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# Skeletal Metabolism, Fracture Risk, and Fracture Outcomes in Type 1 and Type 2 Diabetes

*Diabetes 2016;65:1757–1766 | DOI: 10.2337/db16-0063*

**Fracture risk is significantly increased in both type 1 and type 2 diabetes, and individuals with diabetes experience worse fracture outcomes than normoglycemic individuals. Factors that increase fracture risk include lower bone mass in type 1 diabetes and compromised skeletal quality and strength despite preserved bone density in type 2 diabetes, as well as the effects of comorbidities such as diabetic macro- and microvascular complications. In this Perspective, we assess the developing scientific knowledge regarding the epidemiology and pathophysiology of skeletal fragility in patients with diabetes and the emerging data on the prediction, treatment, and outcomes of fractures in individuals with type 1 and type 2 diabetes.**

Fractures are a significant health issue for patients with diabetes. In type 1 diabetes (T1D), improvements in life expectancy are increasing the number of patients who are living to older age. In addition, over a quarter of adults aged 65 years and older in the U.S. have type 2 diabetes (T2D). In this older age-group, fractures are a common event; a 60-year-old white woman has a 44% probability of having at least one fracture in her remaining lifetime (1). The cost of treating fractures in the U.S. exceeded $17 billion in 2005 and is predicted to increase by 50% by 2025 (2).

Importantly, hip fractures result in a very high risk of mortality and disability. Mortality rates increase five- to eightfold in the 3 months following a hip fracture and remain elevated even 5 years after fracture (3). Furthermore, approximately 29% of hip fracture patients never return to their prefracture status for activities of daily living (4). Extended recovery time and disability are also common after a vertebral fracture.

Individuals with diabetes are at higher fracture risk and have even worse fracture outcomes than normoglycemic individuals. However, strategies to reduce fracture risk appear underutilized in this population, possibly related to challenges of identifying high-risk patients and concerns regarding effective treatments for prevention. The pathophysiology of increased skeletal fragility is complex, differs between T1D and T2D, and is the subject of intense investigation. In this Perspective, we review the current knowledge regarding the epidemiology and pathophysiology of diabetes-induced bone disease. We also discuss current issues pertaining to the prediction, treatment, and outcomes of fractures in individuals with T1D and T2D.

## EPIDEMIOLOGY OF FRACTURES IN INDIVIDUALS WITH T1D AND T2D

Individuals with T1D have double the risk of any fracture and four to five times higher hip fracture risk compared with those without diabetes (5). Higher fracture risk in T1D is evident in childhood and extends throughout the life span, affecting both sexes similarly. T1D is characterized by modest deficits in bone mineral density (BMD) that account for some, but not all, of the increased fracture risk (6). Reduced bone quality also appears to contribute to

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Received 13 January 2016 and accepted 23 March 2016.

increased fracture risk in T1D, as discussed later. In contrast, T2D is associated with overweight and higher bone density, factors that are associated with lower fracture risk in normoglycemic individuals. However, among older adults with T2D, the risk of hip fracture is increased 40–70% compared with normoglycemic individuals (6,7). Among individuals over the age of 65 years participating in the National Health and Nutrition Examination Survey (NHANES), the risk of any fracture in non-Hispanic white adults was similar in those with and without diabetes, as assessed by self-report or $HbA_{1c}$ ≥6.5% (hazard ratio [HR] 1.17 [95% CI 0.89–1.52]) (8). Given the age at diabetes diagnosis and use of insulin, it was estimated that 97% of participants had T2D in this analysis. Risks were higher compared with non-Hispanic black (HR 1.86 [95% CI 1.05–3.30]) and Mexican American (HR 2.29 [95% CI 1.41–3.73]) adults without diabetes. Higher fracture risk does not appear to extend to those with prediabetes, defined by fasting glucose or 2-h glucose (8,9).

Individuals with either T1D or T2D, particularly those with diabetes complications, are more likely to experience delayed healing and postsurgical complications, such as wound infection (10–14). Mortality following hip fracture is 1.44 times higher in those with diabetes (15). Several large case-control studies among individuals admitted with hip fractures have shown an increased risk of postoperative cardiac events among those patients with diabetes and an increased length of stay of 1–4 days (10,16,17).

Prediction of fracture risk in patients with T2D is challenging. Older adults with T2D have fractures at a higher bone density than individuals who do not have diabetes. As a result, while lower BMD does predict fracture risk in patients with diabetes, the BMD T-score underestimates fracture risk (18) (Fig. 1). For example, hip fracture risk in a woman with diabetes and a femoral neck BMD T-score of −1.9 is similar to the risk in a normoglycemic woman of the same age with a T-score of −2.5.

The World Health Organization Fracture Risk Assessment Tool (FRAX) takes into account additional risk factors besides BMD in fracture prediction, including age, sex, race, BMI, previous fracture, parental history of hip fracture, smoking, alcohol consumption, rheumatoid arthritis, and use of glucocorticoids. Glucocorticoid use in particular is higher among those with T2D. However, even with these additional risk factors taken into account, FRAX underestimates fracture risk in patients with T2D; it has been calculated that the effect of diabetes on FRAX estimated fracture risk is equivalent to adding 10 years of age (18).

Traditional risk factors for fracture, including lower BMD, older age, female sex, and glucocorticoid use, predict fractures in patients with diabetes (5,19). In addition, in patients with T2D, longer duration of diabetes and poor glycemic control are each associated with higher fracture risk (20–24). Among participants with diabetes in a U.S. cohort, those with baseline $HbA_{1c}$ >8% had a 1.63 (95% CI 1.09–2.44) higher rate of any fracture than those with lower $HbA_{1c}$ (23). Recent evidence suggests that poor glycemic control is a risk factor for fracture in T1D as well (5). There is evidence that microvascular complications (5,25), stroke, and cardiovascular disease (26) are also risk factors for fracture in T1D and T2D, although current data are limited (25).

The majority of fractures in older adults are the result of a fall with relatively modest trauma. Evidence regarding falls in patients with T1D is lacking, but a recent meta-analysis reported a modestly increased rate of falls in patients with T2D (HR 1.19 [95% CI 1.08–1.31]), with an even higher fall rate in insulin-treated patients with T2D (27). Although the increased propensity for falling likely contributes to the increased fracture risk at a given BMD, observational studies have found that falls do not fully account for the increased risk in T2D (9,21,28,29), suggesting that reduced bone quality is an important contributor. This epidemiological evidence is limited by the imprecision in measuring fall frequency by self-report.

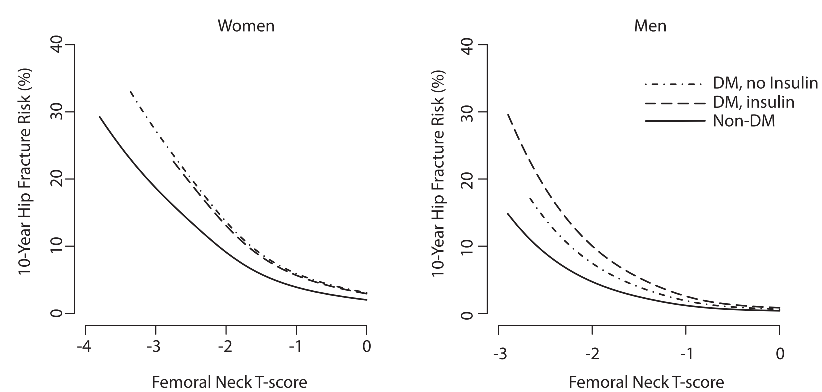


**Figure 1**—Femoral neck BMD T-score and 10-year fracture risk at age 75 years by diabetes status and insulin use. Estimated 10-year cumulative fracture risk at age 75 years in men and women, calculated using the Cox proportional hazards regression model baseline survival function raised to the power of the relative hazard for each combination of diabetes group and T-score. DM, diabetes. Adapted with permission from Schwartz et al. (18).

Rodent models of diabetic bone, discussed below, provide another indication that bone quality is reduced in diabetes.

## PATHOGENESIS OF T1D EFFECTS ON THE SKELETON

### Determinants of Reduced Bone Strength in T1D

The pathogenesis of impaired bone strength and increased fragility fractures in T1D is not fully understood. Skeletal health in this condition is highly variable and, as in normoglycemic individuals, depends on physical activity, lifestyle, and genetic factors. The age at diagnosis of T1D, disease duration and control, and the presence of microvascular complications affect bone mass and strength (30). Patients with T1D onset at childhood, i.e., before the peak bone mass is acquired, have a BMD measured by DXA that is, on average, 0.5–1.0 SD lower (30). Moreover, bones in children with T1D tend to be smaller, translating into an unfavorable geometry to resist fractures. These bone remodeling defects have been linked to a relative lack of the anabolic effects of insulin on osteoblastic bone formation (31) and alterations of the growth hormone/IGF-I axis as a result of poor metabolic control (32). However, bone size may only be transiently decreased; among 10-year-old children with T1D with a duration of 4 years, bone size was normal 5 years later (33). The exact biological basis underlying this "vulnerable phase" for bone development in some children with T1D is unclear.

In adults with T1D, most studies indicate a BMD of approximately 0.5–1.0 SD below subjects without diabetes of the same age, i.e., a *Z*-score of $-0.5$ to $-1.0$ when bone density is measured by DXA. Although the duration of the disease or $HbA_{1c}$ level was not commonly associated with low BMD, diabetic polyneuropathy, retinopathy, and nephropathy have been consistently linked to lower BMD in T1D (30). Trabecular bone score, an indirect assessment of bone microarchitecture derived from DXA scans, has also been shown to be lower in patients with T1D with vertebral fractures (34).

Lower BMD is an important contributing factor to fracture risk in T1D; however, the relatively modest reduction in BMD relative to normoglycemic individuals does not fully account for the increased fracture risk in patients with diabetes (6), suggesting that other aspects of bone quality not captured by DXA are compromised in T1D. Hypothesized mechanisms for reduced bone quality, in both T1D and T2D, include direct effects of hyperglycemia on bone cells, accumulation of advanced glycation end products (AGEs) in bone collagen, and damage to bone vasculature.

Two recent studies have linked microvascular disease to altered bone microarchitecture measured with high-resolution peripheral quantitative computed tomography (HR-pQCT) in T1D. Bone volume/total volume of the proximal tibia was lower in subjects with T1D and retinopathy was associated with lower serum IGF-I levels (35). Similarly, patients with T1D and retinopathy displayed lower total and trabecular volumetric BMD and substantial microarchitectural abnormalities, including lower trabecular thickness and estimated bone strength and greater trabecular separation and network inhomogeneity compared with patients without microvascular disease (36). Bone microarchitecture in the T1D patients without evidence of microvascular complications did not differ from those without diabetes (35,36).

### Alterations at the Bone Cell and Tissue Level

Rodent models of T1D do not fully recapitulate the bone alterations seen in humans; however, such models are useful to study the interactions between bone and energy metabolism. Commonly used models include the two spontaneous NOD mice (37,38) and BioBreeding diabetes-prone rats (39), as well as streptozotocin-induced diabetes in rats and mice (37,40,41). Studies in these animals consistently demonstrate reduced trabecular and cortical bone mass, reduced bone formation rate, and low bone turnover based on gene expression and histomorphometry analysis, possibly the result of increased oxidative stress. Insulin-treated animals showed no differences compared with control animals. Rodent models of diabetes also show a greater accumulation of AGEs in bone collagen, resulting in alterations in the material properties of the bone (42).

In vitro, high glucose levels and AGEs suppress bone formation by increasing sclerostin expression in osteocytes and AGEs inhibit bone resorption by decreasing RANKL expression; both effects can be prevented by pretreatment with parathyroid hormone (43). Osteoblast function has been shown to depend on glucose uptake via the transporter GLUT1, whose expression precedes that of Runx2, the earliest osteoblast transcription factor (44). In the absence of normal glucose uptake, Runx2 does not induce osteoblast differentiation, whereas increased serum glucose levels rescue osteoblast functions in Runx2 deficiency (44).

In humans, T1D is associated with lower serum levels of bone formation markers and vitamin D and results for bone resorption markers are equivocal (45). In contrast, a histomorphometry study of iliac crest biopsies found no major differences in bone formation rates, comparing 18 otherwise healthy patients with T1D and age- and sex-matched control subjects (46). However, this study only included T1D patients without any evidence of microvascular or macrovascular complications. Patients with T1D and a history of fracture showed subtle abnormalities in bone microarchitecture by micro–computed tomography and dynamic histomorphometry. In these T1D patients with fractures, the presence of pentosidine, an AGE, in the bone matrix, along with a higher degree of mineralization, was associated with a reduced modulus of elasticity, thus rendering the bone less flexible (47). In a separate study, serum levels of pentosidine were associated with prevalent fractures in T1D independently of BMD (48).

### Bone Vasculature in Diabetes

Bone vasculature is critical for bone growth, remodeling, and fracture healing as it provides sustained blood supplies of oxygen, nutrients, and regulatory factors and removal of metabolic waste. Bone receives up to 10% of cardiac output, which is distributed within the mineral compartment and the bone marrow by a complex system of sinusoid and classic capillaries. Vasculature also provides a niche for the development of osteoblast progenitors, and capillaries present in Haversian canals deliver osteoclasts and are a source of skeletal stem cells (pericytes) (49). The vascular complications in diabetes include impairment in endothelium-dependent vasodilation, vascular calcification, and defective angiogenesis, and it is conceivable that the same pathological changes develop in bone. Thus, reduction in bone and marrow blood flow and impairment in new vessel formation may have significant consequences for the osteoblast-dependent hematopoietic niche and decrease bone remodeling activity, consequently decreasing bone quality and delaying fracture healing.

Direct studies of diabetes and bone vasculature in humans are not available. However, indirect evidence provides some intriguing clues that vascular damage may be an important component of diabetic bone disease in both T1D and T2D. As discussed earlier, deficits in bone microarchitecture are associated with microvascular complications. The hip is particularly prone to fractures in T1D, which may be related to the peculiar vascular supply of the femoral head by an end artery (A. capitis femoris). In addition, microvascular complications are associated with lower BMD (30) and fracture risk in those with T1D (5).

## PATHOGENESIS OF T2D EFFECTS ON THE SKELETON

### BMD in T2D

As reviewed earlier, fracture risk is increased in patients with T2D despite preserved or even increased BMD by DXA. A meta-analysis reported high *Z*-scores of 0.41 at the spine and 0.27 at the hip in patients with T2D, primarily associated with the higher BMI in these patients (6). Data from a cohort of Chinese postmenopausal women with T2D showed that although obese patients with diabetes and control subjects had similar BMD T- and *Z*-scores at various skeletal sites, nonobese women with T2D had lower BMD than control subjects matched on BMI (50).

Even though obese patients with T2D have increased BMD by DXA, there is evidence that older white women, but not men or black women, with diabetes have more rapid bone loss at the femoral neck and total hip (51). In part, this was associated with weight loss over time in the white women, which did not occur in men or black women. However, the association between T2D and bone loss persisted at the femoral neck in white women even after adjusting for weight loss. Thus, despite having higher baseline BMD, white women with T2D have increased rates of bone loss, particularly at the femoral neck, which may contribute to their increase in fracture risk. This seemingly contradictory finding of higher cross-sectional BMD with more rapid bone loss may reflect the net result of the positive effects of overweight and hyperinsulinemia on bone combined with the negative effects of longer duration of diabetes, including the development of microvascular complications and accumulation of AGEs. In prediabetes and newly diagnosed diabetes, positive effects predominate, whereas with longer duration of diabetes, the negative effects become increasingly significant.

### Bone Turnover in T2D

Similar to T1D, most studies have reported reductions in biochemical markers of bone formation and bone resorption in patients with T2D (45). Whether there is a disproportionate reduction in bone formation relative to bone resorption remains unclear. A potential limitation with the use of serum markers of bone resorption (e.g., serum COOH-terminal telopeptide of type I collagen) in patients with diabetes is that, based on animal data, diabetes may be associated with a reduction in enzymatic cross-links, leading to an underestimation of the bone resorption rate (42). Although bone histomorphometry remains the definitive approach to assess bone remodeling, bone biopsy studies in T2D patients are sparse and have examined relatively small numbers of subjects. Significantly reduced indices of bone formation were found among 8 subjects with diabetes (2 with T1D and 6 with T2D) as compared with 23 control subjects (52). Data on bone resorption were not explicitly provided in this report, though Krakauer et al. (52) commented that "eroded surface was high-normal but osteoclast surface was low-normal (data not shown), probably reflecting prior resorptive activity that was not followed by formation." In another study, reduced dynamic indices of bone formation (bone formation rate and osteoblast numbers/bone surface) were found in 5 subjects with T2D relative to 4 control subjects (53). Eroded surfaces and osteoclast numbers/bone surface did not differ between the T2D and control subjects. Thus, bone formation appears to be reduced in T2D patients, while data regarding bone resorption are less clear.

Increased serum sclerostin, which inhibits bone formation, has been reported in patients with T2D relative to control subjects (54,55); however, the role of sclerostin in mediating impaired bone formation in T2D remains to be established.

### Bone Quality in T2D

Considering that BMD by DXA is preserved, other components of skeletal strength generally categorized as "bone quality" may be abnormal in T2D patients. As high glucose levels lead to the accumulation of AGEs in the organic bone matrix by nonenzymatic glycation, it is possible that the accumulation of AGEs in bone leads to impaired biomechanical properties in T2D patients (56). Support for this hypothesis comes from studies showing that urinary pentosidine is associated with increased fracture incidence in T2D patients (57) and that serum pentosidine is increased in T2D patients with vertebral fractures (58). Thus, the accumulation of AGEs may be a common pathophysiological mechanism of reduced bone quality in T1D and T2D.

Further supporting the notion of defective bone quality (and strength) in T2D, one study using HR-pQCT (59) demonstrated that cortical porosity was markedly increased (by 124%) in 19 T2D postmenopausal women relative to an equal number of control subjects without diabetes (59) (Fig. 2). None of the trabecular parameters (e.g., trabecular bone volume fraction, trabecular number or thickness) differed between the T2D and control subjects. An increase in cortical porosity, albeit of lesser magnitude (26%), was also reported in 22 African American women with T2D relative to 78 control women (60), again with no significant differences in trabecular parameters. Thus, increased cortical porosity, an element of bone quality not assessed by DXA, may contribute to increased fracture risk in T2D patients.

In addition to bone microarchitecture, the material properties of bone also contribute to bone quality. Recently, microindentation of the cortex has gained acceptance as a research tool for estimating bone material strength in humans. Following local anesthesia, this device creates microindents over the shaft of the tibia, which provides a measure of bone material strength (bone material strength index [BMSi]). This technique (61) showed that postmenopausal women with T2D have significant reductions in BMSi as compared with control subjects without diabetes (Fig. 3). This study also found that $HbA_{1c}$ levels were inversely correlated with BMSi in the T2D patients, suggesting that the abnormal bone material properties in these patients may be related to chronic hyperglycemia, perhaps mediated by AGEs.

### Bone Turnover and Insulin Signaling

Hyperinsulinemia and hyperglycemia may affect bone remodeling by either directly modulating activities of bone cells or changing the milieu of the bone marrow environment. Osteoblasts, osteoclasts, and osteocytes express insulin receptors, and animal studies imply that increased insulin signaling correlates positively with bone turnover and bone formation, whereas insulin resistance attenuates bone remodeling (62,63). Bone dependence on insulin and glucose metabolism poses the question as to whether bone develops insulin resistance and whether such resistance is manifested with decreased bone turnover. Clarification of this issue may have significant implications for the development of therapies to treat diabetic bone disease associated with low bone turnover.

### Bone and Fat Relationships in T2D

Impairment in adipose tissue function is one of the consequences of T2D that directly affects carbohydrate and lipid metabolism and insulin sensitivity. Increase in visceral adiposity, which relates to increased inflammation and metabolic syndrome, is negatively associated with lumbar volumetric BMD (64) and with bone volume and bone formation in iliac crest biopsies from premenopausal women (65). Fat infiltration in muscles is increased in diabetes and is associated with incident fractures, although this association does not account for the higher fracture risk in diabetes (66). Diabetes is associated with higher marrow fat in rodent models, although definitive human studies are lacking (37,67). Increased marrow adiposity and decreased levels of unsaturated fatty acids in the bone marrow correlate positively with fractures (68,69). Marrow adipose tissue accumulates in long bones and vertebrae and constitutes up to 10% of total body fat. Marrow adipose tissue is both unique and similar to extramedullary fat in respect to origin, metabolism, and function and possesses characteristics of both white and beige fat (70). Studies in rodents show that the beige phenotype, which is characterized by the production of bone anabolic factors, is attenuated with diabetes despite an expansion of this fat depot (71).

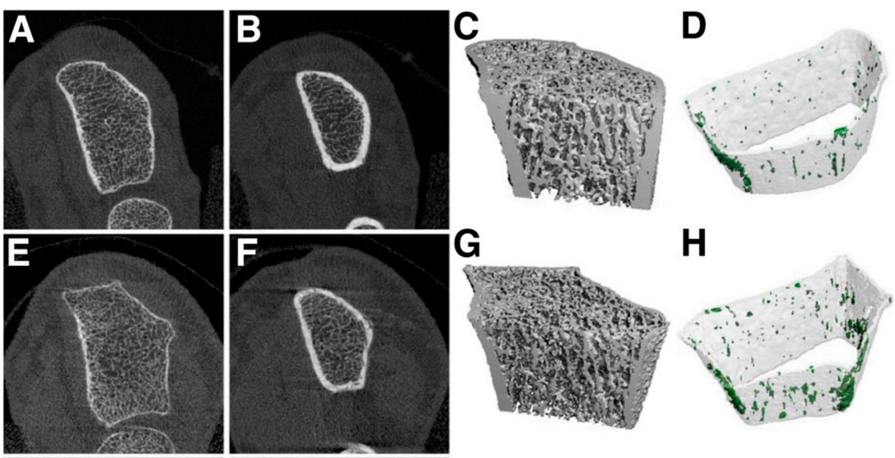


**Figure 2**—Median (by total volumetric BMD) HR-pQCT images of the distal radius from control (top) and T2D (bottom) subjects: distal-most slices (*A* and *E*), proximal-most slices (*B* and *F*), three-dimensional visualization of the mineralized bone structure (*C* and *G*), and three-dimensional visualization of cortical bone (transparent gray) and cortical porosity (dark gray dots) (*D* and *H*). Reprinted with permission from Burghardt et al. (59).

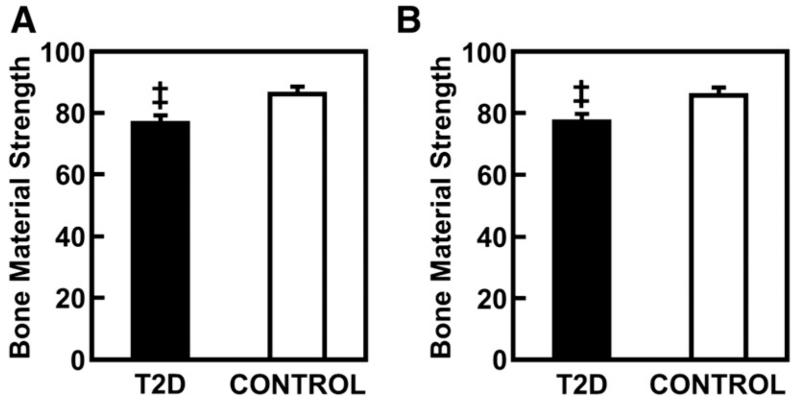


**Figure 3**—Unadjusted (*A*) and BMI-adjusted (*B*) comparisons of bone material strength between patients with T2D and age-matched control subjects without diabetes. Values are shown as mean ± SE. ‡*P* < 0.001. Reprinted with permission from Farr et al. (61).

### Bone and Antidiabetes Medications

As bone is involved with energy metabolism, it can be a target for certain antidiabetes therapies (72). Thiazolidinediones (TZDs), high-affinity ligands and activators of peroxisome proliferator–activated receptor $\gamma$, target hematopoietic and mesenchymal cells in the bone marrow, resulting in unbalanced bone remodeling with high bone resorption and low bone formation and consequent bone loss and accumulation of large quantities of fat in the bone marrow cavity. Increased bone loss at the lumbar spine, total hip, and femoral neck in women on TZD therapy emerged in the recent meta-analysis of 10 randomized clinical trials (73). Therapy with either rosiglitazone or pioglitazone also increased fracture risk by approximately twofold in women, but not in men. Risk appeared to increase with duration of treatment.

Recently, a novel class of antidiabetes medications, sodium–glucose cotransporter 2 inhibitors, has been scrutinized by the U.S. Food and Drug Administration for a potential harmful effect on bone. It has been reported that patients receiving canagliflozin have an increased fracture rate as early as 12 weeks after initiating therapy (74). However, there was no difference in fracture rates for empagliflozin (75). The bone risk associated with sodium–glucose cotransporter 2 inhibitor therapy may include alterations in calcium and phosphate homeostasis or more direct effects on cells involved in bone remodeling owing to the glucose dependence of their metabolism. There is no evidence for negative effects on bone of other antidiabetes therapies, including biguanides, glucagon-like peptide 1 analogs, and dipeptidyl peptidase 4 inhibitors; in fact, some of these therapies may even be protective against fractures (72).

## MANAGEMENT OF LOW BONE MASS AND FRACTURE PREVENTION

### Effects of Diabetes Complications and Improving Glycemic Control as a Means to Reduce Fracture Risk

Diabetic microvascular complications, such as neuropathy, nephropathy, and retinopathy, have been associated with an increased risk of falls and fractures. Additionally, poor glycemic control, generally defined as an $HbA_{1c}$ value >8%, has been shown to increase fracture risk; however, the fracture benefits of reducing $HbA_{1c}$ levels to lower levels have not been established. In randomized trials among individuals with T2D, neither intensive glycemic control (median $HbA_{1c}$ 6.4% in the intensive group vs. 7.5% in the standard glycemic control group) nor intensive blood pressure control affected the risk of falls or fractures, either positively or negatively (76,77). Although there is limited evidence that improved glycemic control may prevent bone loss in T1D (78), significant hypoglycemia has been associated with increased fracture risk in T1D and T2D, possibly related to falls in the older population (79,80). Glycemic control following current guidelines may be helpful to prevent complications, removing the contribution of hyperglycemia and diabetes complications to increased fracture risk; however, hypoglycemia should be avoided, particularly in older individuals. The evidence that TZDs increase fracture risk in postmenopausal women is robust, and these agents should be avoided in postmenopausal women with T2D.

### Prevention of Postfracture Complications in Patients With Diabetes

Animal studies demonstrate reduced rates of cellular differentiation, delayed callus formation, and slowed mineralization after fracture in diabetic animals (81–83). Tight glycemic control and local insulin infusion improve these bone properties in animals (84,85). In humans, higher $HbA_{1c}$ levels at the time of surgery for ankle fracture and within 3 months postoperatively have been associated with an increased risk of infection, delayed union, malunion, and nonunion among patients with T1D or T2D (13,86). Although a baseline and postoperative $HbA_{1c}$ level <7% appears to be beneficial in several reports, data are not available on the optimal level of glycemic control in patients with diabetes with fractures. Until such data are available, current guidelines for inpatient and outpatient glycemic control should be followed.

### Nutrition and Lifestyle Interventions to Reduce Fracture Risk

Age-appropriate intakes of calcium and vitamin D should be ensured in all individuals with diabetes. Calcium intake and calcium supplements are not associated with the amount of calcified plaque in the carotid, coronary, or aortic arteries in individuals with T2D (87). Weight-bearing physical activity increases bone density in children with T1D to a degree similar to that in normoglycemic children (88). Assessment of fall risk and appropriate fall prevention measures should be included in the care of older patients with diabetes. Among overweight adults with T2D, significant weight loss may result in bone loss, although the magnitude of bone loss appears to be small (less than 1% at 4 years), was seen only in men, and fracture rates were not increased (89,90). The optimal exercise regimen for weight reduction in individuals with diabetes while minimizing bone loss has not been determined.

### Effect of Osteoporosis Therapies in Patients With Diabetes

As discussed earlier, serum markers of bone turnover are generally lower in patients with T1D and T2D than in normoglycemic individuals, raising the concern that antiresorptive agents used as osteoporosis therapy may further exacerbate an already decreased remodeling state rather than provide a protective skeletal effect. However, registry data and data from clinical trials of osteoporosis medications support the effectiveness of these agents in individuals with diabetes. Alendronate increased bone density in 297 women with diabetes enrolled in the Fracture Intervention Trial (FIT) equivalently to normoglycemic individuals (91). Raloxifene reduced the risk of vertebral fracture risk by 35% in the Raloxifene Use for The Heart (RUTH) trial, with consistent effects among subgroups including the approximately 4,500 women with diabetes (92). Examination of osteoporosis medication use and fractures in the Danish Registry demonstrated no difference in fracture rates during treatment with bisphosphonates or raloxifene between individuals with T1D or T2D and normoglycemic control subjects (93). No definitive data are available for strontium or teriparatide, for which only case reports exist.

Analysis of bisphosphonate and denosumab randomized fracture trials shows no significant effect of osteoporosis medications on glucose levels or diabetes incidence (94). Observational data among a small number of individuals treated with teriparatide show similar findings (95).

## SUMMARY

Fracture risk is increased in individuals with T1D or T2D, and consequences of fracture are more severe. Reduced bone density contributes to fracture risk in T1D. In T2D, BMD is increased, but in both T1D and T2D, bone quality is negatively affected. Abnormalities of bone cells, bone tissue, and microstructure may all contribute, but the precise mechanisms leading to such abnormalities remain unclear. The roles of hyperglycemia, AGEs, and damage to bone vasculature are current areas of research. Increased falls also contribute to the higher fracture risk. Improved glycemic control may reduce fracture risk and is important to fracture healing but must be balanced against negative effects of hypoglycemia. Nutrition and lifestyle measures to improve bone health are appropriate for individuals with diabetes, and osteoporosis medications have generally proven to be equally effective in patients with diabetes compared with euglycemic individuals. Initiation of osteoporosis medications in patients with diabetes with low bone density or low-trauma fracture is appropriate. More data are needed on identifying patients with diabetes with normal bone density and no history of fracture who will benefit from treatment with osteoporosis medications to prevent fractures. If patients with diabetes develop renal insufficiency, particularly when estimated glomerular filtration rate is below 30 mL/min or the patient undergoes transplantation, additional considerations with respect to renal-related metabolic bone disease or glucocorticoid treatment also need to be addressed. Although skeletal health in T1D and T2D is an area of very active investigation, much remains to be learned regarding the pathophysiology of increased fracture risk, how to estimate fracture risk, and effective strategies to reduce fracture risk in patients with diabetes.

**Funding.** L.C.H. received grant support from Deutsche Forschungsgemeinschaft Sonderforschungsbereiche/Transregio 67 (Project B2). S.K. received grant support from the National Institutes of Health (AG004875 and AR027065). B.L.-C. received grant support from the American Diabetes Association (7-13-BS-089).

**Duality of Interest.** D.E.S. is a member of Data Safety Monitoring Board for Amgen. R.C. received research support from Amgen and has stock ownership in Amgen, Eli Lilly, and Merck & Co. A.V.S. received a speaker honorarium from Chugai Pharmaceutical Co. and served on an advisory board for Janssen Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

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