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Metabolic–Skeletal–Hepatic Crosstalk: Unravelling the Interrelationship Between Type 2 Diabetes Mellitus, Non-Alcoholic Fatty Liver Disease, and Bone Mineral Density

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ABSTRACT

Metabolic diseases are becoming a multisystem disease as opposed to a single-organ disease. There is a close interaction, signifying a complicated metabolic-skeletal-hepatic crosstalk that exists between type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and diminished bone mineral density (BMD). The pathophysiological basis of T2DM and NAFLD has much in common since they include insulin resistance, persistent low-grade inflammation, oxidative stress, disordered lipid metabolism, and so on, which can negatively affect bone remodeling and skeletal integrity. Ironically, BMD in people with T2DM is normal or sometimes elevated, but they have a much higher risk of fracture, which implies that the bone quality and not just its amount is impaired. In the same manner, NAFLD has been observed as a separate risk factor of diminished BMD and osteoporosis in accordance with disturbed secretion of hepatokines, the metabolism of vitamin ¯ D, and systemic inflammatory signals. The presence of hormonal mediators that include insulin, osteocalcin, adipokines, and fibroblast growth factors also indicate the possibility of endocrine control of glucose and energy homeostasis by the bone and liver. Knowledge of this interaction of the three organs is clinically relevant, since it highlights the necessity of combined screening and therapy that would concomitantly target the glycemic control, the condition of liver and bone preservation. The review of the up-to-date evidence on the common mechanisms, clinical associations, and therapeutic implications, as well as determining the main gaps in research, which could be addressed on a longitudinal and mechanistic level, contributes to holistic metabolic care.

Keywords*: Type 2 diabetes mellitus; Non-alcoholic fatty liver disease; Bone mineral density; Insulin resistance; Osteometabolic axis; Chronic inflammation*

INTRODUCTION

Global Burden of T2DM, NAFLD, and Osteoporosis

Type 2 diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD), and osteoporosis are all common metabolic disorders that affect the same people **[1].** The International Diabetes Federation says that in 2021, more than 537.3 million adults around the world had diabetes. More than 90% of them had T2DM, and by 2045, the number is expected to grow a lot **[2].** NAFLD is now the most common long-term liver disease, affecting about 25–30% of adults around the world. People who are overweight or have type 2 diabetes (T2DM) are much more likely to get it **[3,4].** Osteoporosis and low bone mineral density (BMD) are two of the main reasons why older people have fragile bones, become disabled, and have to pay for medical care **[5,6].** These conditions often happen at the same time, which makes them worse and shows how important it is to get a full metabolic evaluation **[7].**

Growing Proliferation of Multimorbidity and Metabolic Clustering

Epidemiological studies from the past few years show that multimorbidity is becoming more common. This is when metabolic diseases come together in people instead of being separate diseases **[1,8].** Insulin resistance can have an effect on the liver and the rest of the body. For example, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) are two examples of this. Metabolic effects are also becoming more well-known, such as skeletal problems that make bones weaker and increase the risk of fractures **[9].** This clustering can happen because of obesity, not getting enough exercise, long-term low-grade inflammation, oxidative stress, and problems with the endocrine system. These factors make it more difficult to identify individuals at risk and develop effective treatment strategies for the disease **[1,10].**

Organ-to-Organ Crosstalk in Metabolic Disease

A systems-based framework emphasizing inter-organ communication has supplanted conventional organ-centric models of metabolic disease **[11].** The liver, pancreas, fat tissue, skeletal muscle, and bones all talk to each other in a way that keeps metabolic homeostasis stable **[12].** Bone is an endocrine organ because it releases osteocalcin, which affects how glucose and lipids are broken down. The liver is the main metabolic hub. Problems with signaling between organs can cause and make metabolic diseases worse **[11,14].**

Skeletal–Hepatic–Metabolic Integrity

Doctors often treat T2DM, NAFLD, and bone health separately, even though there is more and more evidence linking these conditions **[1,15].** This method of dividing things up could cause people to forget about how metabolic diseases make bones weaker and how liver and blood sugar problems affect bone quality all over the body. We need a unified metabolic-skeletal-hepatic framework **[16]** to get better at figuring out how to assess, avoid, and treat risk.

Conceptual Framework: The Metabolic–Skeletal–Hepatic Axis

Definition of Inter-Organ Crosstalk

Inter-organ crosstalk is the biochemical communication between different organs in the body that regulates metabolism, energy balance, and tissue health **[11].** Hormones, cytokines, adipokines, myokines, and metabolites control this network, which includes the liver, bones, pancreas, adipose tissue, and skeletal muscle **[13].** Disruption of this network allows T2DM, NAFLD, and skeletal problems to coexist **[1,9].**

Endocrine Signaling in the Axis

The liver releases hepatokines like fetuin-A and fibroblast growth factor-21 (FGF-21), which change how sensitive insulin is, how much inflammation there is, and how bones grow **[17,18].** Osteocalcin is a hormone that bones release that controls how much insulin is released, how sensitive cells are to insulin, and how the liver breaks down fats **[11, 19].** High levels of TNF-α, IL-6, and CRP are signs of chronic low-grade inflammation, which is linked to hepatic steatosis, insulin resistance, and problems with bone remodeling **[1,20].**

Bidirectional Communication Between Glucose Metabolism, Bone, and Liver

Hepatic insulin resistance alters the transport of glucose and lipids, resulting in systemic hyperglycemia and lipotoxicity that impede osteoblast differentiation and degrade bone quality **[2,21].** On the other hand, osteocalcin from bones makes insulin and pancreatic β-cells work better, which has an indirect effect on how much fat builds up in the liver **[14].** The breakdown of this two-way signaling in T2DM and NAFLD leads to a bad cycle of worse liver disease, worse glycemic control, and weaker bones **[1,14].**

Shared Molecular Mediators

Insulin resistance is the main molecular node that controls how the body breaks down lipids, how osteoblasts work, and how glucose is taken up by the body **[22].** Leptin and adiponectin are two adipokines that help control inflammation in the liver and bone turnover. On the other hand, oxidative stress and problems with mitochondria can hurt cells in the liver, bone, and pancreas **[1,23].** These shared mediators support the idea of a single metabolic–skeletal–hepatic axis rather than separate disease processes **[Table No. 1]. [9]**

Table No. 1: Conceptual Framework of the Metabolic–Skeletal–Hepatic Axis

An interconnected metabolic network links insulin resistance, chronic inflammation, hormonal signaling, oxidative stress, and lipid dysregulation, contributing simultaneously to NAFLD progression, skeletal fragility, and T2DM complications
NAFLD progression, skeletal fragility, and T2DM complications

Component / Domain	Liver (NAFLD)	Bone (Skeletal System)	Glucose Metabolism (T2DM)
Inter-Organ Crosstalk	Hepatic insulin resistance	Hepatokines (Fetuin-A, FGF21) influence bone cells	Insulin resistance
Endocrine & Paracrine Signaling	Hepatokines (Fetuin-A, FGF21)	Inflammatory cytokines (TNF-α, IL-6, CRP)	Hyperglycemia; Advanced Glycation End-products (AGEs)

Bidirectional Metabolic Communication	Chronic inflammation (TNF-α, IL-6, CRP)	Low bone turnover; AGE accumulation	Impaired β-cell function
Shared Molecular Mediators	Altered lipid metabolism	Altered bone microarchitecture	Impaired β-cell function & glucose dysregulation

Type 2 Diabetes Mellitus and Bone Health

Alterations in Bone Mineral Density

Changes in Bone Mineral Density. Individuals with T2DM exhibit an atypical skeletal phenotype characterized by normal or elevated bone mineral density (BMD) coupled with a significantly increased fracture risk, particularly in the hip and spine **[2,24].** This shows that the main reason why people with diabetes have weak bones is because of the quality of their bones, not the amount of bone they have **[25].** Individuals with long-term type 2 diabetes mellitus (T2DM) exhibit increased cortical bone porosity, reduced cortical bone thickness, and compromised microarchitecture, despite maintaining a stable areal bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA). These structural issues increase the risk of bone fractures on DXA **[26,2].** These structural abnormalities explain increased fracture susceptibility **[Table No.2] [24].**

Table No. 2: Type 2 Diabetes Mellitus and Bone Health: The BMD Paradox

Domain	Key Factors / Mechanisms	Impact on Bone
Type 2 Diabetes Mellitus (T2DM)	• Chronic hyperglycemia • Insulin resistance • Oxidative stress • Advanced glycation end-products (AGEs)	Initiates metabolic and vascular changes affecting skeletal tissue
AGE Accumulation	• Impaired collagen cross-linking • Reduced bone elasticity	Increased bone brittleness despite normal density
Low Bone Turnover	• Suppressed osteoblast differentiation • Reduced osteocalcin and P1NP	Decreased bone formation and remodeling capacity
Microvascular Dysfunction	• Impaired nutrient and oxygen delivery to bone	Poor bone quality and delayed repair
Skeletal Outcomes	• Normal or increased BMD (DXA) • Increased cortical porosity • Reduced cortical thickness • Altered trabecular microarchitecture • Increased hip and vertebral fracture risk	**Preserved/elevated BMD with compromised bone quality and higher fracture susceptibility**

Pathophysiological Mechanisms

Chronic Hyperglycemia and Advanced Glycation End-Products

Prolonged elevated blood sugar levels can lead to non-enzymatic glycation of bone collagen. This causes advanced glycation end-products (AGEs) to form, which make collagen less flexible and bones weaker without changing their mineral density (BMD) **[27,2].** Individuals with diabetes exhibiting elevated levels of AGEs are at an increased risk of sustaining fractures **[27].**

Defective Osteoblast Activity and Low Bone Turnover

T2DM is characterized by sluggish bone turnover and impaired osteoblast activity. This is because high blood sugar levels, oxidative stress, and insulin resistance make it harder for osteoblasts to tell the difference between cells **[2].** Osteocalcin and P1NP, which are markers of bone formation, are lower, which makes bones weaker even though BMD stays the same **[27,28].**

Bone Quality and Microvascular Complications

Microvascular Issues and Bone Quality Diabetes-related microvascular issues, like retinopathy, nephropathy, and neuropathy, make bones even weaker **[2].** Neuropathy makes it more likely that you will fall, and a lack of blood flow to your bones makes it harder for oxygen and nutrients to reach them. Both of these things make it more likely that a fracture will happen than just skeletal factors **[29].**

Non-Alcoholic Fatty Liver Disease and Skeletal Metabolism

NAFLD as a Systemic Metabolic Disorder

NAFLD is now known to be a systemic metabolic disorder that affects the whole body **[5,6].** It includes some conditions, such as simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is closely linked to insulin resistance and is the liver's way of showing that someone has metabolic syndrome **[6].**

NAFLD and Bone Mineral Density

Clinical studies indicate that individuals with non-alcoholic fatty liver disease (NAFLD) exhibit diminished bone mineral density (BMD) and an elevated risk of developing osteopenia and osteoporosis, irrespective of their age, body mass index (BMI), or other osteoporosis risk factors **[20,30].** The severity of the disease impacts the bones, with NASH and fibrosis increasing the likelihood of fractures **[48].**

Mechanistic Links Between NAFLD and Bone Health

On a mechanical level, NAFLD and bone health are linked because high levels of hepatokines like fetuin-A stop osteoblast differentiation, and high levels of FGF-21 are linked to lower bone mass and turnover **[17,18].** A lot of people with NAFLD don't get enough vitamin D because their liver doesn't work well, and they store too much fat. This makes it even harder for calcium levels to stay stable and bones to grow **[25,46].** Chronic liver inflammation stops osteoblast activity and starts osteoclastogenesis, which causes bone loss **[Table no.3]. [48].**

Table No. 3: Non-Alcoholic Fatty Liver Disease (NAFLD) and Skeletal Metabolism

Domain / Process	Liver-Related Changes (NAFLD)	Key Molecular / Pathophysiological Mechanisms	Skeletal Consequences
NAFLD as a Systemic Metabolic Disorder	Hepatic steatosis → NASH → fibrosis	Progressive metabolic and inflammatory burden	Reduced bone mineral density
Association with Metabolic Syndrome	Insulin resistance and de novo lipogenesis	Fetuin-A–mediated inhibition of insulin signaling	Increased prevalence of osteopenia and osteoporosis
NAFLD and Bone Mineral Density	Increased hepatokine secretion	FGF21 upregulation affecting bone turnover	Reduced bone formation
Severity-Dependent Skeletal Effects	Advanced fibrosis and severe steatohepatitis	Sustained systemic inflammation	Increased fracture risk (severity-dependent)
Hepatokines and Endocrine Signaling	Elevated fetuin-A and FGF21 levels	Suppression of osteoblast differentiation	Low bone turnover
Vitamin D Metabolism Dysregulation	Impaired hepatic vitamin D hydroxylation	Disrupted calcium–parathyroid hormone axis	Impaired bone mineralization
Hepatic Inflammation and Bone Remodeling	Chronic low-grade hepatic inflammation	Elevated TNF-α and IL-6 promoting osteoclastogenesis	Net bone resorption
Progressive hepatic steatosis and inflammation in NAFLD exert systemic endocrine and inflammatory effects that impair bone remodeling, reduce bone mineral density, and increase skeletal fragility.			

Shared Pathophysiological Pathways

Insulin Resistance

Insulin resistance drives hepatic steatosis, suppresses osteoblast function, and disrupts adipose tissue metabolism, creating a unified metabolic disturbance affecting liver, bone, and glucose homeostasis **[Table No.4]. [1,11].**

Table No.4: Shared Pathophysiological Pathways Linking T2DM, NAFLD, and Bone Mineral Density

System / Organ	Key Features / Mechanisms	Consequences
Liver (NAFLD)	• De novo lipogenesis • Reduced lipid oxidation • Hepatic steatosis → NASH • Pro-inflammatory cytokine release	Promotes systemic inflammation and metabolic dysregulation
Central Node – Insulin Resistance	• Impaired insulin signaling • Chronic low-grade inflammation (TNF-α, IL-6, CRP)	Drives multisystem metabolic impairment

Bone (Skeletal System)	• Suppressed osteoblast differentiation • Low bone turnover • Altered trabecular and cortical microarchitecture	Reduced bone quality and increased fragility risk
Glucose Metabolism (T2DM)	• Chronic hyperglycemia • Impaired β-cell function • Systemic insulin resistance	Sustained metabolic imbalance and AGE formation
Shared Mechanistic Pathways	• Chronic inflammation (TNF-α, IL-6, CRP) • Adipokines & myokines (leptin, adiponectin, irisin) • Oxidative stress & mitochondrial dysfunction • Reactive oxygen species generation	Joint impairment of hepatic metabolism, skeletal integrity, and glucose homeostasis

Chronic Low-Grade Inflammation

Long-term low-grade inflammation: An enduring elevation in TNF-α, IL-6, and CRP results in bone resorption and inhibits bone formation, thereby diminishing bone quality without altering BMD **[1,7].**

Adipokines and Myokines

Leptin, adiponectin, and irisin are myokines and adipokines that help the liver, bones, and muscles talk to each other. On the other hand, oxidative stress and mitochondrial dysfunction hurt the cells in metabolic tissues **[9,23].**

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress can happen when mitochondria don't work properly. Long-term inflammation and insulin resistance can also lead to oxidative stress. Reactive oxygen species damage the mitochondria in pancreatic β-cells, liver cells, and osteoblasts. This slows down the process of turning food into energy and speeds up the death of cells. Oxidative stress slows down the growth of osteoblasts and speeds up the activity of osteoclasts in bones. This makes the bones weaker and changes their microarchitecture. A common way that metabolic disease hurts bone health is by causing mitochondrial dysfunction **[23].**

Role of Bone as an Endocrine Organ

Osteocalcin and Glucose Metabolism

The bone is an endocrine organ, which means it has a direct effect on how the body uses energy. Osteoblasts make osteocalcin, which is a protein that doesn't contain collagen and helps keep blood sugar levels stable. Undercarboxylated osteocalcin helps pancreatic β-cells grow and make insulin. It also makes tissues that are not in the center of the body, like fat and skeletal muscle, more sensitive to insulin **[27,29].** People with T2DM often have low levels of osteocalcin in their blood. This is linked to poor blood sugar control, slow bone turnover, and problems with the skeleton.

Bone-Derived Signals Affecting Hepatic Lipid Accumulation

Osteocalcin, which comes from bones, controls how sensitive the liver is to insulin and how it breaks down fats. This has an indirect effect on how much triglyceride builds up in the liver **[9,11].** Hepatic insulin resistance increases when osteocalcin signaling diminishes. This makes hepatocytes make new lipids and store triglycerides **[9,13].** We can learn more about how skeletal endocrine signaling affects the growth and progression of non-alcoholic fatty liver disease (NAFLD) by looking at how adipocytes from bone marrow, signaling pathways linked to osteoblasts, and the metabolism of lipids in the liver work together **[11,14].**

Feedback Loops Between Bone and Metabolic Organs

The pancreas, liver, fat tissue, and skeletal muscle all work together in complicated ways to control how bones work with hormones **[11].** When insulin tells osteoblasts to, they start making osteocalcin. This makes the pancreas make more insulin and makes insulin work better in other parts of the body. This starts a cycle of positive feedback between how glucose is used and how bones are made **[9,13].** When insulin isn't working right, breaking this loop lowers the activity of osteocalcin, which makes it harder to keep blood sugar levels stable and makes the liver store more fats **[9,11].** These interactions show how important it is to keep your bones healthy in order to keep your metabolism in check all over your body. They also show that bone is not just a passive target organ in metabolic disease; it is an active participant **[Table No. 5] [11,14].**

Table No. 5: Shared Pathophysiological Pathways Linking T2DM, NAFLD, and Bone Mineral Density

System / Organ	Key Features / Mechanisms	Consequences
Liver (NAFLD)	• De novo lipogenesis • Reduced lipid oxidation • Hepatic steatosis → NASH • Pro-inflammatory cytokine release	Promotes systemic inflammation and metabolic dysregulation

Central Node – Insulin Resistance	• Impaired insulin signaling • Chronic low-grade inflammation (TNF-α, IL-6, CRP)	Drives multisystem metabolic impairment
Bone (Skeletal System)	• Suppressed osteoblast differentiation • Low bone turnover • Altered trabecular and cortical microarchitecture	Reduced bone quality and increased fragility risk
Glucose Metabolism (T2DM)	• Chronic hyperglycemia • Impaired β-cell function • Systemic insulin resistance	Sustained metabolic imbalance and AGE formation
Shared Mechanistic Pathways	• Chronic inflammation (TNF-α, IL-6, CRP) • Adipokines & myokines (leptin, adiponectin, irisin) • Oxidative stress & mitochondrial dysfunction • Reactive oxygen species generation	Joint impairment of hepatic metabolism, skeletal integrity, and glucose homeostasis

Clinical Evidence from Observational and Epidemiological Studies

Evidence from Cross-Sectional and Cohort Studies

Numerous observational and epidemiological studies examining both individuals and populations indicate that type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and compromised bone health frequently co-occur. Cross-sectional studies show that people with T2DM can get fragile fractures even if their bone mineral density (BMD) is normal or high. This means that bones are weak because of their quality, not their mass **[1,6,10,18,19,30–32,34].**

Numerous observational and epidemiological studies examining both individuals and populations indicate that type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and compromised bone health frequently co-occur. Cross-sectional studies show that people with T2DM can get fragile fractures even if their bone mineral density (BMD) is normal or high. This means that bones are weak because of their quality, not their mass **[1,6,10,18,19,30–32,34].**

Similarly, population-based and cohort studies demonstrate that individuals with NAFLD exhibit reduced BMD and an elevated risk of osteopenia and osteoporosis compared to metabolically healthy individuals **[11–15,24,26,33–36].** Meta-analyses and systematic reviews indicate that NAFLD independently elevates the risk of fractures, even when considering body mass index and metabolic factors **[13,33].** Longitudinal cohort studies indicate that insulin resistance and hepatic steatosis can serve as predictors of future bone integrity impairment. This backs up the idea of a common metabolic-skeletal-hepatic axis **[3–5,7,35,37].**

Trends Based on Gender and Age

The connection between metabolic disease and bone health is very different for men and women of different ages. Women with T2DM or NAFLD are much more likely to get osteoporosis and weak bones after menopause. This is likely because their estrogen levels are low, they don't respond well to insulin, and they have long-term inflammation **[12,15,35,48].**

Older adults with metabolic diseases are more likely to have bone problems because their remodeling is not working well and their mitochondria are not working as well as they should. On the other hand, younger people with early-onset T2DM may have normal bone mineral density (BMD) but show early signs of microarchitectural deterioration. This means that metabolic bone damage happens before the signs of osteoporosis show up **[25,35,38].**

Ethnic and Regional Disparities

The correlation between metabolism and bone structure significantly varies among distinct racial and regional populations. Individuals from South and East Asia, such as Indians, develop T2DM and NAFLD at lower body mass indices and at younger ages compared to those from Western regions. This is because they have more visceral fat and are more likely to have genetic risk factors **[35–37].**

Epidemiological data from India indicate that diabetes and non-alcoholic fatty liver disease (NAFLD) are rapidly increasing in prevalence. There exists a significant yet underreported issue concerning low bone mineral density (BMD) and vitamin D deficiency **[36,37,39,40].** Research from different parts of Asia shows that people with NAFLD have lower BMD and a higher risk of breaking bones. This illustrates the significance of tailored screening and clinical guidelines for each ethnicity **[12,15,33,36,47].**

Diagnostic and Therapeutic Implications

Clinical Screening Considerations

When doing clinical screening, it's important to do a thorough evaluation early on to figure out the fracture risk in people with T2DM and NAFLD because standard tools may not give an accurate picture of the risk. Dual-energy X-ray absorptiometry (DXA) often gives people with T2DM a higher estimate of their bone strength because their BMD stays the same or goes up even though their bone quality is bad **[6,9].** When looking at DXA results, it's important to think about clinical risk factors like how long the disease has been going on, how well blood sugar is controlled, a history of falls, and microvascular complications **[6,24].** Biochemical markers of bone turnover, such as osteocalcin and procollagen type 1 N-terminal propeptide (P1NP), provide additional insights, especially in T2DM, which is marked by reduced bone turnover **[16,17].** People with NAFLD are more likely to get osteoporosis and fractures, so it's important to check their vitamin D levels, liver function, and inflammatory markers **[12,25,31].**

Therapeutic Interactions

Diabetic Drugs and Bone

Different types of diabetes medications have different effects on bone health. Thiazolidinediones reduce the formation of new bone and increase the risk of fractures, particularly in women who have undergone menopause. This is because they make it more likely for mesenchymal stem cells to become fat cells **[39,41].** Metformin, however, appears to exert no influence on the skeletal system and may even confer protection. This is likely because it makes insulin work better and reduces inflammation throughout the body **[6,9].** Recent evidence indicates that incretin-based therapies may positively influence bone metabolism; however, data regarding long-term fracture outcomes remain limited **[40,42].**

NAFLD Treatment and Bone

Two non-drug treatments for NAFLD that indirectly improve bone health by lowering systemic inflammation and making insulin resistance better are NAFLD treatment and bone exercise and losing weight **[41,43–45].** However, rapid or excessive weight loss may adversely affect bone mass, necessitating careful monitoring of calcium and vitamin D homeostasis.

Lifestyle Interventions: Diet, Exercise, and Weight Loss

One of the best things you can do to deal with metabolic-skeletal disease is to change how you live. Weight-bearing exercise and resistance training put stress on bones, which helps them grow. They also stop fat from building up in the liver and make insulin work better **[43–46].** You need to get enough protein, calcium, and vitamin D to keep your bones healthy, but you shouldn't eat too few calories **[37,46].**

Research Gaps and Future Directions

Lack of Longitudinal and Mechanistic Human Studies

Even though the metabolic–skeletal–hepatic axis is getting more attention, most of the evidence comes from cross-sectional and short-term observational studies, which makes it hard to conclude what causes what **[1,3,37].** Longitudinal studies that look at glycemic control, the severity of liver disease, and the microarchitecture of bones over time are very important in groups with a lot of different ethnic groups **[36,39].** There aren't many mechanistic studies on humans, and most of them are based on animal models. This illustrates the significance of conducting integrative research that amalgamates advanced imaging, biochemical biomarkers, and tissue-level analyses **[2,10].**

Limited Interventional Trials Addressing All Three Systems

Only a small number of interventional trials look at metabolic, hepatic, and skeletal outcomes at the same time. Trials for type 2 diabetes look at glycemic endpoints, trials for nonalcoholic fatty liver disease look at liver histology, and trials for osteoporosis look at lowering the risk of fractures. This makes the proof less clear **[3,37].** We really need randomized controlled trials with composite endpoints, like hepatic steatosis, bone turnover markers, and fracture outcomes.

Integrated Clinical Guidelines and Precision Medicine

Current clinical practice treats T2DM, NAFLD, and osteoporosis as separate entities, risking under-recognition of skeletal fragility in metabolic disease. Integrated, evidence-based guidelines incorporating routine bone health assessment in metabolic disorders and hepatic considerations in osteoporosis management are warranted **[39].**

Recent advancements in precision medicine facilitate the identification of individuals at elevated risk through the utilization of multisystem biomarkers indicative of insulin resistance, inflammation, hepatokine activity, and bone turnover **[10,16,17].** It is essential to evaluate these methodologies on large, diverse populations to formulate individualized prevention and treatment strategies **[10,16,17,31].**

Conclusion

The growing amount of evidence in this review highlights the presence of a highly interrelated metabolic- skeletal- hepatic axis that links type 2 diabetes mellitus (T2DM), non- alcoholic fatty liver disease (NAFLD), and bone mineral density (BMD). There is the appearance of insulin resistance as the primary pathological mechanism, which also affects the impairment of hepatic lipid processing, dysregulation of bone remodeling, and worsens glycemic control. Such metabolic abnormality is further aggravated by chronic low-grade inflammation, oxidative stress, and disregarded of endocrine signaling by hepatokines, adipokines, myokines, and bone-derived hormones like osteocalcin. All of these processes can explain why patients with T2DM and NAFLD can have preserved or even increased BMD but still are at risk of experiencing skeletal fragility or fracture (Karsenty et al., 2019; Lonardo et al., 2021). Besides, the evidences dispute the conventional organ-based disease patterns and present the need to view metabolic diseases as multisystem disorders. The liver, bones, and glucose-controlling organs do not work in a vacuum; nonetheless, they mutually communicate with each other which defines the overall metabolism and bone well-being. The inability to identify this interdependence would lead to unsuccessful diagnosis of bone disease in the patients with metabolism and poor decision-making in therapy.Clinically, these findings justify holistic approaches of managing patients using glycaemic control, liver care and skeletal assessment. It is necessary to perform regular assessment of the bones of people with T2DM and NAFLD, precautiously choose the antidiabetic treatments with taking into account their effects on bones, and focus on lifestyle changes that would be favorable to all three systems. Researchwise, longitudinal, mechanistic, and interventional designs that can embody

multisystem outcomes and could lead to the design of integrated clinical guidelines among others should be given priority in future studies. The future of risk prediction and personalised care of this growing group of multi-organ metabolically complex patients should be further directed towards precision medicine engagements, which include the employment of multi-organ biomarkers.

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