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Review Article

Decoding the Metabolic Dialogue of the "Liver–Bone Axis": The Necessity of Establishing Animal Models to Investigate the Mechanisms Linking Nonalcoholic Steatohepatitis (NASH) and Osteo porosis

Chi-Ming Chiang, MD, PhD[1,2]

[1]*Center for General Education, Chung Yuan Christian University, Taiwan, China*
[2]*Department of Orthopedics, Chon-Inn Hospital, Chon-Inn Medical Corporation, Taiwan, China*

***Corresponding author**
Chi-Ming Chiang, MD, PhD Center for General Education, Chung Yuan Christian University, Taiwan, China Department of Orthopedics, Chon-Inn Hospital, Chon-Inn Medical Corporation, Taiwan, China

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Abstract

Background: The global rise in metabolic syndrome and obesity has turned the coexistence of nonalcoholic fatty liver disease (NAFLD)—particularly its progressive inflammatory phenotype, nonalcoholic steatohepatitis (NASH)—and osteoporosis into an increasingly common clinical scenario. Multiple clinical studies since 2012 have reported that individuals with NAFLD/NASH, including postmenopausal women and obese children, tend to exhibit lower bone mineral density (BMD) and higher fracture risk, suggesting a pathological metabolic linkage within a "liver–bone axis" [1,2]. Yet, human epidemiology is often constrained by cross-sectional designs and residual confounding (e.g., lifestyle behaviors and medication exposure), limiting causal inference.

Purpose: This review synthesizes the current clinical and mechanistic evidence connecting NAFLD/NASH to impaired bone health, highlights the roles of insulin resistance and liver-derived insulin-like growth factor-1 (IGF-1), and critically appraises existing genetic, dietary, and combination animal models for their suitability in modeling NASH-associated bone loss.

Methods: We present a narrative synthesis of human observational studies and mechanistic literature, followed by a structured appraisal of commonly used rodent models of NASH. Model suitability is evaluated through a dual lens: (a) metabolic phenotype (obesity and insulin resistance) and (b) liver histopathology (steatosis, inflammation, and fibrosis), with explicit attention to confounders that are especially consequential for bone research (notably weight loss and malnutrition).

Results: A convergent body of evidence supports an association between NAFLD/NASH and adverse skeletal outcomes. Mechanistically, hepatic dysfunction may reduce circulating IGF-1—an essential anabolic signal for osteoblast function and type I collagen synthesis [3–5]—while systemic inflammation and insulin resistance may further tilt bone remodeling toward net loss. Importantly, not all NASH animal models are equally informative for the liver–bone axis: models that induce severe steatohepatitis at the cost of profound weight loss can obscure whether bone loss is driven by liver inflammation or by catabolic undernutrition.

Conclusions/Implications for Practice: A We argue that establishing a translationally faithful NASH animal model that mirrors key human features—obesity, insulin resistance, and fibrotic liver injury—is a critical foundation for dissecting causality, mapping temporal trajectories of bone loss, and testing integrated interventions. For nursing and interdisciplinary care, recognizing skeletal vulnerability in NAFLD/NASH may support proactive risk assessment, patient education, lifestyle counseling, and fall-prevention strategies alongside liver-directed management.

Keywords: Nonalcoholic steatohepatitis (NASH); osteoporosis; liver–bone axis; insulin resistance; IGF-1; animal models

Introduction: A Hidden Network of Metabolic Comorbidity

In contemporary medicine, organs are no longer viewed as isolated islands but as interdependent nodes of an endocrine–immune–metabolic network. The liver, as a central hub for lipid and glucose flux, communicates with distant tissues through hepatokines and growth factors; conversely, the skeleton is increasingly recognized as an endocrine organ whose remodeling dynamics respond to—and shape—systemic metabolism. Against this background, insulin resistance has become a defining global health challenge, and NASH has emerged as one of the most prevalent chronic liver diseases. Of growing clinical relevance is the observation that NAFLD/NASH frequently coexists with compromised bone health. Since 2012, multiple studies have shown that patients with NAFLD/NASH—including postmenopausal women and obese children—have significantly

lower BMD than metabolically healthier counterparts [1,2].

These observations support a central hypothesis of the liver–bone axis: hepatic inflammation is not confined to the liver but may "export" systemic signals that influence skeletal remodeling. Liver-derived IGF-1 is a compelling mechanistic bridge. The liver is the primary source of circulating IGF-1, and IGF-1 promotes osteoblast activity, including type I collagen synthesis and maintenance of bone mass [3,4]. When hepatocytes are injured by steatosis, lipotoxicity, and inflammation, IGF-1 production may decline, weakening anabolic support for bone formation [5]. Thus, elucidating how NASH perturbs bone metabolism has urgent implications for fracture prevention and quality of life in patients with chronic metabolic disease.

The Clinical Reality of Hepatic Osteodystrophy: A Surgeon's Perspective

Before delving into molecular mechanisms, it is crucial to confront the clinical phenotype of end-stage liver disease in orthopedics. As illustrated in Figure 1, patients with severe hepatic dysfunction present with a distinct "yellow bone" phenotype. This is not merely a cosmetic discoloration due to bilirubin deposition; it represents a fundamental compromise in material competence.

In our clinical observations derived from treating hip fractures in cirrhotic patients (Child-Pugh Class B/C), we frequently encounter a "stiffness cliff"—a profound loss of trabecular connectivity and cortical thickness that makes surgical fixation precarious. These patients, often presenting with profound jaundice (hyperbilirubinemia), exhibit fracture patterns and healing failures that mimic those seen in patients undergoing long-term chemotherapy. This clinical reality forces a critical question: Is the hepatic osteodystrophy observed in NASH and cirrhosis simply a result of nutritional deficiency (Vitamin D, Calcium), or is there a more active, systemic suppression of bone regeneration? The "yellow bone" suggests that the toxic metabolic milieu of the failing liver may be actively inhibiting the osteogenic machinery.

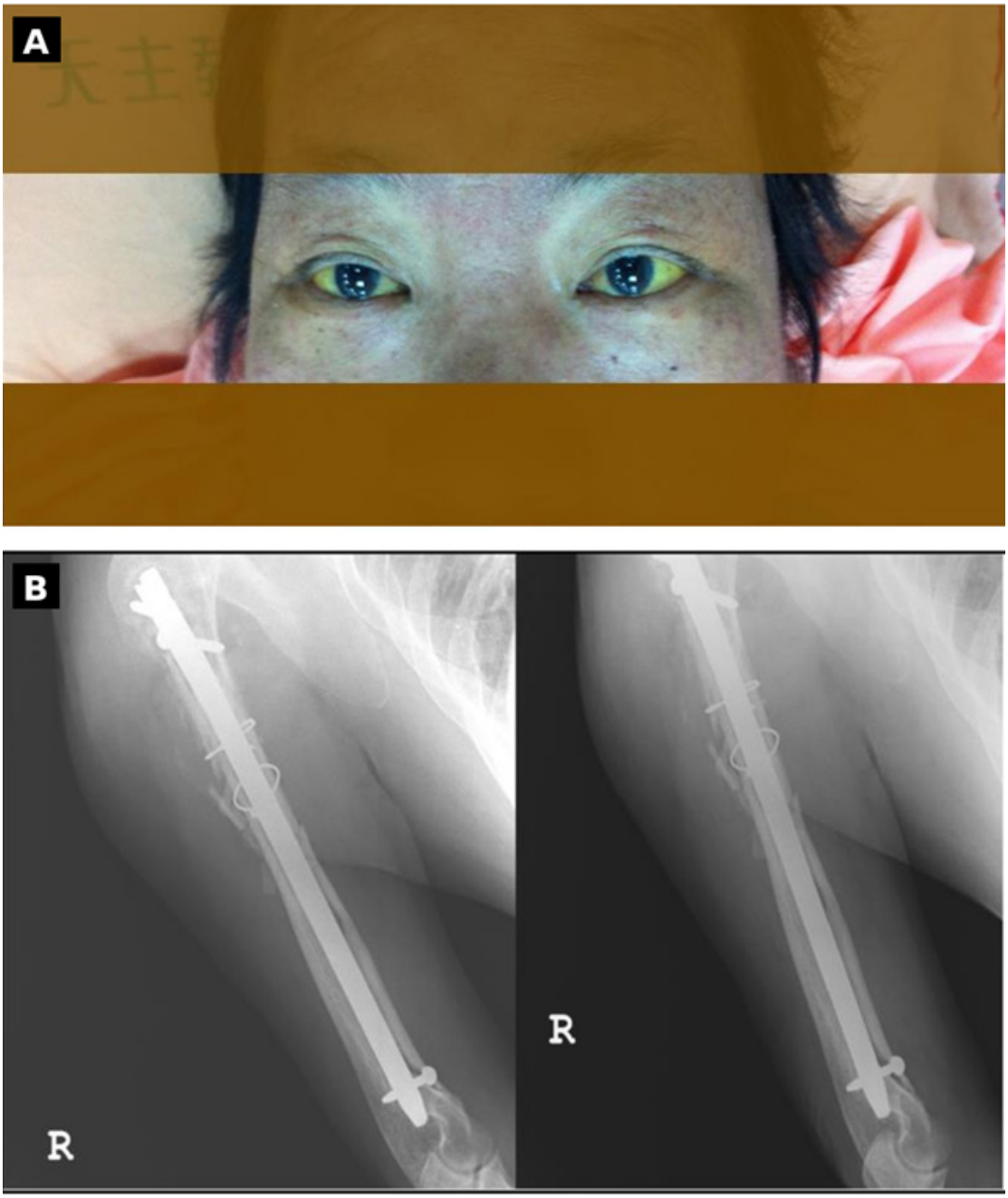

Figure 1. Clinical reality of advanced liver disease relevant to hepatic osteodystrophy: **(A)** marked jaundice (hyperbilirubinemia). **(B)** impaired fracture healing after internal fixation at 6 months (no clear callus).

Clinical Challenge: The Ceiling of Epidemiology for Causal Inference

Clinical observational studies have provided important signals. For example, a 2013 study in a Chinese adult population reported significantly lower hip and femoral neck BMD among individuals with NAFLD and suggested that insulin resistance plays a key mediating role [6]. Nevertheless, several structural limitations constrain what epidemiology alone can resolve.

First, cross-sectional designs capture BMD at a single time point and cannot directly quantify the rate or trajectory of bone loss. Second, residual confounding is difficult to eliminate, because caloric intake, physical activity, alcohol exposure, smoking, and medication use often co-vary with both liver fat and bone health. Third, NAFLD is frequently diagnosed with ultrasound or surrogate indices in routine practice, which introduces measurement error and obscures histological certainty; by contrast, liver biopsy—while more definitive—is not routinely available for population studies. Consequently, although the association between NAFLD/NASH and low BMD is increasingly consistent, the directionality and mechanistic drivers remain incompletely established.

To move from association to mechanism, the field must shift from clinical observation to controlled experimental interrogation. Animal models provide the methodological leverage needed to isolate specific variables, define temporal sequences, and test interventions—capabilities that are ethically or logistically unattainable in humans.

Mechanistic Hypotheses: Insulin Resistance and IGF-1 as Dual Axes of Crosstalk

A mechanistic framework linking NASH to osteoporosis can be conceptualized as a dual-pathway model. On the "supply-side," hepatic dysfunction may lower circulating IGF-1, thereby impairing osteoblast function and bone matrix synthesis [3–5]. On the "damage-side," chronic low-grade inflammation—common in NASH and insulin resistance—may amplify osteoclastogenesis and accelerate bone resorption. These pathways are not mutually exclusive; instead, they likely act in concert, producing net skeletal fragility over time.

Insulin resistance may be more than a shared background trait; it can plausibly function as a biological amplifier. Insulin signaling influences osteoblast metabolism, while hepatic insulin resistance promotes steatosis, inflammatory signaling, and fibrogenesis—processes that can disrupt endocrine outputs such as IGF-1. In this view, the liver–bone axis becomes a clinically relevant "metabolic dialogue" in which hepatic injury and skeletal remodeling are coupled through endocrine and immune mediators. Testing the relative contribution of IGF-1 deficiency versus inflammatory cytokine-driven bone resorption (e.g., TNF-α and IL-6) requires experimental systems in which metabolic state, liver pathology, and body weight can be disentangled.

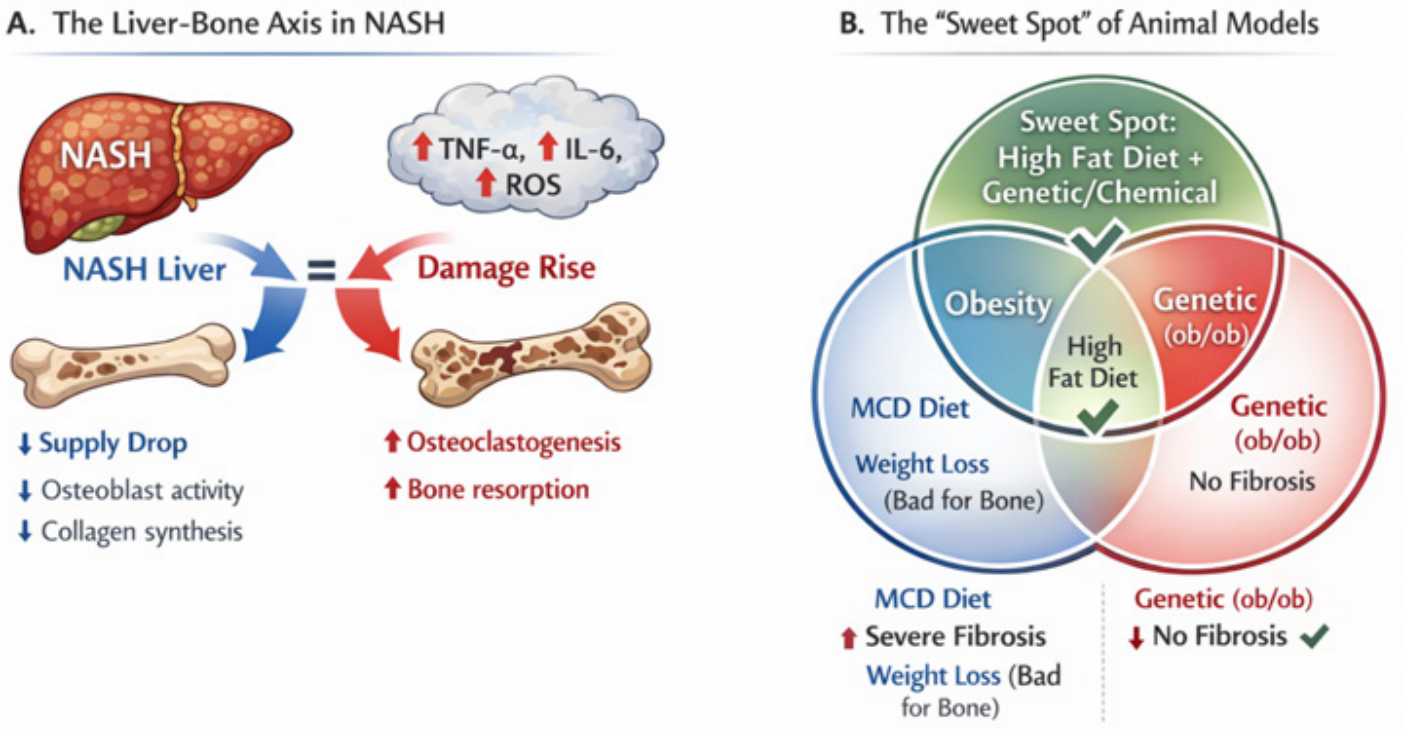

Figure 2. The liver–bone axis in NASH and the "sweet spot" of animal models. **(A)** In NASH, hepatic dysfunction may reduce circulating IGF-1 ("supply drop"), weakening osteoblast activity and collagen synthesis, while inflammatory mediators (e.g., TNF-α, IL-6, and reactive oxygen species [ROS]) increase ("damage rise"), promoting osteoclastogenesis and bone resorption.
(B) Conceptual comparison of commonly used NASH models for bone-focused research: the methionine- and choline-deficient (MCD) diet yields severe fibrosis but induces weight loss (a major confounder for bone outcomes); genetic leptin-pathway models (e.g., ob/ob) generate obesity but often lack fibrosis; combination approaches (e.g., high-fat diet plus genetic/chemical predisposition) represent a pragmatic "sweet spot" that more closely recapitulates human NASH with obesity, insulin resistance, and fibrotic injury.

Bridging the Gap: The Hypothesis of Metabolic Tyrosine Kinase Inhibition (MTKI)

While inflammation and insulin resistance (as discussed above) explain part of the bone loss in NASH, they do not fully account for the profound "anabolic block" observed in advanced liver disease. Drawing from systems biology, we propose a novel theoretical framework: Metabolic Tyrosine Kinase Inhibition (MTKI).

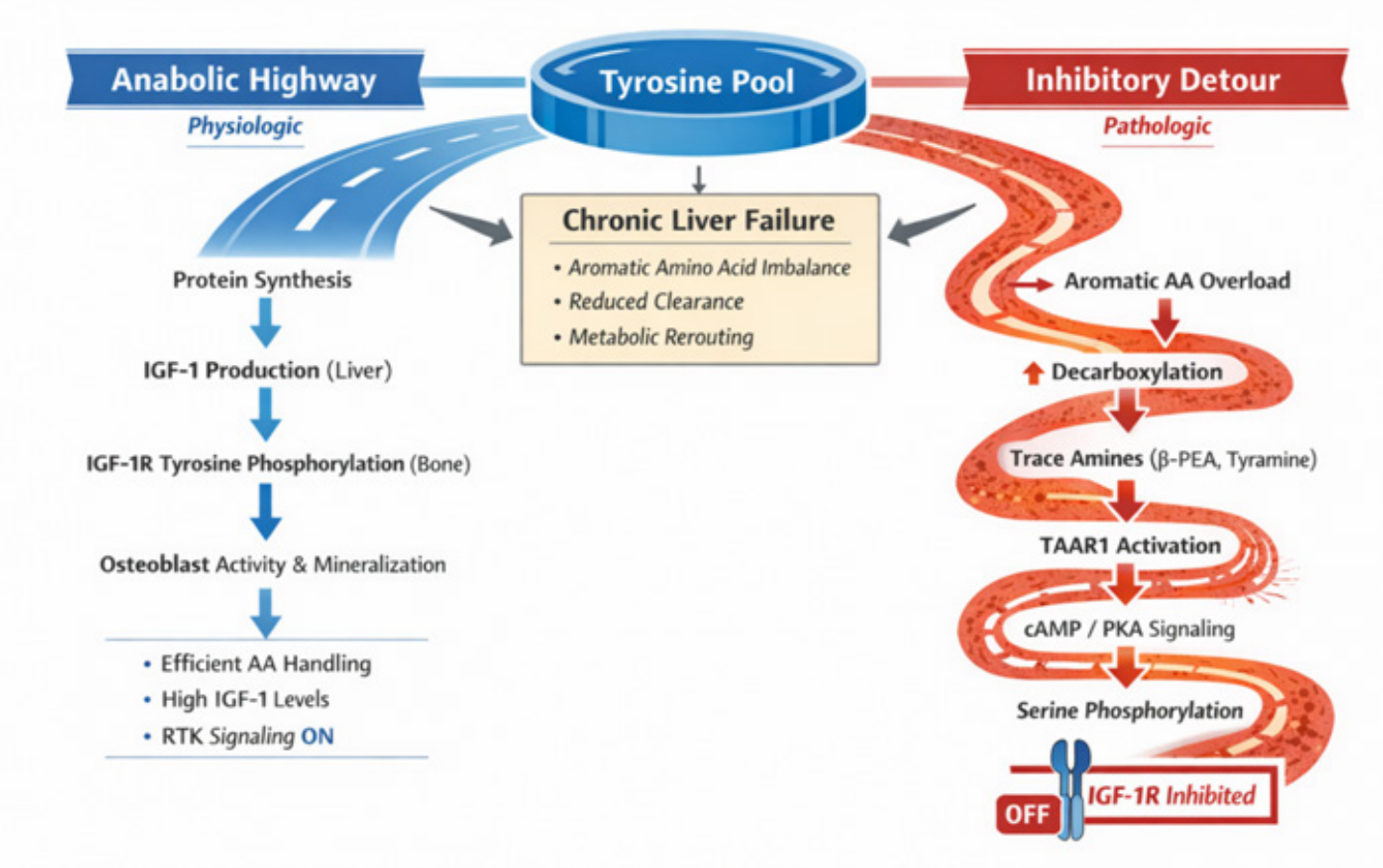

Figure 3. Schematic overview of the MTKI framework, adapted from the author's MTKI manuscript.

The "False Neurotransmitter" Connection

In the failing liver (or advanced NASH with fibrosis), the organ's capacity to metabolize aromatic amino acids (Tyrosine, Phenylalanine) is compromised. Instead of entering the Krebs cycle, these amino acids are shunted into alternative decarboxylation pathways, leading to the accumulation of "trace amines" or false neurotransmitters, such as Octopamine, Tyramine, and Phenylethanolamine. These metabolites are well-known markers of hepatic encephalopathy, but their systemic effect on bone has been overlooked.

Endogenous Pharmacological Blockade

Structurally, these trace amines bear a striking resemblance to Tyrosine Kinase Inhibitors (TKIs)—drugs used in chemotherapy to block cell growth. We hypothesize that these circulating antimetabolites act as "endogenous inhibitors," competitively binding to or structurally interfering with the Insulin-like Growth Factor 1 Receptor (IGF-1R) and the Insulin Receptor (IR) on osteoblasts.

The "Chemotherapy-like" State

This framework reframes Hepatic Osteodystrophy not just as a deficiency state (low IGF-1 output), but as a resistance state (blocked IGF-1 input). The NASH patient's bone is essentially under constant, low-grade "chemotherapy," where the regenerative signals are chemically jammed by the byproducts of their own liver dysfunction. This "MTKI" hypothesis provides a unifying explanation for why simply supplementing Vitamin D or Calcium often fails to restore bone density in these patients—the signaling machinery itself is inhibited.

In Search of a Faithful Surrogate: Appraisal of NASH Animal Models for Bone Research

An ideal animal model for investigating NASH-associated osteoporosis should reproduce both the human metabolic phenotype (obesity and insulin resistance) and key hepatic histopathology (steatosis, lobular inflammation, and fibrosis). Crucially, for bone research, the model should minimize non-specific drivers of bone loss, such as severe caloric restriction, malnutrition, or rapid weight loss, because these factors can independently reduce bone mass and obscure causal interpretation. Existing models can be broadly classified into genetic, dietary, and combination approaches, each with strengths and limitations.

Genetic models

Genetic models are created through targeted or spontaneous alterations that produce metabolic dysfunction. Leptin-signaling deficient mice (ob/ob or db/db) develop severe obesity and insulin resistance. However, they often lack robust spontaneous steatohepatitis and fibrosis, limiting their fidelity to human NASH. From a skeletal perspective, their extreme body weight can increase mechanical loading, which may preserve or even increase bone mass and thereby mask catabolic effects of inflammation, complicating interpretation for liver-driven bone mechanisms [7].

Other genetic approaches, such as hepatic PTEN deletion, can yield liver histology reminiscent of NASH, yet paradoxically may increase insulin sensitivity, diverging from the typical human metabolic context. Such

models may be valuable for studying hepatocarcinogenesis or specific hepatic signaling pathways, but their discordant systemic phenotype reduces suitability when the core question concerns the insulin resistance–fibrosis–bone triad.

Dietary models

Diet-induced models are attractive because they approximate human environmental exposure. The classic methionine- and choline-deficient (MCD) diet rapidly induces severe steatohepatitis and fibrosis, often yielding histological features strikingly similar to those in human NASH. Yet, this apparent advantage becomes a major liability for bone research: animals typically experience marked weight loss and improved insulin sensitivity. Because weight loss itself can drive bone loss, skeletal phenotypes under the MCD diet may reflect catabolic undernutrition rather than liver inflammation per se, undermining causal attribution.

In contrast, high-fat diet (HFD) and Western/fast-food diets more closely reflect caloric excess and fructose exposure in modern lifestyles. These diets produce obesity and insulin resistance, offering a metabolically relevant background for studying bone outcomes. However, steatohepatitis and fibrosis are often mild or slow to develop, and substantial time is required to reach advanced hepatic pathology. This time cost is not merely practical—it also increases heterogeneity in bone phenotypes because aging and changing activity patterns become additional confounders.

Combination models: a pragmatic "sweet spot"

Recognizing the limitations of single-factor models, combination strategies increasingly represent a pragmatic "sweet spot" for liver–bone axis research. By integrating a metabolic predisposition (genetic background or hypothalamic hyperphagia) with diet-induced hepatic injury, these models can simultaneously achieve obesity, insulin resistance, steatohepatitis, and clinically meaningful fibrosis [7].

One illustrative example is the use of gold thioglucose (GTG) to disrupt hypothalamic regulation of appetite, combined with a high-fat diet. This approach produces hyperphagia-driven obesity and insulin resistance while also promoting severe steatohepatitis and fibrosis, thereby offering a potentially powerful platform for studying the comorbidity of NASH and bone loss [8]. For mechanistic rigor, such models should be paired with careful controls (e.g., weight-matched groups, pair-feeding, and activity monitoring) to ensure that observed skeletal changes can be attributed to liver-driven endocrine–inflammatory perturbations rather than to neuroendocrine injury or non-specific catabolism.

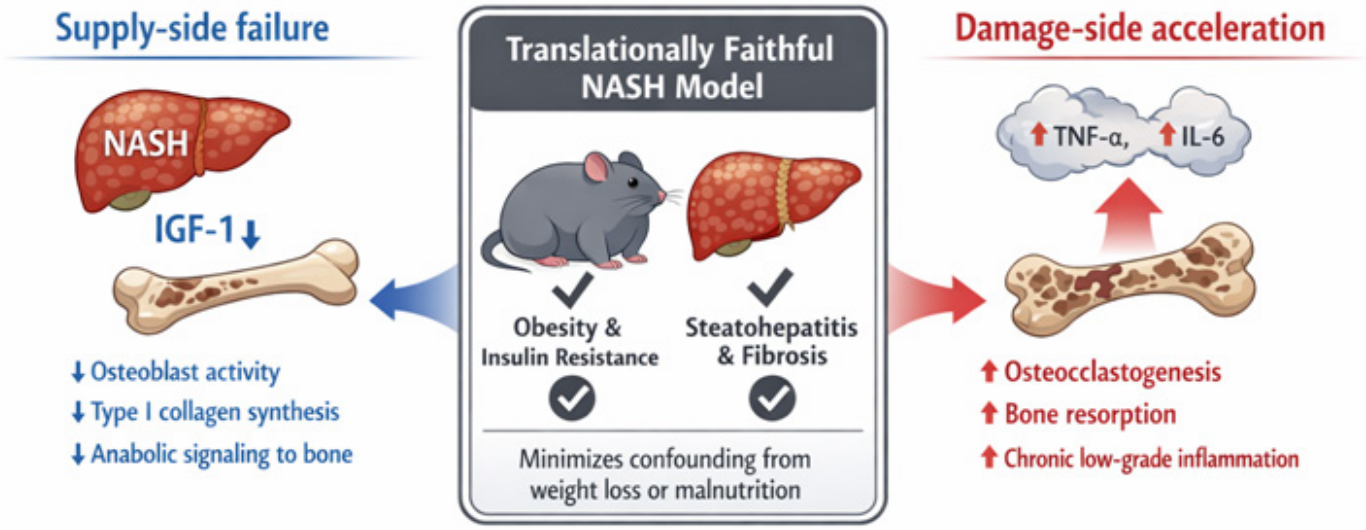

Figure 4. Conceptual framework for a translationally faithful NASH model to interrogate NASH-associated osteoporosis. The schematic summarizes two converging pathways: a supply-side failure in which NASH reduces liver-derived IGF-1, thereby diminishing anabolic signaling to bone (e.g., osteoblast activity and type I collagen synthesis), and a damage-side acceleration in which systemic inflammation increases osteoclastogenesis and bone resorption. The central panel highlights the design goal for preclinical studies: an animal model that simultaneously captures the metabolic phenotype (obesity and insulin resistance) and the liver histopathology (steatohepatitis and fibrosis), while minimizing confounding from weight loss or malnutrition.

Future Directions: From Animal Models to Mechanistic Clarity and Integrated Care

Once a highly translational NASH model is established, research can progress from static correlations to dynamic monitoring. Serial measurements of serum bone turnover markers, micro-computed tomography (micro-CT) of trabecular and cortical compartments, and biomechanical testing can map the tempo of skeletal deterioration across pre-NASH, early NASH, and fibrotic stages. Such longitudinal designs can identify inflection points at which preventive strategies might be most effective.

Mechanistic dissection should prioritize distinguishing whether bone loss is predominantly driven by reduced anabolic support (e.g., IGF-1 deficiency, a "supply-side" failure) or by heightened catabolic pressure (e.g., inflammatory cytokine-mediated osteoclast activation, a "damage-side" acceleration). Experimental manipulations—such as restoring IGF-1 signaling, attenuating inflammatory pathways, or improving insulin sensitivity—can clarify causal hierarchy and reveal actionable nodes for intervention.

Importantly, animal models also provide a platform for translational pharmacology. Therapeutics developed to treat NAFLD/NASH may plausibly influence skeletal outcomes—beneficially by reducing inflammation and improving endocrine profiles, or adversely through weight loss and altered nutrient handling. Preclinical designs that include bone endpoints can therefore anticipate clinical trade-offs and inform integrated "liver–bone co-care" strategies.

For nursing and interdisciplinary care, the clinical implication is straight-

forward: if NASH independently increases skeletal vulnerability, bone health assessment should be incorporated into chronic metabolic liver disease management. This may include fall-risk screening, counseling on resistance exercise and nutrition, and timely BMD testing when appropriate. Conversely, if bone loss is largely driven by weight reduction or malnutrition in specific contexts, care plans should prioritize maintaining lean mass, adequate protein intake, and feasible strength-training regimens. These divergent scenarios underscore why interpretable animal models are essential for causally grounded preventive care.

Conclusions

The metabolic dialogue of the liver–bone axis is a pressing translational question in the era of metabolic syndrome. Clinical evidence has repeatedly linked NAFLD/NASH to lower BMD and increased skeletal risk [1,2,6], yet causal direction and dominant mechanisms remain unresolved. We contend that a NASH animal model that faithfully reproduces human hallmarks—obesity, insulin resistance, and fibrotic liver injury—is the cornerstone for disentangling mechanisms, enabling longitudinal monitoring, and testing integrated interventions. By building such platforms and explicitly incorporating bone endpoints, the field can move beyond organ-specific management and toward cross-system risk governance, aligning scientific discovery with the holistic care needs of patients living with metabolic disease.

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