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EDITED BY
Federica Bellone,
Department of Clinical and Experimental Medicine, Messina, Italy

REVIEWED BY
Malgorzata Brzozowska,
University of New South Wales, NSW, Australia

*CORRESPONDENCE
Riad Sulimani
rsulimani@ksu.edu.sa

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Obesity and bone health: reconciling the density–fragility paradox

Riad Sulimani*

Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

The relationship between obesity and bone health is increasingly recognized as complex and paradoxical. Despite higher bone mineral density (BMD) in individuals with obesity, fracture risk is not uniformly reduced. Instead, fractures tend to occur more frequently at peripheral sites such as the ankle, humerus, and tibia, indicating a mismatch between BMD and true bone strength. In the early stages of weight gain, mechanical loading and adipose-derived hormonal factors may promote bone formation. However, these effects are progressively counterbalanced by chronic inflammation, oxidative stress, and marrow adiposity, which impair bone quality and compromise microarchitecture. Conventional dual-energy X-ray absorptiometry (DXA), while central to clinical assessment, cannot capture these changes and may overestimate skeletal strength in the presence of excess soft tissue. Emerging tools such as trabecular bone score and high-resolution peripheral quantitative computed tomography provide additional insights into bone quality, including microarchitecture and cortical porosity, particularly in individuals with type 2 diabetes. Obesity is also associated with vitamin D deficiency, impaired muscle function, and sarcopenic phenotypes, further increasing fracture risk. Bariatric surgery introduces additional challenges by accelerating bone turnover and loss. This review highlights the need to move beyond BMD alone and adopt comprehensive, individualized approaches to fracture risk assessment and management in obesity.

KEYWORDS
inflammation, obesity, osteoporosis, oxidative stress, sarcopenic adiposity

Introduction

Obesity and osteoporosis are major global health challenges. The prevalence of obesity has risen substantially over recent decades (1), while osteoporosis remains a significant cause of morbidity and fracture worldwide (2). Although individuals with higher body weight often demonstrate greater bone mineral density (BMD) at weight-bearing skeletal sites, accumulating evidence indicates that this does not reliably translate into stronger bone or lower fracture risk. Large cohort studies show that obesity is associated with a distinct fracture pattern—lower risk at the hip and spine but higher risk of fractures at peripheral sites such as the ankle, humerus, and tibia (3–5). These observations highlight a dissociation between bone density and bone quality that is particularly relevant for clinical densitometry. Dual-energy X-ray absorptiometry (DXA) may overestimate skeletal strength in individuals with obesity due to soft-tissue interference and the inherent limitations of two-dimensional, areal rather than volumetric measurement (6). As a result, skeletal fragility may remain

undetected unless complementary tools are used. Advances such as the trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HR-pQCT) offer improved assessment of trabecular microarchitecture, cortical integrity, and estimated bone strength—particularly valuable in individuals with metabolic dysfunction or type 2 diabetes (7–10). The skeletal phenotype associated with obesity reflects the combined influence of mechanical loading, endocrine factors, chronic low-grade inflammation, oxidative stress, and expansion of marrow fat (11–13). Additional contributors—including vitamin D deficiency, reduced muscle strength, sarcopenia, and bone loss after bariatric surgery—further compromise structural resilience and increase the risk of falls and fractures (14–17). Understanding how these mechanisms interact is essential for accurate diagnosis and individualized management. This review summarizes the pathways linking excess adiposity to skeletal fragility and outlines practical strategies for clinical evaluation and treatment.

Positive effects of obesity on bone

Mechanical loading and skeletal adaptation

Increased body mass enhances mechanical loading, stimulating adaptive changes in bone through the mechanostat process. Repetitive loading promotes periosteal expansion, increased cortical thickness, and improved structural geometry at weight-bearing sites (18, 19). Osteocytes act as key mechanosensors; deformation of the lacuno-canalicular network activates mechanosensitive ion channels, integrins, and downstream MAPK/ERK and Wnt/β-catenin signaling pathways, promoting osteoblastogenesis and matrix mineralization (20–22). Mechanical strain also suppresses sclerostin production, further enhancing bone formation (23). The recently characterized Piezo1 ion channel offers an additional mechanistic link between mechanical stress and osteogenic gene expression (24). These adaptive responses may increase bone mineral density in mild to moderate obesity, although mechanosensitivity tends to plateau at higher levels of metabolic dysfunction (25).

Endocrine and metabolic influences

Adipose tissue exerts endocrine effects that may temporarily support bone formation. Insulin enhances osteoblast activity via stimulation of collagen synthesis and osteocalcin production (26). Peripheral conversion of androgens to oestrogen through aromatase reduces osteoclastic resorption and helps preserve trabecular mass, particularly in postmenopausal women (27). Leptin stimulates osteoblastogenesis and suppresses osteoclast formation peripherally, although central sympathetic activation may offset some of these benefits (28, 29). Adiponectin demonstrates context-dependent skeletal effects, with experimental evidence showing both anabolic and catabolic influences depending on metabolic state (30, 31). Overall, endocrine and metabolic factors may enhance bone formation in early obesity, but these effects diminish as inflammation and insulin resistance emerge.

Negative effects of obesity on bone

Inflammation and cytokine signaling

Chronic low-grade inflammation is a hallmark of obesity and a major driver of skeletal deterioration. Visceral adipose tissue becomes infiltrated with pro-inflammatory macrophages that secrete cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6 (32, 33). These mediators stimulate osteoclastogenesis through up-regulation of the receptor activator of nuclear factor κB ligand (RANKL) pathway while simultaneously suppressing osteoblast differentiation and survival (33). The net effect is an uncoupling of bone remodeling in favor of resorption. Population-based studies consistently demonstrate that elevated inflammatory markers correlate with increased fracture risk, particularly among older adults with central obesity (33).

Oxidative stress and impairment of osteogenic pathways

Obesity is associated with heightened oxidative stress, driven by lipid peroxidation, mitochondrial overload, and impaired antioxidant defenses (34, 35). Excess reactive oxygen species reduce osteoblast viability, disrupt osteocytic signaling, and enhance osteoclast activity (34, 35). Oxidative stress also suppresses Wnt/β-catenin signaling, a key regulator of osteogenesis, thereby shifting mesenchymal stem-cell differentiation toward adipogenesis at the expense of osteoblast formation (35). Accumulation of advanced glycation end-products within collagen further increases non-enzymatic cross-linking, leading to greater bone brittleness and reduced toughness (36).

Marrow adiposity and structural fragility

Expansion of bone marrow adipose tissue is a defining feature of obesity-related bone fragility. Increased differentiation of mesenchymal stem cells into adipocytes reduces the pool of osteoprogenitor cells, resulting in diminished bone formation (37). Marrow adipocytes also secrete inflammatory adipokines and free fatty acids that locally impair osteoblast activity and promote osteoclastogenesis (38). Imaging studies using HR-pQCT in individuals with type 2 diabetes and obesity demonstrate increased cortical porosity, reduced trabecular number, and impaired trabecular connectivity (38, 39). Transcriptional regulators such as PRDM16 further influence mesenchymal lineage allocation and may contribute to the preferential expansion of marrow adiposity observed in obesity (40).

Vitamin D deficiency and secondary hyperparathyroidism

Vitamin D deficiency is highly prevalent among individuals with obesity and contributes significantly to impaired skeletal health (14). Several mechanisms underlie this association, including sequestration of vitamin D within expanded adipose stores, reduced cutaneous synthesis due to limited sunlight exposure, and volumetric dilution related to higher body mass (14, 17, 41). Persistent vitamin D deficiency

leads to secondary hyperparathyroidism, with elevated parathyroid hormone (PTH) levels increasing cortical bone resorption in order to maintain calcium homeostasis (17, 42). Over time, this adaptive response results in greater cortical porosity and reduced mechanical competence (42). Consequently, serum 25-hydroxyvitamin D concentrations are frequently low despite adequate intake or sun exposure (14, 17). Clinical guidelines generally recommend vitamin D supplementation of 1,000–4,000 IU/day to achieve and maintain sufficiency, although higher or more prolonged dosing may be required in individuals with obesity due to sequestration and dilution effects (42). Adequate calcium intake—typically 1,000–1,200 mg/day—is also necessary to support optimal mineralization (43).

In post–bariatric surgery patients, vitamin D and calcium management becomes more complex. Reduced gastric acidity and impaired intestinal absorption favor the use of calcium citrate rather than calcium carbonate (44). Long-term vitamin D deficiency is common after Roux-en-Y gastric bypass and sleeve gastrectomy, and regular biochemical monitoring—including serum 25(OH)D and PTH—is essential to prevent persistent hyperparathyroidism and accelerated bone loss (15).

Beyond skeletal effects, correction of vitamin D deficiency also improves muscle function and reduces falls. Meta-analytic data indicate that vitamin D repletion leads to a modest but clinically meaningful reduction in fall risk, which is particularly relevant in individuals with obesity who already exhibit impaired balance and reduced muscle quality (45). Table 1 summarizes the positive and negative effects of obesity on bone.

TABLE 1 Positive vs negative effects of obesity on bone.

Aspect	Positive Effects	Negative Effects
Bone Mineral Density	↑areal BMD at load-bearing sites	DXA overestimates; fractures persist
Architecture	↑ Periosteal expansion; ↑ cortical thickness	Marrow fat → porosity & fragility
Mechanotransduction	↓ Sclerostin, ↑ Wnt signaling	Inflammation/ROS blunt response
Hormones	Insulin, IGF-1, leptin (peripheral), oestrogen	Central leptin, low adiponectin, inflammatory adipokines
Inflammation	–	Chronic low-grade inflammation (TNF-α, IL-6)
Oxidative Stress	–	↑ ROS → collagen cross-links, brittleness
Fracture Risk	↓ Vertebral risk/hip in some cohorts	↑ Peripheral fractures (ankle, humerus)
Muscle Interaction	↑ passive loading	Sarcopenic obesity → falls, fragility
Special Contexts	Aromatase-derived estrogen post menopause	T2DM, vitamin D deficiency, bariatric surgery

Obesity exerts both positive and negative influences on the skeleton. Mechanical loading, periosteal expansion, and hormonal factors (insulin, IGF-1, leptin, aromatized estrogen) tend to increase bone mass, whereas inflammation, oxidative stress, advanced glycation end-products, marrow adiposity, and increased cortical porosity compromise bone quality. The net effect is a phenotype characterized by high BMD but impaired microarchitecture ("dense yet fragile"). Diagnostic challenges include DXA overestimation, the need for TBS and HR-pQCT to assess microstructure, and limitations of FRAX in obesity. Therapeutic strategies incorporate lifestyle measures (resistance training, adequate protein intake) and pharmacologic options tailored to the patient's fracture-risk phenotype.

Sarcopenic and osteosarcopenic obesity

Sarcopenic obesity refers to the coexistence of excess adiposity with reduced skeletal muscle mass or strength, while osteosarcopenic obesity represents the combined presence of obesity, sarcopenia, and osteoporosis (46, 47). These phenotypes share common mechanistic pathways, including chronic inflammation, oxidative stress, mitochondrial dysfunction, and endocrine dysregulation (48–49).

Pathophysiology in sarcopenic obesity

Visceral adiposity plays a central role in driving adverse musculoskeletal changes. Increased infiltration of adipose tissue by macrophages leads to secretion of TNF-α and IL-6, which impair myocyte protein synthesis and promote osteoclast-mediated bone resorption (33). Mitochondrial dysfunction and excess oxidative stress further diminish muscle strength and impair osteoblast function (13, 48). Declines in anabolic hormones such as growth hormone and IGF-1, combined with altered leptin and adiponectin signaling, contribute to progressive losses of both muscle and bone mass (28–30).

From a mechanical perspective, although higher body mass increases passive skeletal loading, reduced muscle strength limits active mechanical strain—an essential stimulus for bone adaptation. This imbalance explains why individuals with sarcopenic obesity may show preserved or elevated BMD yet remain highly susceptible to falls and fragility fractures (49).

Management requires an integrated approach targeting both muscle and bone. Adequate dietary protein intake (typically 1.0–1.2 g/kg/day) supports muscle protein synthesis and optimizes bone turnover (50, 51). Anti-inflammatory and antioxidant-rich dietary patterns may mitigate oxidative stress and improve musculoskeletal outcomes (51). Gradual rather than rapid weight reduction helps preserve lean mass and maintains skeletal loading (52).

Resistance training is one of the most effective therapeutic interventions, consistently improving muscle strength, lean mass, physical performance, and mechanical bone loading (53). The combination of resistance exercise with protein supplementation produces synergistic benefits for muscle mass and function (54).

Pharmacologic therapies, although adjunctive, may also contribute. Osteoanabolic agents such as teriparatide and romosozumab improve trabecular microarchitecture and may exert secondary benefits on muscle–bone crosstalk (55, 56). Emerging therapies—including selective androgen receptor modulators and myostatin inhibitors—are being actively investigated for their ability to deliver coordinated anabolic effects on both muscle and bone (57, 58).

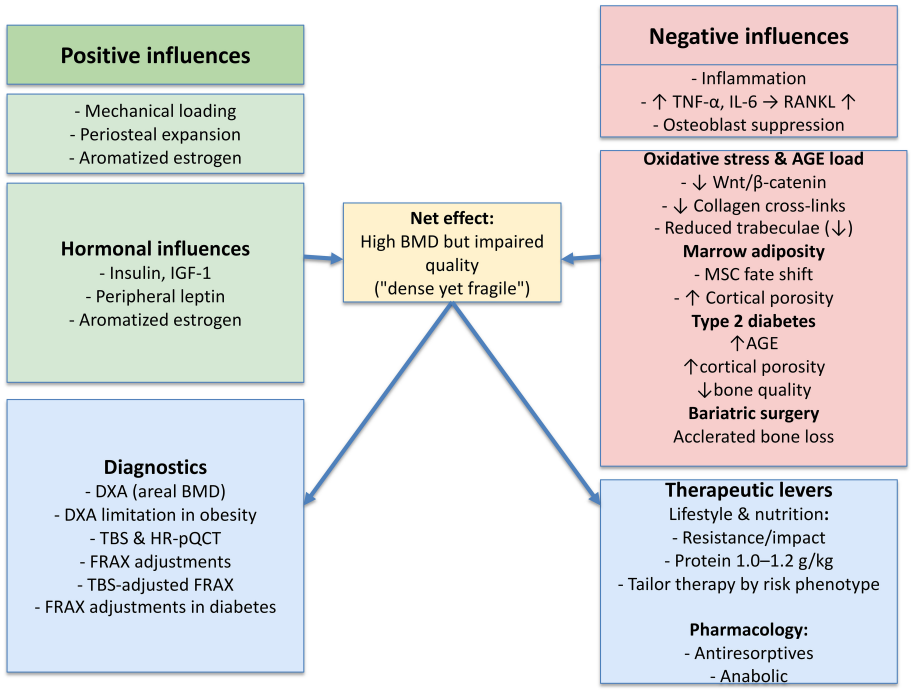

FIGURE 1
Mechanistic, diagnostic, and therapeutic framework for bone health in obesity.

Diagnostic considerations in obesity-related bone disease

Interpretation of skeletal health in individuals with obesity presents important diagnostic challenges. Dual-energy X-ray absorptiometry (DXA), the standard tool for measuring areal bone mineral density, frequently overestimates true skeletal strength in obesity due to soft-tissue interference, increased body size, beam hardening, and the inherent limitations of two-dimensional measurement (6, 59, 60). As a result, individuals with obesity may appear to have normal or even elevated BMD despite the presence of significant deficits in cortical and trabecular microarchitecture (61, 62). This limitation is particularly relevant in patients with central adiposity and type 2 diabetes, where standard DXA-based thresholds often fail to accurately reflect fracture susceptibility (39, 63–65).

To overcome these shortcomings, incorporation of bone-quality measures has become increasingly important in clinical assessment (63, 64). The trabecular bone score, derived from lumbar spine DXA images, provides an indirect index of trabecular microarchitecture (65, 66). Lower trabecular bone score values are consistently observed in individuals with type 2 diabetes and central obesity and are independently associated with increased risk of major osteoporotic and hip fractures (65, 66). Importantly, trabecular bone score captures microarchitectural deterioration that may remain undetected by areal BMD alone, particularly in patients whose skeletal loading artificially elevates density measurements (9, 63).

High-resolution peripheral quantitative computed tomography offers additional three-dimensional assessment of trabecular number, cortical thickness, cortical porosity, and estimated biomechanical competence (9, 68). Although not yet widely available in routine clinical practice, this technology is particularly informative in metabolically unhealthy obesity, where it reveals cortical thinning, increased porosity, and deterioration of trabecular connectivity despite preserved BMD (67, 68). Together, these diagnostic tools demonstrate that reliance on areal BMD alone is insufficient for accurate skeletal risk stratification in obesity and underscore the need for integrated structural assessment whenever available (6, 9, 68).

Fracture-risk assessment

Standard fracture-risk prediction models frequently underestimate fracture probability in individuals with obesity and in those with type 2 diabetes (69–71). This underestimation reflects the inability of conventional algorithms to fully capture altered bone material properties, increased cortical porosity, compromised microarchitecture, higher fall propensity, and the adverse skeletal effects of chronic hyperglycemia (67, 69, 70). As a consequence, many high-risk patients are incorrectly classified as low or intermediate risk when standard tools are applied without adjustment.

Incorporation of trabecular bone score into FRAX significantly improves fracture prediction in individuals with obesity and diabetes by integrating microarchitectural information into probability estimates (9, 66). When trabecular bone score is unavailable, validated practical adjustments can be applied to improve risk estimation, including downward adjustment of the femoral-neck T-score input by approximately 0.5 standard deviations, selection of rheumatoid arthritis as a surrogate risk factor, or increasing the patient's age by 10 years to account for diabetes-related skeletal fragility (72).

In regions where FRAX has been recalibrated using local epidemiological data and population-specific risk coefficients, fracture risk prediction can be further improved (73–76).

Given the multidimensional nature of obesity-related skeletal fragility, fracture-risk assessment is most informative when these domains are considered together rather than in isolation. An integrated evaluation that combines areal BMD, trabecular bone score (when available), indices of metabolic health, cortical structure, muscle strength and fall risk, and prior fracture history provides a more realistic estimate of skeletal vulnerability (77–80).

Future directions

Advances in artificial intelligence and machine learning are transforming fracture-risk prediction. AI-enhanced models incorporating TBS, HR-pQCT microarchitecture, and large-scale clinical data outperform conventional risk algorithms in identifying high-risk individuals (81–83).

At the therapeutic frontier, mesenchymal stem-cell–derived exosomes and metabolic reprogramming strategies show promise in restoring osteogenic potential in metabolically impaired bone (84, 85). Endocrine restoration strategies, including correction of hypogonadism, may help counter sex-steroid–deficiency–related increases in marrow adiposity, while emerging anabolic agents such as selective androgen receptor modulators and myostatin inhibitors may enhance lean mass and musculoskeletal function (86, 87).

The integrated framework is summarized in Figure 1, which links obesity-related positive and negative skeletal influences with diagnostic considerations and therapeutic levers.

Conclusion

In summary, obesity creates a dense-yet-fragile skeletal phenotype in which higher areal BMD can coexist with impaired microarchitecture, reduced muscle quality, and increased peripheral fracture risk. Assessment should therefore move beyond BMD alone and integrate bone-quality measures, metabolic status, muscle function, fall risk, and fracture history. Management should be individualized and combine lifestyle, nutritional, and pharmacologic strategies according to the patient's risk phenotype.

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