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Bone health in type 1 diabetes

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Abstract

Purpose of review—This article reviews recent publications on the effect of type 1 diabetes (T1D) on fracture risk, bone mineral density (BMD), bone structure, and bone tissue quality. Possible fracture prevention strategies for patients with T1D have also been reviewed.

Recent findings—T1D is associated with substantially elevated fracture risk and modestly low BMD at the femoral neck. However, BMD alone does not explain higher observed fracture risk in T1D. T1D also affects bone macro- and microstructure, characterized by thinner cortices and trabecular bone changes such as thinner and more widely spaced trabeculae. Structural bone deficit is pronounced in the presence of microvascular complications. Tissue-level changes, such as accumulation of advanced glycation endproducts, detrimental alterations of the mineral phase because of low bone turnover, and occlusion of vascular channels in bone by mineralized tissue, are implicated in pathophysiology of bone fragility in T1D. There are no guidelines on screening and prevention of osteoporotic fractures in T1D.

Summary—More studies are needed to understand the influence of T1D on structural bone quality and tissue material properties. There is a need for a prospective study to evaluate better screening strategies for diagnosis and treatment of osteoporosis in T1D.

Keywords

bone mineral density; bone quality; falls; fragility fractures; osteoporotic fractures; type 1 diabetes

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Conflicts of interest

V.N.S. conceptualize the idea. V.N.S, R.D.C., and C.F. wrote the first draft of the manuscript. A.V.S. edited and reviewed the manuscript.

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INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease characterized by loss of insulin-producing pancreatic β cells [1]. The management of T1D requires lifelong insulin therapy to achieve glycemic control and reduce diabetes-related complications. Research historically focused on improving glycemic control and optimizing insulin delivery in people with T1D, which significantly reduced microvascular complications and improved longevity [2-4]. The focus has since expanded to understand T1D effects on particular outcomes in older adults, including cardiovascular complications, dementia, and osteoporotic fractures.

Recently, an increasing number of studies have improved our understanding of bone health with T1D. This review summarizes recent research on epidemiology of osteoporotic fractures, effect of diabetes on bone mineral density (BMD), structural and tissue bone quality, and falls. In addition, we review possible fracture prevention and osteoporosis treatment strategies for patients with T1D.

Fracture risk in type 1 diabetes

Diabetes has been recently recognized as one of the risk factors for fragility fractures. Fracture risk is higher in both T1D and type 2 diabetes (T2D) [5]. However, the increase in relative hip fracture risk is higher in T1D than in T2D [6]. A recent meta-analysis of 14 observational studies reported 2066 fracture events among 27,300 adults with T1D (7.6%) and 136,579 fracture events among 4,364,125 people without diabetes (3.1%) [7]. The relative risk for any fracture, hip fractures, and spinal fractures were 3.16 (1.51–6.63), 3.78 (2.05–6.98), and 2.88 (1.71–4.82), respectively, among adults with T1D [7]. Women with T1D had twice the risk for fracture compared with men with T1D. In a population-based cohort study, Weber *et al.* [8] reported increased risk of incident fracture, especially extremity fractures, that began in childhood and extended across the life span in patients with T1D.

Bone mineral density in type 1 diabetes

T1D incidence peaks between the ages of 10 and 14 years [9] and accounts for nearly 85% of all diabetes cases in youth (age <20 years). High glucose, metabolic perturbation, and low level of insulin-like growth factor-1 likely affect bone accrual in young individuals with T1D [10]. Many studies, but not all, have reported lower BMD in children and adolescents with T1D; Shah *et al.* [11] and Pan *et al.* [12] reviewed BMD studies in T1D populations. One study revealed lower BMD at the time of diagnosis of T1D in adults [13]. However, a few small longitudinal studies reported normalization of BMD or bone size over time in patients with T1D [14-16]. The inconsistency in BMD findings between T1D studies in children and adolescents may be because of differences in sample size, duration of diabetes, age at T1D diagnosis, glycemic control, and pubertal staging among study population. A meta-analysis of 16 studies reported a 0.055 g/cm^2 reduction in femoral neck BMD in adults with T1D compared with controls when adjusted for age, sex, and dual X-ray absorptiometry (DXA) instruments [11]. There was no difference in lumbar spine BMD between adults with T1D and controls [11]. Studies are conflicting on the associations of glycemic control and duration of diabetes with BMD, but presence of microvascular complications (retinopathy,

neuropathy, and nephropathy) is consistently associated with low BMD in patients with T1D [6,10,17■■].

The relatively modest reduction in BMD in T1D compared with controls does not fully account for increased fracture risk with T1D. Therefore, aspects of bone quality not captured by DXA have been implicated in increased bone fragility in patients with T1D.

Trabecular bone score in type 1 diabetes

Trabecular bone score (TBS) is a two-dimensional textural index that evaluates pixel gray-level variations in lumbar spine DXA images, providing an indirect index of trabecular microarchitecture that correlates with trabecular bone volume to tissue volume ratio, trabecular number, and connectivity [18-20]. TBS improves fracture risk prediction independent of BMD and has been incorporated into Fracture Risk Assessment Tool (FRAX) [21-22]. Studies on TBS in T1D are conflicting with one reporting lower levels [23] compared with controls and another finding no differences [24].

Bone turnover in type 1 diabetes

In a meta-analysis of bone turnover in patients with T1D, osteocalcin, a marker of bone formation, and CTX, a marker of bone resorption, were modestly lower compared with controls [25,26]. There were no differences in levels of calcium, phosphorus, and parathyroid hormone between patients with T1D and controls [26]. A study of bone histomorphometry showed no differences in bone formation or resorption parameters from 18 well controlled young patients with T1D and 18 age-matched controls [27]. When T1D patients with and without a history of fracture were compared in this same group, reduced activation frequency and increased degree of mineralization were observed in those with fracture [28]. These findings suggest that T1D is a state of low bone turnover particularly in those with a history of fractures. Low bone turnover may result in bone fragility because of inadequate repair of microdamage.

Structural bone quality in type 1 diabetes

Measurements of bone macroscale geometry, including cross-sectional area and cortical thickness, have helped to uncover the effects of T1D on bone structure. Quantitative computed tomography revealed lower cortical thickness and cross-sectional area in the intertrochanteric region of the proximal femur in T1D patients [29]. At the femoral diaphysis, the outer perimeter of the bone and the cross-sectional area of the cortex were also reduced. A follow-up study of the same study participants found that the supero-posterior portion of the femoral neck cortex was thinner in the T1D group [30]. Distal radius cortical thinning using peripheral quantitative computed tomography was reported in male T1D patients [31]. The thinner cortices in T1D were not because of an overall smaller bone size, as the T1D patients also had a larger endosteal circumference at the distal radius. Similar findings at the distal radius were observed using high-resolution peripheral quantitative computed tomography imaging of the radius and distal tibia [32]. The radii of study participants in T1D had a larger overall cross-sectional area and a thinner cortex, again supporting the idea that the cortex in T1D was thinner not because of an overall smaller bone size, but because of an enlarged trabecular bone compartment. There were no

differences in trabecular microarchitecture at the distal radius or tibia between patients with T1D and controls. However, T1D patients with microvascular disease tended to possess trabeculae at the distal radius that were thinner (P=0.09), of lower number per unit volume (P=0.05), and with larger spacing (P=0.05). Similar microarchitecture findings were observed at the distal tibia [32]. Despite the trend toward degraded trabecular structure, neither the finite element-predicted strength nor stiffness of the radius was compromised in T1D. Micromagnetic resonance imaging showed lower trabecular number and increased trabecular spacing in proximal tibiae of women with T1D [33]. These studies suggest that T1D primarily affects cortical bone structure, whereas changes to trabecular bone, characterized by thinner, more widely spaced trabeculae, may occur but to a lesser extent.

Mechanisms for structural bone deficit in type 1 diabetes

The importance of vascular supply for bone formation, remodeling, and fracture repair is well recognized [34,35]. Studies in patients with T1D have shown a consistent link between microvascular complications and bone structural deficits [17■■,32,33]. However, it is unclear whether these deficits in patients with T1D result from microangiopathy caused by microvascular disease resulting in reduction in blood flow and altered bone remodeling, or cellular and molecular changes caused by prolonged hyperglycemia. For example, microangiopathy in an insulin-deficient mouse model [36] revealed diminished cumulative vascular density, suggesting reduction in blood flow, increased vasculature permeability, and depleted endothelial cells. These microvascular changes were associated with increased oxidative stress, DNA damage, and activation of apoptosis of bone marrow cells. Thus, structural deficits observed in human studies may be because of microvascular complications in T1D. Blood flow to the proximal femur is lower than that to the spine [37]. Interestingly, men with T1D showed a structural deficit at the proximal femur, with no changes at the spine [29,30]. Studies have reported higher relative risk for hip than for spine fracture in adults with T1D [6,7]. Thus, microangiopathy may have a more deleterious effect on hip structure.

In addition to microangiopathy, it is postulated that advanced glycation endproducts (AGEs), relatively low insulin-like growth factor-1 despite intensive insulin therapy, and amylin deficiency may have direct effects on osteoblasts and osteocytes, resulting in low bone formation and structural bone deficits [10]. More studies are needed to understand the role of microangiopathy or other mechanisms on pathophysiology of bone fragility in T1D.

Bone tissue quality in type 1 diabetes

In addition to bone geometry and microarchitecture, heterogeneity and toughness, aspects of bone mineral quality influence bone fragility.

Although it is becoming increasingly apparent that bone fragility in T2D is influenced by diminished bone material quality [38], how T1D influences bone material remains underexplored. Within the organic phase, AGE accumulation in bone tissue is associated with increased collagen cross-linking and reduced bone strength in T2D [39]. Collagen cross-links stiffen the organic matrix and increase fracture propensity. Expression of noncollagenous protein expressions may also be altered in T1D and may influence bone

fragility. However, a comprehensive understanding of how bone's organic matrix is affected in T1D is unclear. Reduced bone turnover in T1D, and the resulting accumulation of aging bone mineral, also increases the likelihood of a shift to a bone that is increasingly carbonated and consequently weak [40,41]. If vacancies are created by transition to a more carbonated bone mineral matrix, the unbound water fraction observed in T1D would increase and detrimentally influence bone tissue strength and toughness [42]. Moreover, occlusion of vascular channels with microvascular disease in T1D [32] would also increase bone tissue stiffness and, consequentially, bone fragility.

Falls in type 1 diabetes

Insulin treatment, microvascular complications (i.e., peripheral neuropathy and retinopathy), and hypoglycemia are associated with increased risk of falls in people with T2D [43-45]. However, observational studies have found that falls do not fully account for increased fracture risk in T2D [45]. Currently, prevalence and predictors of falls and the relative contribution of falls to fracture risk are not known in T1D.

PREVENTION AND TREATMENT OF OSTEOPOROSIS IN TYPE 1 DIABETES

Screening

Since BMD is the best single predictor of fracture risk, BMD by DXA is recommended for postmenopausal women and men at high risk for osteoporosis. T1D is associated with substantially elevated risk for fractures even in the younger population (<50 years), yet there are no specific guidelines on BMD screening for T1D patients. In addition, it is likely that BMD by DXA will tend to underestimate fracture risk in patients with T1D, adding complexity to osteoporosis screening. The utility of TBS as a screening tool for osteoporosis in T1D remains to be established.

FRAX is an algorithm, intended for use in primary care, for calculating fracture risk from clinical risk factors (such as age, sex, BMI, steroid use, current smoking, and alcohol intake) with or without the addition of femoral neck BMD. Insulin-dependent diabetes is included as one of the causes of secondary osteoporosis in the FRAX algorithm but it is not a primary variable [46]. Therefore, fracture probability increases when BMD is not included in the FRAX calculation [46]. As seen in T2D, FRAX is likely to underestimate fracture risk in T1D [47]. However, the degree of underestimation of fracture risk is not known. Longitudinal studies are needed to evaluate screening strategies for fracture prediction among the T1D population.

Preventive measures

High glucose levels are known to increase urinary calcium, resulting in negative calcium balance [48]. Therefore, age-appropriate intake of calcium and vitamin D should be ensured in all patients with T1D. However, longitudinal or randomized control trials are lacking that evaluate these dietary supplements for fracture prevention in the T1D population. Appropriate physical activity should be recommended for patients with T1D. Comparable increases in bone density are observed after weight-bearing exercise in children with T1D [49]. However, physical activity increases risk for hypoglycemia in T1D patients and

therefore, adjusting food or insulin doses should be recommended to avoid hypoglycemia [50]. Similarly, fall assessment and prevention should be included in older adults with T1D to reduce risk for fragility fractures.

Microvascular complications are associated with reduced BMD, impaired bone quality, and increased fracture risk in patients with T1D [17■■], and glycemic control can reduce microvascular complications [51]. However, it is not known whether intensive insulin therapy to improve glycemic control is beneficial in improving bone health. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, intensive insulin therapy was not associated with increase or decrease in risk for falls or fractures in patients with T2D [52].

Autoimmune disease such as celiac disease is common among patients with T1D [53]. Celiac disease is associated with lower BMD in children and adolescents with T1D [54,55], and this group may be at particularly high risk for fracture. All patients with T1D should be screened for celiac disease at diagnosis and periodically especially in presence of symptoms or low BMD [56]. Initiation of gluten-free diet improves BMD and bone microarchitecture in patients with celiac disease [57].

Thiazolidinedione, sulfonylureas, and sodium glucose transporter-2 inhibitors, treatments for T2D, are associated with increased fracture risk [10,45]. None of the T2D medications is approved for use in patients with T1D; however, off-label use is common in patients with T1D [58]. Use of thiazolidinediones and sodium glucose transporter-2 inhibitors should be avoided in patients with T1D, given their high risk of fracture.

Treatment

Despite low bone turnover in patients with T1D, analysis from the Danish Registry reported no difference in treatment efficacy of two bisphosphonates (alendronate and etidronate) in patients with T1D compared to patients with T2D [59]. However, the risk for atypical femoral fracture is higher among postmenopausal women with diabetes than in women without diabetes [60]. There are no randomized controlled trials comparing the efficacy and safety of bisphosphonate or anabolic agents (parathyroid hormone or abloparatide) on BMD or fracture outcomes in patients with T1D.

CONCLUSION

T1D is associated with a three-to six-fold higher risk for fractures. BMD is modestly lower, especially at the femoral neck; however, BMD does not fully explain higher fracture risk. Recent findings suggest that T1D affects cortical, and to a lesser extent trabecular, bone microstructure: Thinner cortices and trabecular bone deficits are more pronounced in T1D patients with microvascular complications. Little is known about tissue-level bone quality. Accumulation of AGEs, detrimental alterations of the mineral phase because of low bone turnover, and deficits in bone vasculature because of microvascular disease are implicated in the pathophysiology of bone fragility in T1D. The relative contribution of falls in fracture risk is not known. Research is needed to expand our current limited knowledge on how T1D

influences bone metabolism and to develop clinical guidelines on screening and prevention of osteoporotic fractures in T1D.

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KEY POINTS

- Fracture risk in T1D is three-fold to six-fold higher compared with people without diabetes.
- BMD alone does not explain high fracture risk in T1D.
- Cortical thinning is more pronounced than trabecular changes.
- Structural changes in bone are more apparent in those with microvascular complications.
- T1D is a low bone turnover state; however, little is known about tissue level changes in T1D bone.