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## Type 2 diabetes and bone fractures

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### Abstract

**Purpose of review**—To discuss current literature and hypotheses pertaining to the pathophysiology of increased bone fragility and fracture in men and women with type 2 diabetes mellitus.

**Recent findings**—Despite high bone mineral density, studies have shown that men and women with type 2 diabetes mellitus (T2DM) are at increased risk for fracture. Complications of T2DM including retinopathy and autonomic dysfunction may contribute to bone fracture by increasing fall risk. Nephropathy may lead to renal osteodystrophy. Lean mass and potentially fat mass, may additionally contribute to skeletal health in diabetes. There is increasing acknowledgement that the marrow microenvironment is critical to efficient bone remodeling. Medications including thiazolidinediones and selective serotonin reuptake inhibitors may also impair bone remodeling by acting on mesenchymal stem cell differentiation and osteoblastogenesis. T2DM is associated with significant alterations in systemic inflammation, advanced glycation end-product accumulation and reactive oxygen species generation. These systemic changes may also directly and adversely impact the remodeling cycle and lead to bone fragility in T2DM, though more research is needed.

**Summary**—Fracture is a devastating event with dismal health consequences. Identifying the extrinsic and intrinsic biochemical causes of bone fracture in T2DM will speed the discovery of effective strategies for fracture prevention and treatment in this at-risk population.

### Keywords

bone mineral density; fracture; mesenchymal stem cell; type 2 diabetes mellitus

## INTRODUCTION

Skeletal fracture is a devastating event with dismal health consequences. More than 250 000 hip fractures occur annually in older adults in the USA, and are associated with 25% risk of mortality in the year following fracture [1,2<sup>1</sup>]. For those who survive, their lives may be additionally complicated by loss of independence, financial hardship, as well as an increased overall risk of death [3–5]. All fractures –hip, vertebral and nonvertebral – carry with them significant morbidity and heightened risk for future fracture [6<sup>2</sup>]. As the population ages, identification of those at risk and early intervention to prevent fracture is imperative. The

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urgency is highlighted all the more by looming healthcare costs. It is estimated that fracture-related costs exceed US\$ 20 billion annually, a number that will only rise in the years to come [7,8]. There is no question that bone fractures will continue to be an important topic in clinical investigation and future healthcare debates.

Traditionally, fracture risk is determined using dual X-ray absorptiometry techniques (DXA), which provide real, or two-dimensional, bone mineral density (BMD) measurements at the spine and hip. Definitions of normal, low BMD ('osteopenia') and osteoporosis stem from these BMD measurements [1]. Lower BMD predicts increased fracture risk in aging populations, as parameters of low bone quantity are highly correlated with bone strength and fracture susceptibility. In 2008, a new fracture prediction tool, or FRAX (<http://www.shef.ac.uk/FRAX/>), was introduced by the WHO in an attempt to predict fracture risk with even greater accuracy [9]. Taking other risk factors for osteoporosis and fracture into account (age, family history, weight, etc.), use of FRAX has become more widespread in primary care and metabolic bone clinics alike to assist physicians in managing those at risk for fracture.

## **TYPE 2 DIABETES MELLITUS AND BONE MINERAL DENSITY**

Men and women with type 2 diabetes mellitus (T2DM) typically have normal to high BMD compared with their age-matched healthy peers [10,11]. Several factors likely contribute to this observation. BMD is strongly associated with body weight, and low BMI is as a known risk factor for the development of osteoporosis and fracture [12,13]. Conversely, persons of higher weights such as those with the T2DM will have higher BMD compared with age-matched controls. In part, increased BMD in those with T2DM may represent biomechanical adaptation to greater loads placed on the skeleton [14,15]. Lean mass, often increased in proportion to weight gain, places biomechanical strain on bone and can potentiate bone formation in T2DM [16]. Insulin is anabolic to bone, and the hyperinsulinemic states associated with T2DM may also promote skeletal acquisition [17,18]. It should be noted that the finding of increased BMD in men and women with T2DM is in stark contrast to the low BMD of those with type 1 diabetes (T1DM). An autoimmune disease of insulin deficiency, T1DM is often accompanied by nutritional deficits, low body weight and other factors, which cause impaired bone formation and decreased BMD [19,20].

## **TYPE 2 DIABETES MELLITUS AND FRACTURE**

Paradoxically, despite elevations in BMD, which should portend increased skeletal strength, men and women with T2DM are at an increased risk of fracture [21–23]. In the Rotterdam Study, consisting of a large cohort study of 6655 men and women (ages 55), nonvertebral fracture risk was increased for patients with T2DM (HR 1.33) compared with weight and age-matched controls [24]. These findings are further supported in other longitudinal investigations. Women 65 years or older in the Study of Osteoporotic Fractures with T2DM were at an increased risk of hip fracture [relative risk (RR) 1.82], as well as proximal humerus and foot fractures [25]. In the men and women (ages 70–79 years) of the Health Aging and Body Composition study, T2DM was associated with accelerated bone loss at the hip, as well as an increased risk of overall fracture (RR 1.64) even after adjustment for hip

BMD [26]. In the Nurse's Health Study, the age-adjusted RR of hip fracture was 70% greater in women aged 34–59 years with T2DM compared with those without diabetes [27]. These abundant data highlight the discrepancy between bone quantity, as measured by DXA, and bone quality and the capacity to withstand fracture in T2DM. The pathophysiology of the increased fracture risk in T2DM remains under investigation, though likely stems from numerous conditions associated with diabetes that have detrimental effects on the skeleton (Fig. 1).

## MEDICATIONS

Thiazolidinediones (TZDs) have long been used in persons with T2DM as an oral medication to promote insulin sensitivity through activation of the nuclear receptor, peroxisome proliferator-activated receptor  $\gamma$  [28]. Among the many controversies encountered by this class of drugs has been their adverse effects on the skeleton [29]. Randomized controlled trials have shown that TZDs are associated with significant bone loss [30,31]. In A Diabetes Outcome Progression Trial, premenopausal and postmenopausal women treated with rosiglitazone were at twice the risk for fracture compared with those taking metformin or glyburide [32]. A similar increase in fracture risk has been reported in those taking pioglitazone [33]. Mechanistically, glitazones promote the differentiation of the bone's pluripotent, mesenchymal stem cells (MSCs) into adipocytes rather than bone-building osteoblasts. TZDs may also have adverse effects on circulating hormones that are anabolic to bone by decreasing insulin-like growth factor 1 (IGF-1) and estrogen levels [34]. Recognized now as a consequence and possible precipitant of T2DM is clinical depression, commonly treated with selective serotonin reuptake inhibitors (SSRIs) [35,36]. Of the many recent and exciting discoveries in the bone field, serotonin and bone metabolism appear linked [37]. Gut-derived serotonin reduces osteoblast proliferation and the accrual of bone mass [38,39]. There has, therefore, been some concern that medications used to antagonize the serotonin transport protein and increase local serotonin activity could have negative implications for bone health. Indeed, several cross-sectional and longitudinal studies have shown associations between SSRI use and bone loss [40–42]. Fracture rates, too, appear to be increased in users of SSRIs compared with nonusers in clinical and prospective studies [43,44]. Because serotonin may also have positive effects on bone mass via activity in the central nervous system, additional investigation is needed to determine the net effect of SSRIs on bone strength [38,39,45].

## COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

With the progression of T2DM, both microvascular and macrovascular complications often arise. These complications of longstanding T2DM have definite implications for bone density and strength [46]. Men and women with T2DM are at an increased risk for falls when compared with those without diabetes [47]. Whereas hypoglycemic episodes may lead directly to syncopal events, gait instability due to autonomic neuropathy and orthostatic hypotension, peripheral neuropathy and retinopathy can also lead to falls [23,47]. Renal dysfunction leads to secondary hyperparathyroidism and bone loss via accelerated skeletal resorption and mineralization defects. Persistently elevated blood glucose levels can lead to renal calcium losses that are not appropriately corrected through elevations in parathyroid

hormone, termed ‘functional hypoparathyroidism’ [48]. The microvascular disease that accompanies T2DM may also impair blood flow to the marrow microenvironment and alter local remodeling, though these processes remain under investigation [49<sup>••</sup>,50–52].

## HORMONAL ALTERATIONS

Although insulin is anabolic to bone, there are several hormonal disturbances associated with insulin resistance, metabolic syndrome and T2DM that have negative repercussions on bone integrity. IGF-1 is one of many positive regulators of bone metabolism and may be lower in persons with diabetes [53,54]. Further, serum IGF-1 levels have been reported as inversely associated with the presence of vertebral fractures in postmenopausal women with T2DM [55<sup>•</sup>]. Testosterone is also anabolic to bone primarily through its aromatization to estrogen in adipose tissue [56]. Low testosterone in the setting of low or inappropriately normal luteinizing hormone and follicle-stimulating hormone is common in the diabetic population and may contribute to impaired bone strength in this population [57–59]. Vitamin D deficiency, associated not only with increased fall risk and fracture in older individuals, is extremely common in men and women with T2DM [60,61]. Sequestered in adipose stores as a fat-soluble vitamin, insufficient levels of both local and circulating vitamin D may lead to osteomalacia, secondary hyperparathyroidism and accelerated bone loss [62,63]. When coupled with renal dysfunction that impairs the conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D, the effects on bone metabolism in T2DM can be severe.

## BODY COMPOSITION

Although higher BMI is typically associated with higher BMD, it is important to consider the components of body mass – lean, fat and skeletal. When evaluating lean and fat mass separately, lean mass appears most critical in determining bone mass throughout the life cycle [64,65]. The biomechanical forces of muscle activity on bone promote bone remodeling. Thus, lean mass is a positive determinant of BMD [66]. Men and women with osteoporosis are routinely advised to increase the time they spend performing resistance and weight-bearing exercise to capitalize on the influence of lean mass on osteoblast activity [67]. In T2DM, lean mass is positively associated with both BMD and parameters of hip geometry including buckling ratio and section modulus, surrogate measures of hip strength [68<sup>••</sup>,69<sup>••</sup>]. Declines in lean mass with progressive insulin resistance, termed ‘sarcopenic obesity’, may, therefore, have immediate implications for bone quality in T2DM [70<sup>••</sup>,71].

The effects of fat mass on bone density and strength are less clear. Some investigators have reported significant associations between fat mass and bone density in older men and women [72–75]. In women with noninsulin requiring diabetes mellitus, fat mass is associated with bone density and hip strength [68<sup>••</sup>,69<sup>••</sup>]. The association was not significant in men. With the recognition that adipose is, in fact, an endocrine organ, there has been increased interest in the effects of adipokines as mediators of bone metabolism [76]. Leptin and adiponectin affect both bone formation and bone resorption and have been proposed as mediators of a fat-bone association. Leptin promotes osteoblast differentiation and proliferation while diminishing osteoclast recruitment [77–79]. In the central nervous system, leptin may have a catabolic effect on bone through its interactions with insulin

secretion and neuropeptides [80,81]. Adiponectin, produced in visceral, subcutaneous and bone marrow fat, has been shown to be downregulated in diabetes and obesity [82,83]. Like leptin, its effects on bone may be mixed, promoting osteoblastogenesis, whereas inhibiting osteoprotegerin and thus bolstering osteoclastogenesis [84]. The potentially independent effects of body composition on bone density will be a promising area of research in the future given that it can be modified in men and women with T2DM.

## NOVEL MEDIATORS OF BONE METABOLISM AND FRACTURE

T2DM represents a state of multisystem homeostatic disruption. Many of the systemic changes associated with T2DM have detrimental local effects on the skeleton. These more novel mediators of skeletal metabolism, though not entirely understood, require some attention. Increased with aging and T2DM, circulating advanced glycation end products (AGEs) interfere with collagen cross-links in bone and can cause structural incompetence [85,86,87<sup>\*\*</sup>]. Both serum and urine pentosidine, an AGE, are associated with an increased clinical fracture risk in men and women with T2DM [88,89]. At the level of the bone marrow microenvironment, altered systemic factors in T2DM may have additional adverse effects in the bone remodeling cycle. As noted, MSCs are important determinants of bone quality given their capacity to differentiate into bone-building osteoblasts versus adipocytes [90,91]. The proliferation and differentiation of these osteogenic cells are dependent on extrinsic and intrinsic factors. Locally, osteocyte signaling, inflammatory cytokines, growth factors, reactive oxygen species and other signaling molecules contribute to MSCs' activity [92–94]. The MSCs are also continually bathed in systemic, circulating factors, which flow freely into the bone microenvironment through the sinusoidal circulation. In T2DM, fluctuations in systemic factors including anabolic hormones, AGEs, inflammatory cytokines and oxidative stressors have the potential to directly and adversely influence MSCs' activity with downstream effects on skeletal fragility [95<sup>\*\*</sup>,96–98]. The interplay of the bone microenvironment, MSCs' activity and fragility in the diabetic skeleton is currently unknown.

## FRACTURE RISK ASSESSMENT IN TYPE 2 DIABETES MELLITUS

The underpinnings of bone fragility in T2DM are unquestionably multifactorial, making assessment for fracture risk in those with glucose intolerance all the more challenging. To date, screening for increased fracture risk and initiation of osteoporosis treatment are based on BMD measurements. Unfortunately, older adults with T2DM fracture despite normal BMD. Though studies have shown that persons with T2DM who sustain fractures do so at a lower BMD than diabetic patients who do not, the majority of these fractures occur despite what physicians would consider 'normal BMD'. Thus, BMD alone is not an adequate determinant of fracture risk in men and women with deranged glucose homeostasis. Traditional DXA measurements fail to accurately predict fracture in this at-risk population. FRAX calculations that take into account factors for bone fragility in addition to BMD may also underestimate fracture risk in T2DM [99].

Although bone biopsy is the gold standard in defining causation of idiopathic fracture, the procedure is both invasive and impractical as an osteoporosis screening tool in persons with

T2DM [100]. Rather, with the advent of new technologies, there has been some hope that alternative imaging techniques will cast light on the cause of bone fractures in T2DM and lead to improved osteoporosis prevention and screening. In the research setting, high resolution peripheral quantitative computed tomography (HR-pQCT) enables investigators to quantify trabecular and cortical bone microarchitecture in the radius and tibia [101,102]. Unfortunately, this noninvasive measure of bone microarchitecture does not appear to correlate with the gold standard, or histomorphometry from bone biopsy. Cohen *et al.* [103\*] compared in-vivo HR-pQCT of the tibia and radius to histomorphometry of transiliac bone biopsies in 54 premenopausal women with idiopathic fracture. Only two measures of bone quantity were significantly correlated, including trabecular bone volume ( $r=0.30$ ) and cortical thickness ( $r=0.36$ ). There were no significant correlations between measures of bone quality including trabecular number, thickness or spacing. Using HR-pQCT, Burghardt *et al.* [104\*] additionally reported that cortical microarchitecture may be compromised in patients with T2DM. However, without clear correlation of data acquired from this imaging technique with bone biopsy, clinical use of HR-pQCT will be limited. Microindentation, a technique in which a small probe inserted into the tibia to displace periosteum, shows promise in quantifying the toughness of bone, or its susceptibility to microfracture [105\*\*]. There have been no reported studies, however, utilizing this technology in T2DM.

Many of the remaining and less-invasive techniques for measuring bone strength and remodeling are similarly inadequate in those with T2DM. In a recently published study, calcaneal quantitative ultrasound was not significantly associated with the presence of vertebral fractures in patients with T2DM [106]. Markers of bone resorption and formation, or bone turnover markers, measured in blood and urine samples also appear to have limited utility in determination of T2DM fracture risk. C-telopeptide and osteocalcin are markers of bone resorption, while procollagen 1 N-terminal peptide is a marker of bone formation. Some studies have shown that markers of both bone resorption and formation are low in T2DM, suggestive of impaired remodeling [107–109]. However, these data are conflicting and prevent applicability of bone turnover testing to fracture risk assessment in T2DM.

## FRACTURE PREVENTION AND TREATMENT IN TYPE 2 DIABETES MELLITUS

As with any disease process, prevention and treatment rest heavily on an understanding of the pathophysiology of the disease. Fracture in T2DM is no different. As this rich area of research casts light on why persons with T2DM break bones despite normal BMD, modalities of fracture prevention and treatment will grow. Without question, modification of the known risk factors for bone loss and fragility should be implemented in T2DM. Glycemic control to prevent end-organ damage has important implications for the skeleton, potentially reducing falls and renal osteodystrophy. Screening for vitamin D deficiency should be employed in men and women with T2DM. Vitamin D should be replaced, as needed, to prevent osteomalacia and secondary hyperparathyroidism. The importance of a diet high in calcium and vitamin D, as well as weight-bearing exercise, stressed most commonly in those with metabolic bone disease, should also be discussed with T2DM patients. Medications that might adversely impact the skeleton should be prescribed with

some caution, the risks and the benefits of drug initiation carefully weighed. There is no prospective data in the literature to show that the use of antiresorptive or anabolic therapy will prevent future fractures in those with T2DM and normal BMD. Retrospectively, studies have shown that antiresorptive therapy worked equally well in reducing fracture risk in diabetic and nondiabetic patients [110]. However, this group did not report baseline BMD or indication for drug initiation in either group, preventing generalizability of the conclusions to those with T2DM and normal BMD. Without a better understanding of the changes in bone quality and strength in T2DM, treating persons with glycemic derangement and normal BMD is difficult to justify.

## CONCLUSION

Additional research in men and women with T2DM will provide the basis for determining when and how to screen those at risk for fracture beyond BMD measurement. This knowledge will assist physicians in deciding when to initiate treatment to prevent fracture in T2DM and which existing therapy will best treat fragility when it occurs. Insight into declines of bone quality in persons with T2DM will one day guide disease-specific interventions. This may mean that physicians will one day treat persons with T2DM and normal BMD to prevent fracture. This paradigm shift may be necessary in this at-risk population in whom BMD measurements are falsely reassuring.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 146).

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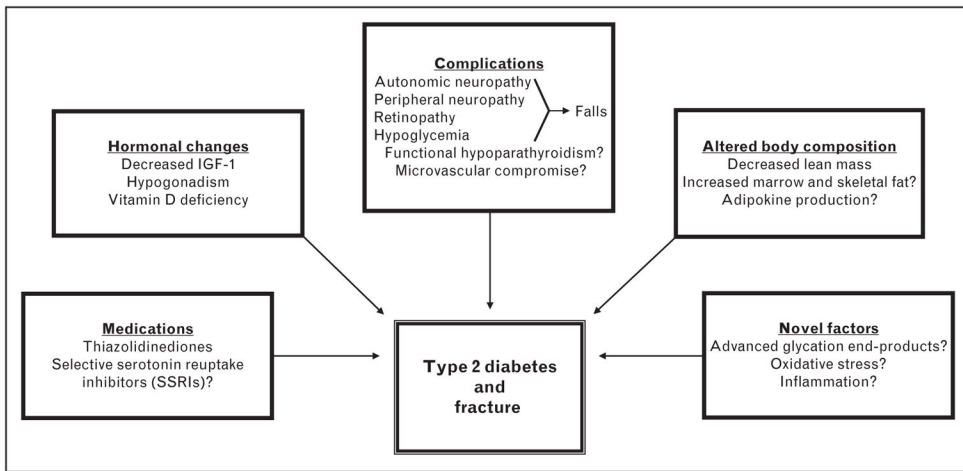
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**KEY POINTS**

- Despite normal to high bone density, men and women with type 2 diabetes are at increased risk for fracture.
- Medications like thiazolidinediones may increase fracture risk in persons with type 2 diabetes.
- Lean and fat mass may differentially affect bone strength in type 2 diabetes mellitus.
- Fracture risk assessment is challenging in men and women with type 2 diabetes given that dual X-ray absorptiometry does not necessarily predict fracture risk.



**FIGURE 1.**  
Proposed mechanisms of bone fragility in type 2 diabetes mellitus.