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BONE HEALTH IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): AN OVERVIEW OF THE EPIDEMIOLOGY, PATHOGENESIS, AND MANAGEMENT

Introduction

Metabolic bone disease is prevalent in persons with immune-mediated inflammatory diseases, including inflammatory bowel disease (IBD). Within these conditions the most common are osteoporosis and reduced bone mineral density (BMD), often termed osteopenia in adult patients, and refer to a decreased mineralization of the bone matrix. This decreased mineralization weakens the resistance of the bone to external forces, thus increasing the risk of fractures when external compressive or deforming forces are applied.[1] Osteoporosis is asymptomatic in the absence of a fracture, and diagnosis generally occurs through the use of programmatic screening (most commonly dual energy x-ray absorption [DEXA]) or incidentally following the occurrence of a fracture. Osteoporosis is defined as a DEXA-measured BMD at the lumbar spine or proximal femur which falls more than 2.5 standard deviations below the mean value for healthy young adults (known as a T-score). BMD decreases of a lesser degree (a T-score falling between -1 and -2.5) are referred to as osteopenia.[2] Osteoporosis is a major public health concern, owing to the significant morbidity and mortality that is attributed to fractures. While fractures may represent a time-limited hardship among persons in otherwise good health and function, major osteoporosis-related fractures, especially those of the femur and spine, can lead to permanent disability and premature mortality. In Canada, approximately 150 people per 100,000 suffer a hip fracture per year,[3] which confers a 3-fold higher risk of mortality.[4]

There are several reasons why persons with IBD may be at increased risk of osteoporosis, and why IBD-clinicians should be concerned about metabolic

bone disease. Osteoporosis is most common in post-menopausal women and in men over the age of 50 years. Additionally, the prevalence of IBD is rising more quickly among persons over the age of 60 years. Osteoporosis is also more common among persons with low body mass, which can result from the inflammatory pro-catabolic state seen in active IBD, and systemic inflammation itself could lead to an increase in bone turnover. Also, corticosteroid use, which remains common in IBD despite the more widespread use of steroid-sparing therapies, is a significant accelerant of the loss of BMD. Moreover, absorption of the necessary nutrients, vitamins, and minerals necessary to maintain bone health (calcium, magnesium, vitamin D) may be affected by small intestinal involvement in IBD; consequently, persons living with IBD may have insufficient intake of the dietary components which contain the essential elements for bone health. Finally, especially in the elderly, persons living with IBD may experience increases in frailty and reduced mobility, which may increase their risk of injurious falls. As such, it is important that physicians who are tasked with the care of persons living with IBD be cognizant of these bone-related comorbidities.

This review aims to provide an overview of the pathophysiology and epidemiology of bone health disorders in persons with IBD, and to provide guidance to the IBD clinician on prevention and management.

Epidemiology of Osteoporosis and Osteoporosis-Related Fractures in IBD

The prevalence of metabolic bone disorders among individuals living with IBD exhibits considerable variability across studies, with estimates ranging from 4.4% to 77%.[11] This broad range is attributable to differences in study designs, sampling frames (e.g., tertiary centre studies versus population-based studies), and outcome definitions (i.e., osteoporosis or reduced BMD). Notably, the variability in the reported prevalence may be influenced by ascertainment bias, given that BMD screening is not universally conducted among persons at risk; consequently, the prevalence may be overestimated in tertiary care populations and underestimated in regions with limited access to DEXA scans.

In a 2020 systematic review, Karnsund et al. investigated the prevalence of osteoporosis and low BMD in population-based studies.[12] The prevalence of osteoporosis demonstrated considerable heterogeneity, ranging from 4% to 9% in studies involving the overall IBD population, while varying from 2% to 9% in studies focusing on patients with ulcerative colitis (UC), and ranging between 7% and 15% in studies specifically addressing patients with CD. They found that a diagnosis of CD, low BMI, and low body weight were risk factors associated with osteoporosis or low BMD.[12]

A population-based study conducted in Manitoba reported that after adjusting for age, sex, BMI, corticosteroid use, estrogen replacement therapy, and osteoprotective medications, IBD was not associated with an increased risk of osteoporosis at the different measurement sites. The study also observed that IBD had only a marginal effect on lower T-scores. CD was associated with lower T-scores at all of the measurement sites except the lumbar spine and was associated with an increased risk of osteoporosis at all of the measurement sites except the total hip. Within individuals with IBD, advancing age and decreasing BMI consistently emerged as factors associated with lower T-scores and a heightened risk of osteoporosis.[13]

In addition to the increased risk of osteoporosis, an IBD diagnosis has been linked to an increased risk of osteoporotic fractures. In a population-based study from Sweden, Ludvigsson et al. found an association between IBD diagnosis and time to hip fracture (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.36–1.48), which was stronger in individuals diagnosed with CD compared to those diagnosed with UC ($p<0.001$). Interestingly, the association between IBD and hip fracture lacked statistical significance among individuals without a history of corticosteroid treatment (HR 1.11; 95% CI 0.86–1.44), with an excess risk of hip fracture predominantly observed among elderly patients with IBD who were exposed to corticosteroids.[14]

Another population-based study from Manitoba found that IBD diagnosis was not associated with an increased hazard of major osteoporotic fractures even after adjusting for the World Health Organization Fracture Risk Assessment tool (FRAX), which integrates BMD and clinical risk factors to predict the person's 10-year fracture risk.[15]

These findings suggest that while individuals living with IBD face an increased risk of osteoporosis and osteoporosis-related fractures, this heightened risk appears to be influenced by factors such as changes in anthropometric measurements and the use of corticosteroids rather than solely being attributed to IBD itself. Considering that these risk factors may be more prevalent among persons with IBD than in the general population, this may explain the increased risk of fracture among persons with IBD.

Pathogenesis of Reduced BMD in Patients with IBD

Normal Bone Homeostasis:

Bone homeostasis is a complex and dynamic process that involves the coordinated and opposed work of osteoblasts, which are responsible for bone deposition, while osteoclasts participate in bone resorption. The combined activity of these cells leads to bone remodelling.[5] A key regulatory pathway of the relative activity of osteoblasts and osteoclasts is the receptor activator of NF-κB (RANK)-RANK ligand (RANKL)-osteoprotegerin (OPG) system **(Figure 1)**. The RANKL is produced by osteoblasts and bone marrow

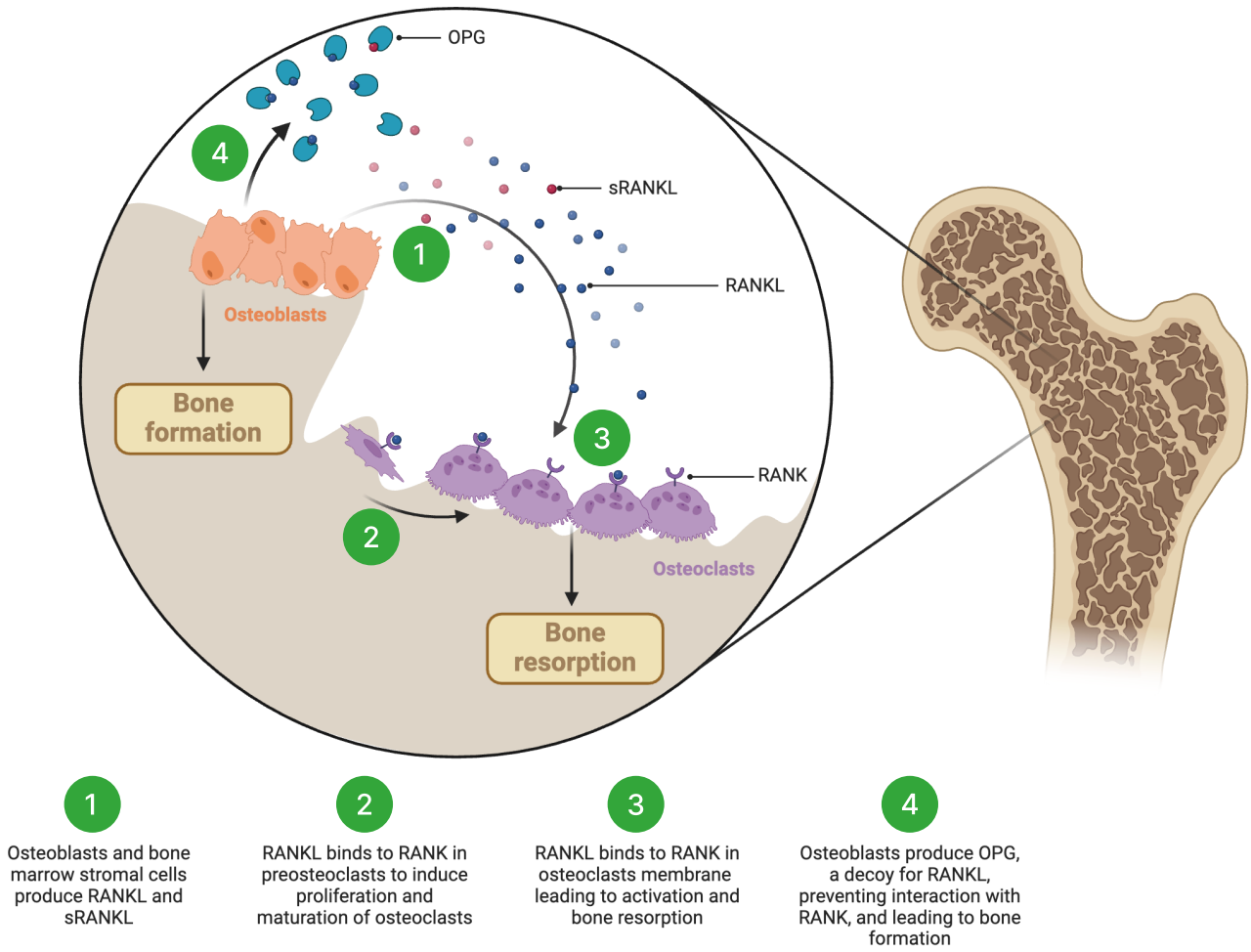


Figure 1: Normal bone homeostasis. RANK: receptor activator of nuclear factor-kB; RANKL: RANK ligand; sRANKL: soluble RANK ligand; OPG: osteoprotegerin. Created in BioRender.com

stromal cells, while the soluble sRANKL is secreted by osteoblasts and activated T-cells. Engaging RANKL with RANK, leads to the activation of osteoclasts and subsequent bone loss. Osteoblasts also produce OPG, which is a decoy receptor for RANKL, and its role is to prevent the interaction between RANK and RANKL. By doing so, OPG inhibits osteoclast differentiation and activation, thus tilting the balance toward bone formation.[6]

Bone Metabolism Derangements in IBD:

In the setting of systemic inflammation, as is observed with IBD, several cytokines are upregulated, such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, and interferon-γ.These pro-inflammatory cytokines increase the secretion of RANKL, leading to accelerated bone resorption. Interestingly, it appears that the inflammatory milieu, rather than individual cytokines, determines the shift to a bone resorption state. An in-vitro study exposed osteoblast models to the following cytokines, IL-6, IL-1β, and TNF-α, individually and in combination, at concentrations observed in patients with active Crohn's disease (CD). They found that none of the individually applied cytokines affected RANKL or OPG expression. However, when applied in combination, these cytokines shifted the RANKL/OPG ratio toward bone resorption. Moreover, when dexamethasone was added, this shift was further increased.[7] Despite these observations, the direct impact of systemic inflammation on the risk of osteoporosis is not definitively established, and the clinical significance of this effect remains to be fully characterized.

Impact of IBD on Nutrition and Body Habitus:

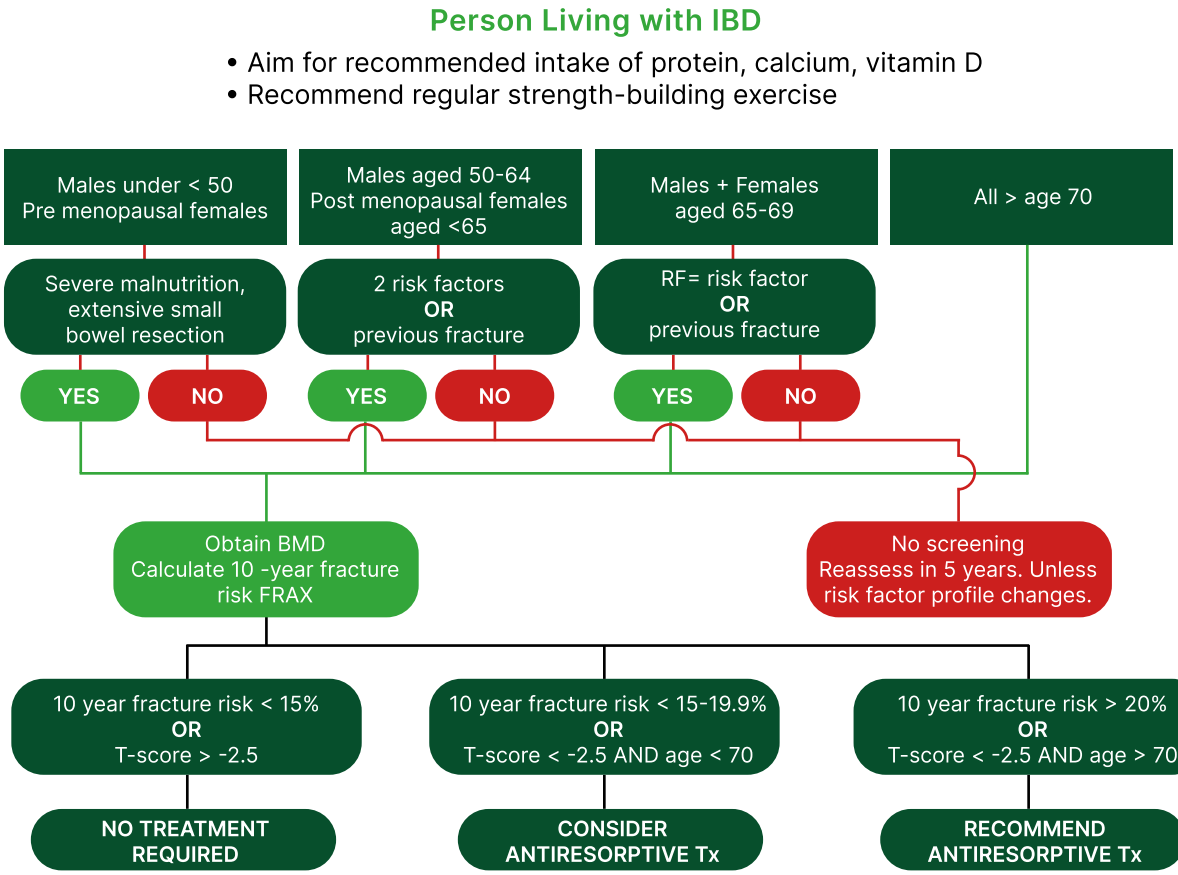
Nutritional factors are also believed to play a role in the development of reduced BMD in individuals with IBD. A decrease in body mass index (BMI) has been associated with a decrease in BMD in patients with IBD.[8] Nonetheless, given that fat mass does not reliably predict bone health, sarcopenia may be more strongly correlated with osteoporosis than BMI. A cross-sectional study of 137 patients with IBD has observed that both low lean mass and sarcopenia were independently associated with reduced BMD, while neither BMI nor fat mass showed such an association.[9] Key components for maintaining bone homeostasis, such as calcium and vitamin D, may be deficient in those with IBD.[10] This deficiency can result from reduced intake due to avoidance behaviours

driven by concerns about triggering symptoms or poor absorption following bowel resections or extensive areas of active disease. Additionally, inadequate exposure to sunlight may contribute to vitamin D deficiency in individuals with IBD.

Prevention and screening for osteoporosis in IBD

Given that the risk of fractures in patients living with IBD is primarily driven by traditional risk factors for osteoporosis, we suggest that prevention and screening for osteoporosis should largely follow the recommendations for screening in the general population **(Figure 2.)** IBD clinicians, however, should be mindful of the increased prevalence of risk factors for osteoporosis in persons with IBD, including the impact of chronic systemic inflammation, a higher prevalence of vitamin D deficiency, low BMI, and a history of corticosteroid use. Consequently, persons with IBD who are younger than the age of 50 and/or pre-menopausal may be at increased risk of osteoporosis and may be candidates for screening. In addition, the risk of fracture at a given BMD may be higher for patients with IBD because of the presence of concomitant risk factors for falls and/or injury following a fall.

The 2023 Osteoporosis Canada Guidelines recommend screening for osteoporosis with BMD testing along with DEXA in all persons aged 70 or over, in persons aged 64–69 with one risk factor, in men over the age of 50, and in post-menopausal women with 2 or more fracture risk factors.[3] These guidelines consider IBD to be a fracture risk factor, although realistically IBD only independently contributes if there is significant ongoing or recent inflammatory activity. In addition, it is recommended that all persons at risk for osteoporosis engage in balance and muscle-strengthening exercises at least twice weekly, obtain the recommended daily allowance of protein (>0.8 mg/kg/day, 1.2 mg/kg/day for active IBD), calcium (500 mg elemental calcium) and vitamin D (400 IU daily, 1000-2000 IU/day if deficient)



Risk Factors (RF) Include

- ACTIVE IBD in last year
- Previous low-trauma fracture before age 40
- CS exposure >3 months in the previous year
- Recurrent falls or known gait issues
- Family history of hip fracture
- Low body mass index or sarcopenia
- Current smoking
- >3 alcoholic drinks/day
- Hypogonadism or premature menopause

Figure 2: Schema for Evaluation of Osteoporosis and Fracture Risk in Persons with IBD; *adapted from Morin SN, et al., 2023*
Abbr.: IBD: inflammatory bowel disease; CS: corticosteroids.

either from dietary or supplemental sources. Calcium and vitamin D supplementation may specifically lower the risk of fracture in persons who have been using corticosteroids at a dose of >10 mg for three months or greater. The FRAX risk stratification tool here is recommended to determine a patient's 10-year estimated risk of fracture, and anti-resorptive therapies are recommended for those with a 10-year fracture risk of 15% or greater. It is recommended that persons with IBD who require anti-resorptive therapy have their bone health managed by an osteoporosis specialist. The FRAX tool has been shown to be predictive of fracture risk in persons with IBD, though it is not widely utilized by IBD specialists. Bisphosphonates are recommended as first-line therapy for persons at increased risk for fracture. A network meta-analysis that assessed the efficacy and safety of therapeutic interventions for low BMD in patients with CD observed that zoledronate ranked highest for increasing spinal BMD, while risedronate was noted for its favourable safety profile.[16] There may be some unique considerations regarding osteoporosis screening and surveillance that apply for persons with IBD. The American College of Gastroenterology provided a conditional recommendation to screen for osteoporosis with BMD testing at the time of IBD diagnosis and periodically thereafter in patients with conventional risk factors for abnormal BMD, though this recommendation is based on a very low level of evidence.[17] Similarly, the European Crohn's and Colitis Organisation recommends screening for osteoporosis in high-risk patients with IBD using DEXA scans, though the term high risk is not well defined. There are no clear recommendations for BMD screening in persons with IBD who are under the age of 50 or who are pre-menopausal, and baseline fracture rates in this population are very low. BMD testing still might be considered in IBD patients who either have had or anticipate having >3 months of continuous corticosteroid use, those with a BMI <20 and those with evidence of malnutrition, extensive small bowel disease, or with extensive small bowel resections.[18] There are no specific guidelines on how often persons with IBD should undergo repeat BMD testing, though the Canadian guidelines suggest those with a 10-year risk of fracture that is under 15% should be re-evaluated at 5 years unless there are incident risk factors for osteoporosis, or a new fracture is diagnosed.[3]

Conclusions

In the chronic and often unpredictable disease course of IBD, several factors might produce imbalances in bone hemostasis, namely repeated bouts of inflammation, cumulative exposure to steroids, and nutritional deficiencies. It is paramount for clinicians to be aware of the risk of metabolic bone disorders, especially given that these conditions are often asymptomatic and may only become apparent with the occurrence of an osteoporotic fracture, which itself can be asymptomatic. In the context of the increasingly complex management of IBD, the assessment of osteoporosis risk and the implementation of preventive and therapeutic measures for bone health and other aspects of health maintenance are sometimes overlooked. However, physicians should aim to incorporate these assessments regularly into the management of IBD to ensure comprehensive care for their patients.

Key Takeaways:

1. Metabolic bone disease is prevalent in persons with immune-mediated inflammatory diseases, including IBD. Within these conditions the most common are osteoporosis and reduced bonemineral density BMD.
2. The prevalence of metabolic bone disorders among persons living with IBD exhibits considerable variability owing to ascertainment bias. As a result, the prevalence may be overestimated in tertiary care populations and underestimated in regions with limited access to DEXA scans.
3. During the disease course of IBD, several factors might produce imbalances in bone hemostasis (e.g. repeated flares-ups of inflammation, cumulative exposure to steroids, and nutritional deficiencies).
4. Prevention and screening for osteoporosis should largely follow the recommendations for screening in the general population. However, clinicians should recognize that persons living with IBD have an increased prevalence of risk factors of metabolic bone disorders and adjust screening and prevention strategy accordingly.

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References:

1. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-2381. doi:10.1007/s00198-014-2794-2
2. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int. 2014;25(5):1439-1443. doi:10.1007/s00198-014-2655-z
3. Morin SN, Feldman S, Funnell L, Giangregorio L, Kim S, McDonald-Blumer H, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. Cmaj. 2023;195(39):E1333-e1348. doi:10.1503/cmaj.221647
4. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. Cmaj. 2009;181(5):265-271. doi:10.1503/cmaj.081720
5. Bravenboer N, Oostlander AE, van Bodegraven AA. Bone loss in patients with inflammatory bowel disease: cause, detection and treatment. Curr Opin Gastroenterol. 2021;37(2):128-134. doi:10.1097/mog.0000000000000710
6. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008;473(2):139-146. doi:10.1016/j.abb.2008.03.018
7. Blaschke M, Koepp R, Cortis J, Komrakova M, Schieker M, Hempel U, et al. IL-6, IL-1β, and TNF-α only in combination influence the osteoporotic phenotype in Crohn's patients via bone formation and bone resorption. Adv Clin Exp Med. 2018;27(1):45-56. doi:10.17219/acem/67561
8. Targownik LE, Leslie WD, Carr R, Clara I, Miller N, Rogala L, et al. Longitudinal change in bone mineral density in a population-based cohort of patients with inflammatory bowel disease. Calcif Tissue Int. 2012;91(5):356-363. doi:10.1007/s00223-012-9650-1
9. Bryant RV, Ooi S, Schultz CG, Goess C, Grafton R, Hughes J, et al. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41(9):895-906. doi:10.1111/apt.13156
10. Iijima H, Shinzaki S, Takehara T. The importance of vitamins D and K for the bone health and immune function in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2012;15(6):635-640. doi:10.1097/MCO.0b013e328357f623
11. Wei H, Zhao Y, Xiang L. Bone health in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2023;17(9):921-935. doi:10.1080/17474124.2023.2248874
12. Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. World J Gastroenterol. 2020;26(35):5362-5374. doi:10.3748/wjg.v26.i35.5362
13. Targownik LE, Bernstein CN, Nugent Z, Leslie WD. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clin Gastroenterol Hepatol. 2013;11(3):278-285. doi:10.1016/j.cgh.2012.10.022
14. Ludvigsson JF, Mahl M, Sachs MC, Björk J, Michaelsson K, Ekbom A, et al. Fracture risk in patients with iInflammatory bowel disease: a nationwide population-based cohort study from 1964 to 2014. Am J Gastroenterol. 2019;114(2):291-304. doi:10.14309/ajg.0000000000000062
15. Targownik LE, Bernstein CN, Nugent Z, Johansson H, Oden A, McCloskey E, et al. Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013;28(5):1007-1013. doi:10.1002/jbmr.1848
16. Zhao X, Zhou C, Chen H, Ma J, Zhu Y, Wang P, et al. Efficacy and safety of medical therapy for low bone mineral density in patients with Crohn disease: A systematic review with network meta-analysis. Medicine (Baltimore). 2017;96(11):e6378. doi:10.1097/md.0000000000006378
17. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol. 2017;112(2):241-258. doi:10.1038/ajg.2016.537
18. Gordon H, Burisch J, Ellul P, Karmiris K, Katsanos K, Allocca M, et al. ECCO Guidelines on extraintestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2024;18(1):1-37. doi:10.1093/ecco-jcc/jjad108