genetic and molecular level guides towards supplementing calcium and vitamin D prophylactically in IBD patients and at the same time ensuring that glucocorticoids are not used in high doses [32,35,36]. It also opens door to explore other treatment options for secondary osteoporosis as seen in IBD patients, with Denosumab, Raloxifene (SERM), RANKL inhibitors, and anabolic therapies, especially if bisphosphonates are contraindicated [6,10,11,34].

Conclusion

Osteoporosis being a common entity seen in clinical practice, requires thorough investigations for the secondary causes as well, especially if encountered in the younger population. While many studies indicate the prevalence of low BMD in IBD patients, there are studies that state the contrary as well. Some of them cite bias in the previous studies for including subjects from referral centers, certain longitudinal studies have found the BMD to be normal in IBD patients and others attribute the low BMD to be age-related [37,38]. It is important to carry out further research in order to eliminate these inconsistencies. Moreover, understanding the bone remodelling process and close interplay of the immune system with the bone physiology is important to formulate an appropriate treatment plan. The association of systemic inflammation with bone loss also helps appreciate osteoporosis due to other secondary causes like infection, autoimmune diseases, cancer and graft rejections, which involve activated T-cells and cytokine release as well.

Conflict of Interest Statement by Authors

No conflict of interest.

Compliance with Ethical Standards

Not applicable.

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