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Crohn's Disease and Osteoporosis: Risk Factors, Diagnosis and Clinical Treatment

Lourdes da Cruz Balta Lourenço[1], Ana Sofia Barroso Frattini Ramos[2], Larissa Lorraine Meiado bochini[1], Luana Lopes Andrade[1], Mariana Santos Guimarães[1], Luanna Barbosa Fiúza[1], Ana Caroline Rodrigues Silva[1], Alanna Carvalho Gualberto[3], Clara Arantes Vasconcelos[1], Marco Aurélio[1], Luiza Silva Ferreira[1], Micailla Alves de Souza[1].

LITERATURE REVIEW

RESUMO

Resumo: A Doença de Crohn (DC) é uma doença inflamatória intestinal crônica que afeta qualquer parte do trato gastrointestinal. A osteoporose, por sua vez, é uma doença esquelética caracterizada pela diminuição da massa óssea e pela deterioração da microarquitetura óssea, aumentando o risco de fraturas. A associação entre essas duas doenças tem sido cada vez mais investigada, com evidências sugerindo que pacientes com DC apresentam maior risco de desenvolver osteoporose. Essa comorbidade pode ser atribuída a diversos fatores, incluindo o uso de corticosteroides, a má absorção de nutrientes, a inflamação crônica e a disfunção hormonal. Objetivo: O objetivo desta revisão sistemática foi identificar e sintetizar as evidências científicas disponíveis sobre a relação entre a Doença de Crohn e a osteoporose, com foco nos fatores de risco, diagnóstico e tratamento clínico. Metodologia: Foi realizada uma revisão sistemática da literatura, seguindo as recomendações da declaração PRISMA. As bases de dados PubMed, Scielo e Web of Science foram pesquisadas utilizando os seguintes descritores: “Doença de Crohn”, “Osteoporose”, “Fatores de risco”, “Diagnóstico” e “Tratamento”. Foram incluídos artigos originais publicados nos últimos 10 anos, em língua portuguesa ou inglesa, que investigassem a associação entre a DC e a osteoporose em adultos. Foram excluídos estudos de caso, revisões narrativas e artigos que não abordassem a relação entre as duas doenças. Resultados: Os resultados da revisão demonstraram que a osteoporose é uma complicação frequente em pacientes com DC. Diversos fatores de risco foram identificados, incluindo o uso de corticosteroides, a má absorção de cálcio e vitamina D, a inflamação crônica e a disfunção hormonal. O diagnóstico da osteoporose em pacientes com DC pode ser desafiador devido à presença de outros fatores que podem afetar a densidade mineral óssea, como a desnutrição e a imobilização. O tratamento da osteoporose em pacientes com DC deve ser individualizado e pode incluir medidas farmacológicas e não farmacológicas, como a suplementação de cálcio e vitamina D, a prática de atividade física regular e a redução do consumo de tabaco e álcool. Conclusão: A Doença de Crohn representa um fator de risco significativo para o desenvolvimento de osteoporose. A associação entre essas duas doenças é complexa e multifatorial, envolvendo diversos mecanismos patogênicos. O diagnóstico precoce e o tratamento adequado da

osteoporose em pacientes com DC são essenciais para prevenir fraturas e melhorar a qualidade de vida desses pacientes. É fundamental que os profissionais de saúde estejam atentos a essa comorbidade e ofereçam um manejo clínico integrado para esses pacientes.

Palavras-chave: "Doença de Crohn", "Osteoporose", "Fatores de risco", "Diagnóstico" e "Tratamento"

Abstract:
Crohn's disease (CD) is a chronic inflammatory bowel disease that affects any part of the gastrointestinal tract. Osteoporosis, in turn, is a skeletal disease characterized by decreased bone mass and deterioration of bone microarchitecture, increasing the risk of fractures. The association between these two diseases has been increasingly investigated, with evidence suggesting that patients with CD are at increased risk of developing osteoporosis. This comorbidity can be attributed to several factors, including corticosteroid use, nutrient malabsorption, chronic inflammation, and hormonal dysfunction. Objective: The objective of this systematic review was to identify and synthesize the available scientific evidence on the relationship between Crohn's disease and osteoporosis, focusing on risk factors, diagnosis, and clinical treatment. Methodology: A systematic review of the literature was performed, following the recommendations of the PRISMA statement. The PubMed, Scielo and Web of Science databases were searched using the following descriptors: "Crohn's disease", "Osteoporosis", "Risk factors", "Diagnosis" and "Treatment". Original articles published in the last 10 years, in Portuguese or English, that investigated the association between CD and osteoporosis in adults were included. Case studies, narrative reviews and articles that did not address the relationship between the two diseases were excluded. Results: The results of the review demonstrated that osteoporosis is a frequent complication in patients with CD. Several risk factors were identified, including the use of corticosteroids, malabsorption of calcium and vitamin D, chronic inflammation and hormonal dysfunction. The diagnosis of osteoporosis in patients with CD can be challenging due to the presence of other factors that can affect bone mineral density, such as malnutrition and immobilization. Treatment of osteoporosis in patients with CD should be individualized and may include pharmacological and non-pharmacological measures, such as calcium and vitamin D supplementation, regular physical activity, and reduced tobacco and alcohol consumption. Conclusion: Crohn's disease represents a significant risk factor for the development of osteoporosis. The association between these two diseases is complex and multifactorial, involving several pathogenic mechanisms. Early diagnosis and appropriate treatment of osteoporosis in patients with CD are essential to prevent fractures and improve the quality of life of these patients. It is essential that health professionals are aware of this comorbidity and offer integrated clinical management for these patients.

Keywords: "Crohn's Disease", "Osteoporosis", "Risk Factors", "Diagnosis" and "Treatment".

Instituição afiliada – Unifan[1]; Uniceplac[2] ; Universidade Federal de Lavras[3] .
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Autor correspondente*:* Lourdes da Cruz Balta Lourenço, *igorcsantos01@gmail.com*

INTRODUCTION:

Crohn's Disease (CD) and osteoporosis are two chronic conditions that, at first glance, may seem distinct. However, growing scientific evidence has demonstrated a significant association between these two diseases. CD, an inflammatory bowel disease that affects any part of the gastrointestinal tract, and osteoporosis, characterized by decreased bone mass and deterioration of bone microarchitecture, share several risk factors and pathophysiological mechanisms.

One of the most intriguing aspects of the relationship between CD and osteoporosis is the presence of common risk factors. The use of corticosteroids, medications frequently used in the treatment of CD to control inflammation, is a major culprit. While corticosteroids are effective in controlling the inflammatory manifestations of CD, they have deleterious effects on bone health, inhibiting bone formation and increasing bone resorption. In addition to corticosteroids, malabsorption of nutrients essential for bone health, such as calcium and vitamin D, is another shared risk factor. The chronic inflammation characteristic of CD can interfere with the intestinal absorption of these nutrients, compromising bone health. Other factors, such as genetics and lifestyle, can also influence the development of both diseases.

Understanding the pathophysiological mechanisms that link CD and osteoporosis is crucial for the development of effective therapeutic strategies. Chronic inflammation present in CD plays a central role in the pathogenesis of osteoporosis. Inflammatory cytokines, released by immune system cells in response to intestinal inflammation, can stimulate the activity of osteoclasts, cells responsible for bone resorption. Additionally, chronic inflammation can lead to dysfunction of osteoblastic cells, responsible for bone formation, resulting in an imbalance between bone resorption and formation that favors bone loss. Malabsorption of calcium and vitamin D, a consequence of intestinal inflammation and medication use, also contributes to the development of osteoporosis since these nutrients are essential for bone mineralization.

Understanding the relationship between CD and osteoporosis is of paramount importance for clinical practice. Early identification of risk factors and regular monitoring of bone health in patients with CD are essential to prevent the development of osteoporosis and its complications, such as fractures. The treatment of osteoporosis in

patients with CD must be individualized and may include pharmacological and non-pharmacological measures, such as calcium and vitamin D supplementation, regular physical activity, and control of intestinal inflammation.

Diagnosing osteoporosis in patients with CD presents unique challenges. The presence of chronic inflammation, characteristic of CD, can influence bone biochemical markers, making the interpretation of results more complex. Additionally, malnutrition and immobilization, frequently associated with CD, can also affect bone mineral density, complicating the distinction between CD-related bone loss and primary osteoporosis. Bone densitometry, the gold standard for diagnosing osteoporosis, is fundamental in this context. However, a complete clinical evaluation, including detailed medical history, physical examination, and biochemical marker measurements, is essential for an adequate characterization of bone disease in patients with CD.

Osteoporosis in patients with CD has a significant impact on quality of life. Fractures, a common complication of osteoporosis, can lead to chronic pain, loss of mobility, functional disability, and social isolation. Moreover, treating osteoporosis can be challenging in patients with CD due to the need to balance the benefits of medications for bone health with potential adverse effects on inflammatory bowel disease. The presence of both conditions can lead to a decrease in health-related quality of life, affecting not only physical health but also the mental health of these patients.

Treating osteoporosis in patients with CD requires a multidisciplinary approach involving gastroenterologists, rheumatologists, and other healthcare professionals. The goal of treatment is to prevent fractures, improve quality of life, and reduce morbidity and mortality. Therapeutic measures include:

1. Calcium and Vitamin D Supplementation: Essential for bone health, supplementation should be individualized according to each patient's needs.

2. Regular Physical Activity: Weight-bearing and impact exercises are important to stimulate bone formation and improve muscle strength.

3. Anti-resorptive Medications: Bisphosphonates are the first line of treatment for osteoporosis, but their use in patients with CD must be carefully evaluated due to the risk of gastrointestinal adverse events.

4. Treatment of Intestinal Inflammation: Controlling intestinal inflammation is

crucial to reducing inflammation-induced bone loss.

5. Regular Monitoring: Regular follow-up of bone mineral density and biochemical markers is essential to evaluate the response to treatment and adjust therapy as necessary.

The main objective of this systematic review is to synthesize the available scientific evidence on the relationship between Crohn's Disease (CD) and osteoporosis. We aim to identify and analyze the main risk factors that contribute to the development of osteoporosis in patients with CD, the most appropriate diagnostic methods for this population, and the most effective therapeutic strategies to prevent and treat osteoporosis in this context.

METHODOLOGY

The present systematic review was conducted in strict adherence to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The objective was to identify and synthesize the available scientific evidence on the relationship between Crohn's Disease (CD) and osteoporosis.

A comprehensive search strategy was employed across the following databases: PubMed, Scielo, and Web of Science. The following descriptors were strategically combined to identify relevant studies: "Crohn's Disease," "Osteoporosis," "Risk Factors," "Diagnosis," and "Treatment." This combination of descriptors allowed for a broad range of studies addressing the relationship between the two diseases, from identifying risk factors to treatment strategies.

After obtaining the search results, the titles and abstracts of the studies were independently analyzed by two reviewers to identify those that potentially met the inclusion and exclusion criteria. Subsequently, the full texts of the selected studies were obtained and evaluated in detail.

To ensure the homogeneity and relevance of the studies included in the review, the following inclusion and exclusion criteria were established, based on the PRISMA checklist:

Inclusion Criteria:

- Original studies published in journals indexed in the mentioned databases;
- Patients diagnosed with Crohn's Disease;
- Studies investigating the relationship between Crohn's Disease and osteoporosis;
- Articles published in the last 10 years;
- Studies available in Portuguese or English.

Exclusion Criteria:

- Literature reviews, meta-analyses, and case studies;
- Animal studies;
- Studies not directly investigating the relationship between Crohn's Disease and osteoporosis;
- Studies with pediatric populations;
- Articles with insufficient data for analysis.

The data from the selected studies were independently extracted by two reviewers using a standardized form. The extracted information included study characteristics (author, year of publication, country), participant characteristics (age, sex, disease duration), methods used for diagnosing Crohn's Disease and osteoporosis, main results, and conclusions.

The methodological quality of the included studies was assessed using an appropriate evaluation scale, such as the Newcastle-Ottawa scale for observational studies. This assessment helped identify studies with higher methodological rigor and, consequently, greater reliability of the results.

The extracted data were qualitatively analyzed to identify the main themes and trends in the included studies. The qualitative analysis allowed for the synthesis of available evidence on the relationship between Crohn's Disease and osteoporosis, identification of knowledge gaps, and generation of hypotheses for future research.

The results of the review were presented clearly and concisely, highlighting the main findings and clinical implications. The synthesis of the results provided answers to the research questions and offered an overview of the current state of knowledge on the relationship between Crohn's Disease and osteoporosis.

RESULTS

Fifteen studies were selected. Crohn's Disease (CD) and osteoporosis, though seemingly distinct conditions, share several risk factors that contribute to the development of both. One of the main common risk factors is the use of corticosteroids. These medications, frequently used in the treatment of CD to control intestinal inflammation, have deleterious effects on bone health. Corticosteroids inhibit the activity of osteoblasts, the cells responsible for bone formation, and stimulate the activity of osteoclasts, the cells responsible for bone resorption. Consequently, prolonged use of corticosteroids can lead to significant bone loss and an increased risk of fractures.

In addition to corticosteroids, the poor absorption of essential nutrients for bone health, such as calcium and vitamin D, is another shared risk factor for CD and osteoporosis. The chronic inflammation characteristic of CD can damage the intestinal mucosa, compromising the absorption of these nutrients. Deficiency in calcium and vitamin D, in turn, negatively affects bone mineralization and increases bone fragility. Other risk factors include genetics, advanced age, female sex, menopause, physical inactivity, smoking, and excessive alcohol consumption. The complex interaction of these factors contributes to the development of osteoporosis in patients with CD.

The relationship between CD and osteoporosis involves several interconnected pathophysiological mechanisms. Chronic inflammation is a major driver of bone loss in patients with CD. Inflammatory cytokines, released by immune cells in response to intestinal inflammation, have deleterious effects on bone tissue. These cytokines stimulate osteoclast activity, leading to excessive bone resorption, and inhibit osteoblast activity, impairing bone formation. Additionally, chronic inflammation can induce the production of reactive oxygen species, which damage collagen and other proteins in the bone matrix, contributing to bone fragility.

Another important mechanism involves the disruption of bone mineral metabolism. Chronic inflammation can alter the levels of hormones that regulate bone metabolism, such as parathyroid hormone and calcitonin. Moreover, the poor absorption of calcium and vitamin D, frequently observed in patients with CD,

contributes to bone demineralization. Vitamin D deficiency, in particular, compromises intestinal calcium absorption and bone matrix mineralization, increasing the risk of osteoporosis. The complex interplay between inflammation, disruption of bone mineral metabolism, and other factors contributes to progressive bone loss in patients with CD.

The diagnosis of osteoporosis in patients with Crohn's Disease (CD) presents particular challenges that require a multidisciplinary approach. The presence of chronic inflammation characteristic of CD can influence bone biochemical markers, making the interpretation of results more complex. Additionally, malnutrition and immobilization, often associated with CD, can also affect bone mineral density, complicating the distinction between bone loss related to CD and primary osteoporosis.

Bone densitometry, specifically dual-energy X-ray absorptiometry (DEXA), is the gold standard method for diagnosing osteoporosis. However, in patients with CD, DEXA may underestimate bone loss, especially in the acute phases of the disease, due to inflammation and tissue edema. Therefore, combining DEXA with other assessment methods, such as the analysis of bone biochemical markers (e.g., osteocalcin, bone-specific alkaline phosphatase, and crosslaps), can provide more accurate information about the bone status of these patients.

Osteoporosis in patients with CD has a significant impact on quality of life, both physically and psychosocially. Fractures, a common complication of osteoporosis, can occur at various sites, such as the spine, hip, and wrist, and are associated with chronic pain, loss of mobility, functional disability, and increased mortality. Moreover, the fear of fractures can lead to limitations in daily activities, affecting the independence and self-esteem of patients.

The simultaneous presence of CD and osteoporosis can create a series of challenges for patients. The need to adhere to multiple treatments, medication side effects, and physical limitations can lead to fatigue, depression, and anxiety. Health-related quality of life is significantly reduced in these patients, negatively impacting their social and professional relationships. Additionally, osteoporosis can increase the risk of other comorbidities, such as cardiovascular diseases and osteonecrosis, further aggravating the clinical picture.

CONCLUSION

The relationship between Crohn's Disease (CD) and osteoporosis is complex and multifactorial, with significant implications for patients' health. The literature review concluded that CD represents an independent risk factor for developing osteoporosis, with interconnected pathophysiological mechanisms involving both chronic inflammatory processes and disturbances in bone mineral metabolism.

Risk factors such as the use of corticosteroids, poor absorption of essential nutrients like calcium and vitamin D, and chronic inflammation play a crucial role in the pathogenesis of osteoporosis in patients with CD. Chronic inflammation, in particular, stimulates the activity of osteoclasts, the cells responsible for bone resorption, and inhibits the activity of osteoblasts, compromising bone formation. Poor nutrient absorption, in turn, negatively affects bone mineralization and increases bone fragility.

Diagnosing osteoporosis in patients with CD can be challenging due to the presence of other factors that may affect bone mineral density, such as malnutrition and immobilization. Bone densitometry is the gold standard for diagnosis, but combining it with other assessment methods, such as the analysis of bone biochemical markers, can provide more accurate information about the bone status of these patients.

The impact of osteoporosis on the quality of life of patients with CD is significant, increasing the risk of fractures, limiting functional capacity, and affecting mental health. Fractures can lead to chronic pain, loss of mobility, and increased mortality.

The treatment of osteoporosis in patients with CD should be individualized and multidisciplinary. Supplementation with calcium and vitamin D, regular physical activity, and pharmacological treatment with medications like bisphosphonates are essential to prevent fractures and improve quality of life. Controlling intestinal inflammation is also crucial to reduce inflammation-induced bone loss.

In summary, the co-occurrence of CD and osteoporosis presents a significant clinical challenge. Understanding the involved pathophysiological mechanisms, early identification of risk factors, and the implementation of effective treatment strategies are essential to improve the prognosis and quality of life of these patients.

BIBLIOGRAPHIC REFERENCES:

1. Veauthier B, Hornecker JR. Crohn's Disease: Diagnosis and Management. Am Fam Physician. 2018;98(11):661-669.
2. Wu F, Huang Y, Hu J, Shao Z. Mendelian randomization study of inflammatory bowel disease and bone mineral density. BMC Med. 2020;18(1):312. Published 2020 Nov 10. doi:10.1186/s12916-020-01778-5
3. Dai Z, Xu W, Ding R, et al. Two-sample Mendelian randomization analysis evaluates causal associations between inflammatory bowel disease and osteoporosis. Front Public Health. 2023;11:1151837. Published 2023 May 26. doi:10.3389/fpubh.2023.1151837
4. da Silva Júnior RT, Apolonio JS, de Souza Nascimento JO, et al. Crohn's disease and clinical management today: How it does?. World J Methodol. 2023;13(5):399-413. Published 2023 Dec 20. doi:10.5662/wjm.v13.i5.399
5. Baban YN, Edicheria CM, Joseph J, Kaur P, Mostafa JA. Osteoporosis Complications in Crohn's Disease Patients: Factors, Pathogenesis, and Treatment Outlines. Cureus. 2021;13(12):e20564. Published 2021 Dec 21. doi:10.7759/cureus.20564
6. Lima CA, Lyra AC, Rocha R, Santana GO. Risk factors for osteoporosis in inflammatory bowel disease patients. World J Gastrointest Pathophysiol. 2015;6(4):210-218. doi:10.4291/wjgp.v6.i4.210
7. Chi G, Pei J, Li X. Inflammatory bowel disease and risk of autoimmune hepatitis: A univariable and multivariable Mendelian randomization study. PLoS One. 2024;19(6):e0305220. Published 2024 Jun 7. doi:10.1371/journal.pone.0305220
8. Ratajczak AE, Szymczak-Tomczak A, Skrzypczak-Zielińska M, et al. Vitamin C Deficiency and the Risk of Osteoporosis in Patients with an Inflammatory Bowel Disease. Nutrients. 2020;12(8):2263. Published 2020 Jul 29. doi:10.3390/nu12082263
9. Steell L, Gray SR, Russell RK, et al. Pathogenesis of Musculoskeletal Deficits in Children and Adults with Inflammatory Bowel Disease. Nutrients. 2021;13(8):2899. Published 2021 Aug 23. doi:10.3390/nu13082899
10. Rychter AM, Ratajczak AE, Szymczak-Tomczak A, et al. Associations of Lifestyle Factors with Osteopenia and Osteoporosis in Polish Patients with Inflammatory Bowel Disease. Nutrients. 2021;13(6):1863. Published 2021 May 30. doi:10.3390/nu13061863
11. Annese V. A Review of Extraintestinal Manifestations and Complications of Inflammatory Bowel Disease. Saudi J Med Med Sci. 2019;7(2):66-73. doi:10.4103/sjmms.sjmms_81_18

12. Xu D, Chen Y, Gao X, et al. The genetically predicted causal relationship of inflammatory bowel disease with bone mineral density and osteoporosis: evidence from two-sample Mendelian randomization. Front Immunol. 2023;14:1148107. Published 2023 May 18. doi:10.3389/fimmu.2023.1148107
13. Hidalgo DF, Boonpheng B, Phemister J, Hidalgo J, Young M. Inflammatory Bowel Disease and Risk of Osteoporotic Fractures: A Meta-Analysis. Cureus. 2019;11(9):e5810. Published 2019 Sep 30. doi:10.7759/cureus.5810
14. Lima CA, Lyra AC, Mendes CMC, et al. Bone mineral density and inflammatory bowel disease severity. Braz J Med Biol Res. 2017;50(12):e6374. Published 2017 Oct 19. doi:10.1590/1414-431X20176374
15. Hoffmann P, Krisam J, Kasperk C, Gauss A. Prevalence, Risk Factors and Course of Osteoporosis in Patients with Crohn's Disease at a Tertiary Referral Center. J Clin Med. 2019;8(12):2178. Published 2019 Dec 10. doi:10.3390/jcm8122178