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Review Article

The osteo-hepatic axis: a review of bone disease, insulin-like growth factor-1, and fracture risk in fatty liver disease

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcoholic fatty liver disease (AFLD) represent emerging global health burdens with significant extra-hepatic complications. Among these, metabolic bone disease, particularly osteoporosis, has gained recognition as a major determinant of patient morbidity and quality of life. This narrative review synthesizes current evidence on the pathophysiological interplay between fatty liver diseases and bone health, with special emphasis on insulin-like growth factor-1 (IGF-1) dysregulation and bone mineral metabolism. The liver serves as the primary source of circulating IGF-1 and is crucial for vitamin D metabolism. In MASLD and AFLD, hepatocellular injury leads to IGF-1 deficiency, which impairs osteoblast function and bone formation. Concurrently, vitamin D deficiency and secondary hyperparathyroidism promote increased bone resorption. Chronic inflammation, characterized by elevated cytokines like TNF-α and IL-6, further exacerbates bone loss through the RANKL/OPG pathway. In AFLD, additional direct toxic effects of alcohol on osteoblasts compound the problem. Clinical studies consistently demonstrate reduced bone mineral density and increased fracture risk in these populations. Despite this evidence, standardized screening protocols and management guidelines for bone disease in non-cirrhotic fatty liver disease patients are lacking. This review highlights the critical need for integrated care models that address both hepatic and skeletal health, advocating for routine bone density assessment in MASLD/AFLD clinics. Future research should focus on comparative studies between MASLD and AFLD, exploration of IGF-1 as a dual biomarker, and development of targeted therapeutic strategies to mitigate fracture risk in this vulnerable and growing patient population.

Keywords: MASLD, AFLD, Osteoporosis, IGF-1, Bone mineral density, Vitamin D, Fracture risk, Osteo-hepatic axis

INTRODUCTION

The global landscape of chronic liver disease has undergone a significant transformation in recent decades. MASLD, encompassing the spectrum previously known as non- AFLD (NAFLD), and AFLD have emerged as the predominant etiologies, collectively affecting approximately 25-30% of the global population.[1] These epidemic parallels the rising trends of obesity, type 2 diabetes mellitus, metabolic syndrome, and harmful alcohol consumption patterns worldwide.

Traditionally, clinical focus and research efforts have centred on the hepatic consequences of these conditions-progression from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. However, with improved diagnostic capabilities and longer patient survival, the spectrum of extra-hepatic manifestations has gained increasing recognition.[2] Among these, cardiovascular disease has been extensively studied, but metabolic bone disease, particularly osteoporosis, has only recently emerged as a critical determinant of long-term morbidity, mortality, and quality of life in affected individuals.[3]

The biological plausibility for this association lies in the liver's fundamental role in skeletal homeostasis. The hepatocyte is the primary site for the synthesis of IGF-1, a pivotal anabolic hormone essential for bone formation, remodeling, and maintenance of bone mass.[4] Furthermore,

the liver performs the initial hydroxylation step in the activation of vitamin D, converting it to 25-hydroxyvitamin D [25(OH)D], the major circulating and storage form crucial for calcium-phosphate homeostasis.[5] Thus, hepatic dysfunction inevitably disrupts these endocrine pathways, creating a physiological predisposition to bone loss.

Epidemiological evidence substantiates this connection, indicating that patients with chronic liver disease, including those with MASLD and AFLD, experience a two-fold increased risk of fragility fractures compared to the general population. This heightened fracture risk translates to significant personal suffering, functional disability, increased healthcare utilization, and substantial economic burden on healthcare systems. Paradoxically, despite this clear evidence, skeletal health assessment remains conspicuously absent from routine clinical management protocols for non-cirrhotic fatty liver disease.[6]

This comprehensive review aims to elucidate the complex, bidirectional relationship between fatty liver diseases and bone metabolism-a nexus we term the "osteo-hepatic axis." We provide a detailed examination of the pathophysiological mechanisms, with particular emphasis on the central role of IGF-1 and bone mineral dysregulation. We synthesize current clinical evidence, identify critical gaps in knowledge and practice, and propose future research directions and clinical strategies to address this under-recognized complication, ultimately advocating for a holistic, integrated approach to patient care.

PATHOPHYSIOLOGICAL MECHANISMS: THE OSTEO-HEPATIC AXIS

The association between fatty liver disease and osteoporosis is mediated through a multifactorial and interconnected web of endocrine, inflammatory, metabolic, and toxic disturbances. Understanding this "osteo-hepatic axis" requires examining each component and their synergistic interactions.

Disruption of the growth hormone/IGF-1 (GH/IGF-1) axis

The liver is the principal source (over 90%) of circulating IGF-1, which is synthesized by hepatocytes in response to pituitary-derived growth hormone (GH). In both MASLD and AFLD, hepatocellular injury, steatosis, and inflammation lead to impaired synthetic function.

This manifests as a marked decline in IGF-1 production, a phenomenon that can occur early in the disease course, often preceding abnormalities in conventional liver function tests.[7] The resulting state is characterized by low IGF-1 alongside normal or elevated GH levels, indicative of hepatic GH resistance.

IGF-1 exerts potent anabolic effects on bone. It stimulates the proliferation and differentiation of osteoblast precursors, enhances the function of mature osteoblasts, increases collagen type I synthesis (the primary organic component of bone matrix), and inhibits osteoblast apoptosis. Consequently, hepatic IGF-1 deficiency directly impairs bone formation, reduces bone turnover rate, and leads to a net loss of bone mass.[8] Clinical studies have consistently demonstrated a positive correlation between serum IGF-1 levels and bone mineral density (BMD) in various populations, including those with liver disease.

Alterations in vitamin D metabolism and the parathyroid hormone (PTH) axis

Vitamin D, a secosteroid hormone, undergoes its first hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D]. Hepatic impairment, particularly in cholestatic conditions or advanced fibrosis, can compromise this conversion. Vitamin D deficiency is highly prevalent among patients with chronic liver disease, with studies reporting rates between 60-90%, depending on disease severity and latitude.[5]

The skeletal consequences of vitamin D deficiency are twofold. First, it reduces intestinal absorption of dietary calcium, leading to hypocalcemia. Second, and more critically, hypocalcemia stimulates the parathyroid glands to increase the secretion of PTH, resulting in secondary hyperparathyroidism (SHPT). Elevated PTH increases bone turnover by stimulating both osteoclast-mediated bone resorption and osteoblast-mediated bone formation. However, the resorptive effect predominates, leading to a net loss of bone, particularly from cortical sites. This high-turnover bone loss is a hallmark of hepatic osteodystrophy.

The role of chronic inflammation and pro-inflammatory cytokines

Both MASLD and AFLD are fundamentally inflammatory conditions. Steatohepatitis is characterized by hepatic infiltration of immune cells and the release of a plethora of pro-inflammatory cytokines and chemokines. Key players include tumor necrosis factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and C-reactive protein (CRP).

These circulating inflammatory mediators have direct catabolic effects on bone. TNF-α and IL-1β are potent stimulators of osteoclastogenesis. They act by upregulating the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on the surface of osteoblasts and bone marrow stromal cells. RANKL binds to its receptor RANK on osteoclast precursors, promoting their differentiation, activation, and survival.[9] Simultaneously, inflammation downregulates the production of osteoprotegerin (OPG), a soluble decoy receptor for RANKL that normally inhibits osteoclast formation. The resulting RANKL/OPG imbalance creates

a microenvironment highly conducive to increased bone resorption. IL-6, while having complex effects, also promotes osteoclast differentiation and inhibits osteoblast function.

Direct toxic effects of alcohol (specific to alcoholic liver disease)

In AFLD, the pathogenesis of bone disease includes all the above mechanisms but is compounded by the direct and indirect toxic effects of ethanol and its primary metabolite, acetaldehyde.

Direct inhibition of osteoblasts

Ethanol and acetaldehyde suppress the proliferation, differentiation, and metabolic activity of osteoblasts. They reduce the expression of genes critical for bone formation, such as RUNX2, osteocalcin, and type I collagen.

Stimulation of osteoclasts

Alcohol can enhance osteoclast activity and lifespan.

Nutritional deficiencies

Chronic alcohol abuse is associated with poor dietary intake, malabsorption, and deficiencies in calcium, vitamin D, magnesium, and protein-all essential for bone health.

Endocrine dysfunction

Alcohol can cause hypogonadism (low testosterone in men, menstrual irregularities in women), which is a major risk factor for osteoporosis.

Increased risk of falls

The neurological effects of alcohol increase the risk of traumatic falls, further elevating fracture risk in patients who already have compromised bone strength.[10]

Other contributing factors

Additional elements contribute to the multifactorial bone loss:

Shared risk factors

Physical inactivity, smoking, and poor nutritional status are common in both MASLD and AFLD populations and independently increase osteoporosis risk.

Medications

Patients with autoimmune components or those undergoing transplantation may receive long-term corticosteroid therapy, a well-known cause of glucocorticoid-induced osteoporosis.

Altered adipokine profile

In MASLD, adipose tissue dysfunction leads to altered secretion of adipokines like adiponectin (often decreased) and leptin (often increased), which may have modulatory effects on bone metabolism, though their precise role remains debated.

CLINICAL AND BIOCHEMICAL EVIDENCE

A robust and growing body of clinical research validates the epidemiological link between fatty liver disease and impaired bone health, translating pathophysiological concepts into measurable clinical outcomes.

Bone mineral density (BMD) assessments

Numerous cross-sectional and case-control studies utilizing dual-energy X-ray Absorptiometry (DXA) have consistently reported significantly lower BMD at both the lumbar spine (trabecular bone) and femoral neck (cortical bone) in patients with MASLD and AFLD compared to age-and sex-matched healthy controls. This reduction is observed even in patients without established cirrhosis, suggesting that bone loss begins early in the disease course. The severity of osteopenia/osteoporosis often correlates with the degree of liver fibrosis, as assessed by non-invasive markers (FIB-4, APRI) or transient elastography (FibroScan). For instance, a meta-analysis by Lee et al found that patients with MASLD had a 1.5-fold increased risk of osteoporosis compared to controls, with the risk being higher in those with significant fibrosis.[8]

Biochemical parameter alterations

Characteristic laboratory findings in these patients include:

Low serum IGF-1

Levels are frequently below the age-adjusted normal range and show a direct correlation with BMD measurements. IGF-1 levels decline progressively with worsening liver disease severity.

Vitamin D deficiency and elevated PTH

Serum 25(OH)D levels are commonly low (<20 ng/mL), accompanied by elevated intact PTH levels, confirming secondary hyperparathyroidism.

Altered bone turnover markers (BTMs)

The bone resorption marker serum C-terminal telopeptide of type I collagen (CTX) is often elevated, indicating increased osteoclastic activity. The bone formation marker serum N-terminal propeptide of type I procollagen (PINP) may be normal, low, or slightly elevated, reflecting the

complex, often "low-turnover" state of hepatic osteodystrophy in advanced disease.

Liver-derived parameters

While not specific, alterations in standard liver function tests (elevated ALT, AST, GGT) and markers of synthetic function (albumin) often parallel the severity of bone disease.

Fracture risk epidemiology

The most clinically significant endpoint is fracture. Longitudinal cohort studies and analyses of large healthcare databases have confirmed a significantly increased incidence of fragility fractures. A systematic review by Paternostro et al concluded that patients with MASLD have a 20-40% higher risk of overall fractures and a nearly two-fold increased risk of vertebral fractures.[9] The risk appears to be independent of traditional risk factors like age, sex, and the BMI. In AFLD, fracture risk is further amplified by the increased propensity for the falls.

CURRENT MANAGEMENT AND UNMET CLINICAL NEEDS

Despite clear evidence of increased fracture risk, a significant gap exists between knowledge and clinical practice. There are currently no formal, society-endorsed guidelines specifically addressing the screening, prevention, and management of bone disease in patients with pre-cirrhotic MASLD or AFLD. Management is often reactive and extrapolated from guidelines for post-menopausal osteoporosis, glucocorticoid-induced osteoporosis, or bone disease in cirrhosis.[11]

Current pragmatic approaches

Correction of underlying deficiencies

Oral supplementation with elemental calcium (1000-1200 mg/day) and vitamin D (to achieve and maintain serum 25(OH)D >30 ng/mL) is the foundational, low-risk intervention for all patients.

Lifestyle modifications

Counseling on weight-bearing physical activity (as tolerated), smoking cessation, and fall prevention strategies is essential. For AFLD, complete alcohol abstinence is paramount.

Pharmacological therapy

For patients diagnosed with osteoporosis (T-score≤-2.5) or those with osteopenia and high fracture risk (e.g., previous fragility fracture), anti-resorptive agents are considered. Oral bisphosphonates (alendronate, risedronate) are typically first-line.

Intravenous zoledronic acid or subcutaneous denosumab (a RANKL inhibitor) are alternatives, especially in patients with esophageal varices where oral bisphosphonates may be contraindicated. Anabolic agents like teriparatide are generally reserved for the severe cases.[12]

Critical unmet needs and knowledge gaps

Lack of comparative data

It remains fundamentally unknown whether the pathophysiology, progression rate, and clinical presentation of bone disease differ in meaningful ways between MASLD (primarily metabolic-inflammatory) and AFLD (toxic-inflammatory). Head-to-head comparative studies are virtually non-existent.

Absence of standardized screening protocols

There is no consensus on which patients with fatty liver disease should undergo BMD testing (DXA scan). Should it be routine for all? Or reserved for those with specific risk factors (e.g., age >50, postmenopausal women, history of fracture, advanced fibrosis)? Evidence-based screening criteria are urgently needed.

Underexplored role of IGF-1

Serum IGF-1 holds promise as a potential dual biomarker, reflecting both hepatic synthetic function and skeletal anabolic status. Its utility in stratifying fracture risk/ monitoring response to therapy in this population is not defined.

Limited data on therapeutic efficacy

The efficacy and safety profiles of osteoporosis medications have been established in post-menopausal and glucocorticoid-induced osteoporosis populations, but not specifically in MASLD/AFLD cohorts. Drug metabolism and potential hepatic side effects require specific evaluation.

Integrated care models

Hepatology clinics are not typically equipped to manage bone health, and endocrinology/bone clinics may not prioritize liver disease assessment. Multidisciplinary care pathways are lacking.[13]

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Addressing these gaps is imperative to improve long-term outcomes for the vast population affected by fatty liver disease.

Priority areas for future investigation include:

Prospective, comparative cohort studies

Well-designed, longitudinal studies directly comparing matched cohorts of MASLD and AFLD patients are needed. These should employ comprehensive phenotyping (detailed metabolic profile, liver histology or advanced imaging, BMD serial measurements, BTMs, IGF-1 levels) to delineate distinct and shared pathways of bone loss.

Mechanistic and translational research

Deeper exploration of the molecular signaling pathways is required. This includes studying how liver-derived factors (hepatokines) beyond IGF-1, such as fetuin-A, fibroblast growth factor 21 (FGF21), and selenoprotein P, influence bone metabolism. Investigating the gut-liver-bone axis, where dysbiosis and increased intestinal permeability may modulate systemic inflammation and nutrient absorption, is another promising frontier.

Diagnostic and biomarker development

Research should evaluate the cost-effectiveness of different screening strategies. The potential of combining non-invasive liver fibrosis scores (FIB-4) with IGF-1 levels or other biomarkers to create a "fracture risk in liver disease" (FRLD) score should be explored.

Interventional clinical trials

Randomized controlled trials are needed to: Assess the efficacy of established osteoporosis drugs (bisphosphonates, denosumab) specifically in MASLD and AFLD populations. Investigate whether therapies that improve liver disease (e.g., GLP-1 receptor agonists, SGLT2 inhibitors for MASLD; alcohol cessation programs for AFLD) concomitantly improve BMD and reduce fracture risk. Evaluate the role of IGF-1 replacement therapy, which has shown promise in other conditions with IGF-1 deficiency.

Guideline development and implementation science

National and international liver and bone societies must collaborate to formulate evidence-based consensus statements and clinical practice guidelines. Subsequently, research should focus on implementing these guidelines into real-world hepatology practice and measuring their impact on fracture rates and patient quality of life.

CONCLUSION

In conclusion, osteoporosis and increased fracture risk are prevalent, serious, and yet frequently overlooked complications of both MASLD and AFLD. The pathogenesis is rooted in a dysfunctional "osteo-hepatic axis," wherein the diseased liver fails in its endocrine roles-most notably the production of IGF-1 and activation of vitamin D-while simultaneously generating a pro-inflammatory, pro-resorptive systemic milieu. In AFLD, direct alcohol toxicity adds another damaging layer. The clinical consequence is a substantial, two-fold increase in fragility fractures, leading to pain, disability, loss of independence, and increased mortality.

Despite this compelling evidence, bone health remains a neglected aspect in the standard care model for fatty liver disease. There is a pressing need for a paradigm shift from a purely hepatocentric view to a holistic, patient-centric approach. This necessitates raising awareness among hepatologists, endocrinologists, and primary care physicians about this association. Future research must prioritize comparative studies and the development of practical screening and management algorithms. Ultimately, the integration of routine bone health assessment into MASLD/AFLD clinics is not merely an added option but an essential component of comprehensive care, crucial for mitigating the growing global burden of fractures in this vast and vulnerable patient population.

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