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Obesity, Diabetes, and Metabolic Bone Health: An Emerging Clinical Intersectiong

Dilek Gogas Yavuz, MD[1,*]

[1]Marmara University School of Medicine, Department of Endocrinology and Metabolism, Istanbul, Turkiye

[*]Correspondence should be addressed to Dilek Gogas Yavuz, dilekgogas@gmail.com

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Editorial

Obesity, Type 2 Diabetes (T2D), and osteoporosis have long been treated as separate epidemics, each with its own guidelines, specialist clinics, and literature. That separation is no longer tenable. As global obesity and diabetes prevalence have risen, osteoporosis prevalence has risen in close parallel, and a rapidly expanding literature has exposed a mechanistic entanglement between adipose tissue, glucose metabolism, and bone [1]. Bone is not a passive bystander in metabolic disease: it is an active endocrine organ, shaped by adiposity and glycemic control while itself modulating both [1]. Clinicians who manage obesity or diabetes without considering skeletal health, and those who manage osteoporosis without considering metabolic status, are each working from an incomplete picture.

The Paradox: Preserved Density, Elevated Risk

The paradox that defines this interface is that patients with obesity and T2D usually have normal or increased Bone Mineral Density (BMD) on Dual-energy X-ray Absorptiometry (DXA), but have a quantitatively increased risk of fracture compared with metabolically healthy peers of the same age. In a meta-analysis of eight cohorts, T2D was associated with a 38% increased risk of hip fracture, despite higher BMD Z-scores at the spine and hip (RR 1.38, 95% CI 1.25–1.53) [2]. According to the largest synthesis to date, involving >13 million participants across pooled cohort studies, this excess risk is not evenly distributed across the skeleton: T2D disproportionately elevates fracture risk at sites of the lower extremities (hip, ankle, foot), while its impact on sites of the upper limb is more modest and less consistent, a site-specific signature indicative of fall mechanics and lower extremity bone quality, rather than generalized bone loss, as the dominant driver [3]. In the Rotterdam Study, participants with poorly controlled T2D (HbA1c≥7.5%) had more fractures than those with well-controlled diabetic or non-diabetic peers, despite higher BMD and thicker, narrower femoral cortices, implicating glycemic control itself in degrading bone quality independent of mass [4]. Non-diabetic obesity has a similar, but smaller, dissociation: obese adults are at ~60% greater risk of ankle fractures and slightly lower risk of hip and wrist fractures, inconsistent with any simple protective effect of body mass on the skeleton [5].

Type 1 Diabetes (T1D) follows the opposite, more conventional pathway: fracture risk tracks genuinely low BMD. The same meta-analysis found a hip fracture RR in T1D of 6.94 (95% CI 3.25–14.78)—roughly five times the relative increase seen in T2D, alongside reduced, not increased, BMD Z-scores at the spine and hip [2]. "Diabetic bone disease" is therefore not one entity but at least two divergent pathophysiology's that likely warrant different risk-stratification strategies [1].

Mechanisms Connecting Metabolic Disease with Skeletal Fragility

Metabolically "dense" bone may still be mechanically weak, and several mechanisms can explain this. Advanced Glycation End-Products (AGEs) accumulate in the collagen matrix in response to chronic hyperglycemia. Biomechanical testing demonstrates that AGE-mediated non-enzymatic cross-linking stiffens bone tissue but also reduces the toughness and energy absorption required to resist fracture, a defect not detectable by BMD [6]. Diabetes and obesity are also associated with a reduced bone formation and increased cortical porosity and marrow adiposity at the expense of osteoblast genesis, indicative of competition within a common mesenchymal

progenitor pool [7]. Circulating sclerostin, a Wnt-pathway inhibitor of osteoblast activity, is ~ 40% higher in T2D than non-diabetic controls and is correlated with measures of adiposity [8]. Additional, incompletely delineated, cross-talk between fat, muscle and bone occurs via adipokines, myokines, incretin signaling and inflammatory mediators [1].

These mechanisms explain why identical BMD can mask very different real-world fracture risk, and why the Trabecular Bone Score (TBS), a DXA-derived texture index approximating trabecular microarchitecture—has gained traction as a BMD-independent predictor of fracture in T2D [9]. This was built on earlier evidence, from a large cohort of older adults with T2D, that standard BMD and FRAX scores substantially under-predicted the fractures subsequently observed [10].

Failures of Current Risk Assessment Tools

Existing fracture prediction methods were not built for diabetics or obese people. In a large Manitoba registry cohort, diabetes remained an independent predictor of major osteoporotic fracture (Hazard ratio 1.61, 95% CI 1.42–1.83) even after adjustment for the FRAX-calculated probability [11]. The workarounds of utilizing rheumatoid arthritis as a proxy risk factor, adding years to the patient's age, or adopting a TBS-based adjustment are unproven and uncertain [11,9]. Unrelated to diabetes, obesity is a problem. FRAX and unadjusted DXA values may be misleading regardless of glycaemia since BMI corresponds with areal BMD. Pilot studies using FRAXplus-based correction on higher-BMI diabetes populations show that the standard method consistently under-calls risk [12]. Higher body mass can technically affect DXA, eroding physicians' confidence in the numbers. In practice, obese and diabetic patients' fracture risk is likely underdiagnosed and undertreated.

Weight Loss is Not Unambiguously Good for Bone

A further complication is that treating obesity can itself jeopardize bone. Bariatric surgery, especially malabsorptive techniques like Roux-en-Y gastric bypass, accelerates bone remodeling and loss, with hip BMD falling significantly within the first year and the hip being the most affected [13]. A meta-analysis of 14 trials, 717 individuals, demonstrated equivalent BMD drop between gastric bypass and sleeve gastrectomy after two years, showing that weight loss, not surgery, causes skeletal cost [14]. Lifestyle-driven weight loss costs less generally [13].

Pharmacologic weight reduction adds subtlety rather than answering the question, and the database now includes multiple compounds and lengthier follow-up than a year. Trial-level meta-analysis of GLP-1 receptor agonists in T2D indicates no fracture increase, with modest protection and enhanced bone turnover markers [15]. Real-world data pooling semaglutide and tirzepatide, followed for a median of 34 months, show a more cautious story: BMD fell significantly at the spine, femoral neck, and total hip, tracking with weight loss, and 13% of patients fractured, more than twice as often in diabetics (20.5%vs7.0%) [16]. A large retrospective cohort found semaglutide had a 26% lower fracture risk than sleeve gastrectomy over three years (Hazard ratio 0.74, 95% CI 0.56–0.98), suggesting pharmacologic weight loss may be gentler on bone than surgical weight loss [17]. In contrast, tirzepatide at higher doses shared with T2D and obesity reasons had a 44% higher risk of incidence osteoporosis or fragility fracture than other GLP-1 receptor agonists in a roughly 460,000-patient TriNetX cohort (Hazard ratio 1.44, 95% CI 1.22–1.69) [18]. The rate and magnitude of weight loss appear to drive skeletal risk after weight loss, and only secondarily by the specific agent or procedure used. This distinction matters as these therapies reach an increasingly large population on evidence still thinner than the confidence with which it is often invoked.

Not All Glucose-Lowering Drugs are Equal for bone

Beyond weight-loss agents, the choice of glucose-lowering drug carries its own skeletal signature. Thiazolidinediones have a well-documented, sex-specific risk: a pooled analysis of three national registries found a 44% increased risk of fracture in women on current thiazolidinedione therapy (adjusted hazard ratio 1.44, 95% CI 1.35–1.53), with no corresponding increase in men (Hazard ratio 1.05, 95% CI 0.96–1.14) [19]. There is no consistent evidence that SGLT2 inhibitors cause skeletal harm and in the largest recent network meta-analysis that included 117 randomized trials across nine classes of antidiabetic drugs, they were the only class associated with a significant reduction in fracture risk compared to placebo and comparators (odds ratio 0.85, 95% CI 0.74–0.98) – though earlier, smaller meta-analyses were more equivocal and this finding should not yet be considered settled [20]. Incretin-based medicines remain overall more attractive than thiazolidinediones, although as above not uniformly so at obesity-range doses [15,16,18].

Clinical and Research Implications

Three practical implications arise. BMD alone should not reassure obese or diabetic patients that their skeleton is healthy, and the conversation should be informed by fall history, clinical risk factors and when possible, TBS-adjusted FRAX [9,11]. Any planned major purposeful weight loss—surgical, pharmaceutical, or behavioral—should be coupled with baseline and longitudinal skeletal evaluation, sufficient calcium, vitamin D, and protein intake, and resistance exercise during the period of most rapid weight change [13]. And this is still a very much multidisciplinary problem: endocrinologists,

obesity medicine specialists, and doctors for bone health need unified frameworks rather than parallel non-communicating care routes.

The research gaps are equally urgent. Algorithms for diabetes and obesity-specific fracture have not been tested at scale. Ultimately, individual incretin medicines need prospective properly powered validation of their differential skeletal trajectories rather than retrospective signals from a single database [18]. And the basic biology linking marrow obesity, AGE accumulation and bone material strength has to be translated from preclinical models to clinically actionable indicators [6,7]. With the field of obesity and diabetes pharmacotherapy expanding at a rapid rate, addressing these gaps is no longer an academic exercise, but a precondition to administering these medicines safely for a patient's whole skeletal lifespan.

Obesity, diabetes and bone fragility are not three coincidental disorders in the same patient. They are part of one metabolic profile, and only now is clinical practice beginning to catch up with that reality.

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