DOI: https://doi.org/10.61841/n81j3616 Publication URL: https://nnpub.org/index.php/MHS/article/view/2036

THE SYSTEMATIC REVIEW OF OSTEOPOROSIS AND BONE FRACTURES IN ALCOHOLIC LIVER DISEASE

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ABSTRACT

Background: *Osteoporosis is classified as primary when it is age-related or occurs in postmenopausal women and secondary when caused due to other etiologies. Previous studies have shown that the prevalence of osteoporosis in patients with cirrhosis ranges from 12% to 70% based on the diagnostic approach and etiology of the underlying liver disease.*

The aim: *This study aims to show osteoporosis and bone fractures in alcoholic liver disease.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 29 articles, whereas the results of our search on SagePub brought up 77 articles. The results of the search conducted for the last year of 2013 yielded a total 21 articles for PubMed and 28 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 17 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *The liver is an organ involved in a number of metabolic and hormonal processes whose dysregulation may lead to the development of bone homeostasis disorders and ultimately to osteopenia and osteoporosis. Complications of chronic liver disease should therefore include pathologic osteoporotic fractures, which significantly reduce quality of life.*

Keyword: *Osteoporosis, bone fracture, alcoholic liver disease.*

INTRODUCTION

Chronic liver disease (CLD) causes more than 1 million deaths every year and remains a pandemic in the last decade affecting more than 600,000 patients in the United States. Previous studies found patients with CLD had increased risk of osteoporosis, so fractures were inferred to be complications of this condition. The aim of this meta-analysis is to summarize the best evidence that correlates CLD patients and the risk to develop osteoporotic fractures versus control patients without CLD.[1]

Osteoporosis denotes a state in which the bones become porous resulting in increased risk for fractures. The general population started first associating this condition with menopause and loss of estrogen, even though it was clear to members of the medical profession from the beginning that it is a condition associated with a great variety of diseases ranging from inadequate calcium intake or uptake to abnormalities in various bone-associated cell functions. Because of the involvement of the liver in many metabolic effects it is not surprising that one of the secondary causes of osteoporosis is liver disease.[2]

The bone represents the pool that allows for the tight regulation of circulating calcium. Indeed, calcium is a most tightly controlled electrolyte in the blood stream. This takes place at the level of the bone forming cells - the osteoblasts -, the bone resorbing cells, - the osteoclasts -, or the bone-embedded cells - the osteocytes. In this review we discuss the evidence on the role of these cells in the pathogenesis of osteoporosis associated with liver disease. Most of the bone consists of a collagen matrix, but a great number of proteins and growth factors such as insulin like growth factor-I (IGF-I) have also been found in this matrix and affect osteoblast function as they are produced or osteoclast function when bone is resorbed.[2]

Alcoholics may have an increased risk of trauma and subsequent fractures, alcohol itself has a negative impact on bone metabolism. Alcoholism has been associated with growth impairment, osteoporosis, osteomalacia, fractures, delayed fracture healing, and aseptic necrosis (primarily necrosis of the femoral head). The mechanisms that explain the loss of structural integrity of bone are partially known. These include a direct toxic effect of ethanol on bone synthesis and systemic alterations such as malnutrition and malabsorption, liver disease, altered hormonal and cytokine profiles, alcoholic myopathy, and neuropathy. In this review we will outline each of these mechanisms.[3]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast osteoporosis and bone fractures in alcoholic liver disease. It is possible to accomplish this by researching or investigating osteoporosis and bone fractures in alcoholic liver disease. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about osteoporosis and bone fractures in alcoholic liver disease. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " Osteoporosis and bone fractures in alcoholic liver disease." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Osteoporosis*"[MeSH Subheading] OR "*bone fracture*"[All Fields] OR "*liver disease*" [All Fields]) AND ("*Alcoholic liver disease*"[All Fields] OR "* Effect of alcoholic liver*"[All Fields]) AND ("*alcoholic liver and osteoporosis*"[All Fields]) OR ("*bone problems in alcoholic liver" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

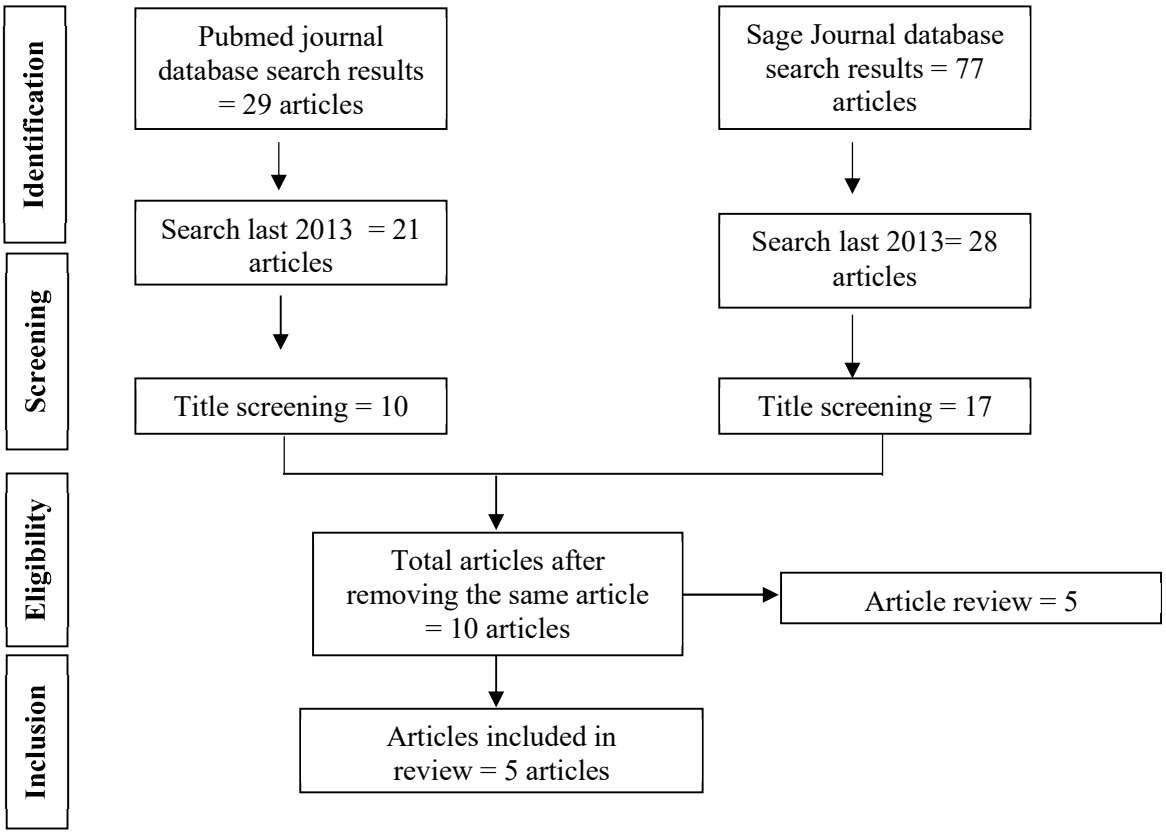

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 29 articles, whereas the results of our search on SagePub brought up 77 articles. The results of the search conducted for the last year of 2013 yielded a total 21 articles for PubMed and 28 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 17 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Mikami, K *et al* (2020)[4] showed although the BMD levels were the same, regardless of the presence or absence of FLD, elderly participants with FLD showed decreased bone formation and increased bone resorption, with sex differences. Because our results suggest that FLD in elderly individuals is detrimental for bone metabolism, and that it leads to bone loss and osteoporosis, further studies using a cohort population are warranted.

Gokcan, H *et al* (2020)[5] showed the prevalence of bone disease was found to be higher in cirrhotic patients. Although osteoporosis and vitamin D deficiency were found to decrease survival, this effect was not statistically significant. We suggest designing multi-institutional and/or multinational studies with larger and more heterogenous patient groups would enable better testing of this phenomenon.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Mikami, K *et al*., 2020[4]	Japan	A Community-based Study	1020 participants	The BMD (percentage of the young adult mean) was the same level in both male and female participants with and without FLD. Both men and women showed an age-dependent decrease in their bone formation index and bone resorption index values. Men of ≥70 years of age and women of 60-69 years of age with FLD had significantly lower bone formation index values and higher bone resorption index values. However, similar findings were not seen in women of ≥70 years of age.
Gokcan, H *et al*., 2020[5]	Turkey	Retrospective study	218 patients	One hundred forty-seven (67.4%) patients were female (mean age, 50.4±11.7). Patients were Child A by 40.8%, Child B by 47.1%, and Child C by 12.1%. Mean MELD Na score was 8.4±2.8. Data of the BMD were established in 218 patients and 25-OH D levels in 122 patients. Mean serum 25-OH D level was 14.26±9.44 ng/mL. Osteoporosis was identified in 42 (19.3%) and osteopenia in 115 (52.8%) patients, according to BMD. Osteocalcin levels and collagen type 1 levels were high in 25.6% and 12.5% of patients, respectively. No statistically difference was found, including gender (p=0.69), age (p=0.38), etiology (p=0.16), BMI (p=0.32), CP score (p=0.42), MELD (0.14), albumin (p=0.11), total bilirubin (p=0.99), Ca (0.67), PTH (0.88), osteocalcin (0.92), collagen type 1(p=0.25) between osteoporotic and non-osteoporotic patients. Patients were followed-up for a median of 30.07±11.83 months after BMD measurement. Fifty-four (24.8%) patients died during the follow-up period, none of them are related to bone fracture. There was no statistically difference on

				survival between osteoporosis group (32.2±2.3 months) and non-osteoporosis group (37.2±1.7 months; p=0.26) or when patients with 25-OH D_3 ≤10 ng/mL were compared to patients with 25-OH D_3 >20 ng/mL (34.4±2.0 months vs. 39.1±1.6 months, p=0.308).
Yadav, E *et al.*, 2022[6]	India	Case control	200 participants	The whole-body, LS-spine, and hip BMDs in CLD cases were found to be significantly lower as compared to controls. When the participants among both groups were stratified by age and gender, a significant difference in LS-spine and hip BMD was observed in elderly patients (>60 years), and in both the male and female patients. HOD was found in 70% of CLD patients. After multivariate analysis in CLD patients, we identified that being a male patient (odds ratio [OR] = 3.03), older age (OR = 3.54), duration of illness for more than 5 years (OR = 3.89), decompensated liver dysfunction with Child–Turcotte–Pugh-B and C grading (OR = 8.28), and low level of Vitamin D (OR = 18.45) were the risk factors for HOD.
Pereira, F *et al.*, 2021[7]	Portugal	A prospective observational study	94 patients	Ninety-four patients were included; 24.5 % (n = 23) had prior fragility fractures and ten patients suffered new osteoporotic fractures during the study period. Hepatic osteodystrophy was diagnosed in 79.8 % (n = 75) and osteoporosis in 21.3 % (n = 20) of cases. Patients with hepatic osteodystrophy presented significantly worse Child-Turcotte-Pugh (p < 0.05) and Model for End-Stage Liver Disease (MELD-sodium) scores (p = 0.01). According to the multivariate analysis, lower body mass index (BMI) (OR = 0.787, 95 % CI: 0.688-0.901, p = 0.001) and vitamin D deficiency (OR = 6.798, 95 % CI: 1.775-26.038, p = 0.005) were significantly and independently associated with hepatic osteodystrophy. Patients with osteoporosis also had a lower BMI (p = 0.01). Female patients and those with prior fragility fractures were

				more likely to suffer from osteoporosis ($p < 0.05$).
Kim, MJ *et al*., 2022[8]	Korea	Cohort study	180,519 participants	A total of 2,720 participants (1.5%) were newly diagnosed with fracture during the study period (median 4.6 years). The participants were grouped according to FLI quartiles (Q1, 0 to <5.653; Q2, 5.653 to <15.245; Q3, 15.245 to <37.199; and Q4 ≥37.199). The cumulative fracture incidence was significantly higher in the highest FLI group than in the lowest FLI group (Q4, 986 [2.2%] and Q1, 323 [0.7%]; p<0.001). The adjusted hazard ratio indicated that the highest FLI group was independently associated with a higher incidence of fracture (hazard ratio for Q4 vs Q1, 2.956; 95% confidence interval, 2.606 to 3.351; p<0.001). FLI was significantly associated with a higher incidence of fracture, independent of the baseline characteristics of the participants.

Yadav, E *et al* (2022)[6] showed a greater proportion of CLD patients in a rural setting experienced HOD. It was also evaluated that progression of HOD correlates with a longer duration of illness and more severity. In addition, elderly subjects may require to be screened for low BMD in our rural communities. This study buttresses the need for prescribing calcium and Vitamin D in CLD cases and the generation of additional information on it.

Pereire, F *et al* (2021)[7] showed our study revealed a high prevalence of hepatic osteodystrophy and osteoporosis in patients with ALD cirrhosis (particularly in those with a lower BMI) and a concerning high rate of fragility fractures. Bone mineral density should be assessed in order to allow for an early diagnosis and the implementation of preventive measures.

Kim, MJ *et al* (2021)[8] showed the present findings obtained using the NHIS-NSC 2.0 cohort clearly demonstrate that Korean adults with high FLI are predisposed toward fractures. FLI can be easily calculated in the clinic, and more attention should be paid to individuals with a high FLI score with respect to the primary prevention of fracture. Further mechanistic insights regarding the liver-bone axis will be required in the future to explain the epidemiological observations made in the present study.

DISCUSSION

Hepatic osteodystrophy refers to osteoporosis and osteomalacia associated with chronic liver disease. Osteoporosis is a disorder of low bone mass, microarchitectural malformation and structural weakness while osteomalacia is a disorder of decreased osteoid mineralization at sites of bone formation. Liver is involved in a number of metabolic mechanisms. Therefore, it is not surprising that liver disease is one of the secondary causes of osteoporosis and approximately 30% of patients with chronic liver disease suffer from osteoporosis. However, aetiology of bone loss is multifactorial and not entirely understood. Patients with cholestatic liver disease are particularly susceptible to osteoporosis due to the interference of cholestasis with vitamin D metabolism.[9]

Osteoporosis, which results in a high risk of fragility fractures, is a frequently observed complication in patients with chronic liver disease, especially in liver cirrhosis, cholestatic liver diseases and hemochromatosis. In addition, the problem is critical in patients who undergo a liver transplant when bone loss is accelerated, leading to a greater incidence of fractures during the period immediately after transplantation. Nevertheless, few studies have evaluated bone diseases in patients with more frequently observed chronic liver disease, such as chronic viral hepatitis, non-alcoholic fatty liver disease and alcoholic liver disease. The detection of osteoporosis in patients with chronic liver disease requires a high index of suspicion, as approximately one-third of vertebral fractures are asymptomatic. In contrast, femoral neck fractures are uncommon in patients with liver cirrhosis as they occur approximately a decade later than vertebral fractures, which is beyond the life expectancy of most patients with cirrhosis.[10]

Chronic excessive alcohol consumption is a well-established risk factor for low bone density and bone fractures. This is included in the fracture risk assessment tool (FRAX), which estimates the 10-year probability of bone fractures combined with other clinical risk factors and the bone mineral density (BMD) of the femoral neck. It is assumed that the decreases in bone mass and strength resulting from heavy alcohol use are due to an imbalance between bone formation and resorption. However, ingestion of light or moderate amounts of alcohol is known to be associated with higher BMD and decreased fracture rates, although conflicting results exist because of inconsistent standards of classification of light, moderate, or heavy alcohol consumption.[11,12]

The pathogenesis of osteoporosis in chronic liver disease is complex and related to both increased bone resorption and reduced bone formation. Unstable bone remodelling is caused by a number of mechanisms, some of which remain unknown. In many cases, the mechanisms of impaired bone metabolism are largely caused by the unique characteristics of the specific liver disease being considered. However, there remain a number of common factors related to chronic liver disease in general that affect bone metabolism. These include vitamin D and calcium metabolism alterations, vitamin K deficiency, and hormonal dysregulation, the release of cytokines and deficiency of insulin-like growth factor 1 (IGF-1).[9,13]

Vitamin D3 is hydroxylated in the liver to 25-hydroxy vitamin D (25-OH-vitamin D) and then in the kidneys to 1,25-hydroxyvitamin D. Decreased 25-OH-vitamin D production is associated with altered liver function and it results in impaired osteoclast-mediated bone resorption, osteoblast-mediated mineralization and decreased calcium resorption in the gastrointestinal tract. Additionally, disturbed secretion of bile leads to decreased fat absorption and abnormal uptake of vitamin D as a result. To summarize, disturbed metabolism of calcium and vitamin D results from impaired 25-hydroxylation, intestinal malabsorption and decreased skin synthesis in patients with jaundice.[9,14]

CONCLUSION

The liver is an organ involved in a number of metabolic and hormonal processes whose dysregulation may lead to the development of bone homeostasis disorders and ultimately to osteopenia and osteoporosis. Complications of chronic liver disease should therefore include pathologic osteoporotic fractures, which significantly reduce quality of life.

REFERENCES

[1] Hidalgo DF, Boonpheng B, Sikandar S, Nasr L, Hidalgo J. Chronic Liver Disease and the Risk of Osteoporotic Fractures: A Meta-Analysis. Cureus. 2020;12(9).
[2] Nakchbandi IA. Osteoporosis and fractures in liver disease: Relevance, pathogenesis and therapeutic implications. World J Gastroenterol. 2014;20(28):9427–38.
[3] González-Reimers E, Quintero-Platt G, Rodríguez-Rodríguez E, Martínez-Riera A, Alvisa-Negrín J, Santolaria-Fernández F. Bone changes in alcoholic liver disease. World J Hepatol. 2015;7(9):1258–64.
[4] Mikami K, Endo T, Sawada N, Igarashi G, Kimura M, Hasegawa T, et al. Association of bone metabolism with fatty liver disease in the elderly in Japan: A community-based study. Intern Med. 2020;59(10):1247–56.
[5] Gokcan H, Kayhan MA, Demir SO, Kacar S, Cam P, Kaplan M, et al. Prevalence and characteristics of bone disease in cirrhotic patients. Hepatol Forum. 2020;1(2):48–52.
[6] Yadav E, Kaur R, Sasan A, Garg S. Investigation of the influential factors for hepatic osteodystrophy in chronic liver disease: A case-control survey among the patients attending a tertiary care hospital in a rural region of Northern India. Tzu Chi Med J. 2023;35(1):95–102.
[7] Pereira F, Azevedo R, Linhares M, Pinto J, Leitão C, Caldeira A, et al. Hepatic osteodystrophy in cirrhosis due to alcohol-related liver disease. Rev Esp Enfermedades Dig. 2021;113(8):563–9.
[8] Kim MJ, Kim MS, Lee HB, Roh JH, Jeon JH. Relationship between the High Fatty Liver Index and Risk of Fracture. Gut Liver. 2023;17(1):119–29.
[9] Handzlik-Orlik G, Holecki M, Wilczyński K, Duława J. Osteoporosis in liver disease: pathogenesis and management. Ther Adv Endocrinol Metab. 2016;7(3):128–35.
[10] Jeong HM, Kim DJ. Bone diseases in patients with chronic liver disease. Int J Mol Sci. 2019;20(17).
[11] Bang CS, Shin IS, Lee SW, Kim JB, Baik GH, Suk KT, et al. Osteoporosis and bone fractures in alcoholic liver disease: A meta-analysis. World J Gastroenterol. 2015;21(13):4038–47.
[12] Godos J, Giampieri F, Chisari E, Micek A, Paladino N, Forbes-Hernández TY, et al. Alcohol Consumption, Bone Mineral Density, and Risk of Osteoporotic Fractures: A Dose–Response Meta-Analysis. Int J Environ Res Public Health. 2022;19(3).
[13] Kang J, Gopakumar H, Puli SR. Prevalence of Osteoporosis in Cirrhosis: A Systematic Review and Meta-Analysis. Cureus. 2023;15(1):10–7.
[14] Al-Mendalawi MD. Bone mineral density loss in patients with cirrhosis. Saudi J Gastroenterol. 2019;25(3):201.