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Bone Microarchitecture in Type 1 Diabetes: It's Complicated

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Abstract

Patients with type 1 diabetes (T1DM) experience a disproportionate number of fractures for their bone mineral density (BMD). Differences in bone microarchitecture from those without the disease are thought to be responsible. However, the literature is inconclusive. New studies of the microarchitecture using three-dimensional imaging have the advantage of providing *in vivo* estimates of “bone quality,” rather than examining areal BMD alone. There are drawbacks in that most studies have been done on those with less than 30 years duration of T1DM, and the techniques used to measure vary as do the sites assessed. In addition to the rise in these imaging techniques, very recent literature presents evidence of an intimate relationship between skeletal health and vascular complications in T1DM. The following review provides an overview of the available studies of the bone microarchitecture in T1DM with a discussion of the burgeoning field of complications and skeletal health.

Keywords

Bone quality; microarchitecture; type 1 diabetes; diabetes; complications; bone fragility

Introduction

Type 1 diabetes (T1DM) is characterized by insulin deficiency due to pancreatic β -cell destruction. Diabetes and fracture have been associated with early mortality and increased morbidity and have a significant effect on quality of life. The major burden of early mortality in those with T1DM is from renal disease and CVD, both of which have been

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Conflict of Interest

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linked with bone disease [1]. Dual-energy X-ray absorptiometry (DXA) studies assessing bone mineral density (BMD) indicate an increase in risk for fracture in this group, but do not explain the excess risk in hip fracture experienced by those with T1DM relative to those with type 2 diabetes (T2DM) (HR 6.3 v 1.4) [2–6] and those without diabetes. In a further effort to understand the paradox of a relatively small shift in BMD curve and an almost 5-fold increase in risk over those with T2DM for fracture it has been hypothesized that there are differences in the geometry and/or microarchitecture of those with T1DM.

The microarchitecture or quality refers to the structural integrity and strength of the bone rather than just density measured by x-ray. These factors comprise internal design including geometry, trabeculae distribution and porosity of different compartments, and make-up, such as collagen content and cross-linking [7]. These are important differentiations as each anatomical site consists of varying proportions of cortical versus trabecular bone, varying in strength and potential for failure. As the balance of formation and turnover of each type of bone is subject to different mechanisms each site may be affected differently by the systemic influences of hypoinsulinemia, hyperglycemia and the effects of vascular dysfunction.

Riggs et al estimated from a population based study from Rochester, MN, of whom 96% were white between 20–29 years, that the lumbar spine indeed is mainly composed of trabecular bone (>80%), while the ultra-distal radius and the ultra-distal tibia are made up of more than 95% cortical bone [8]. The femoral neck is also considered to be predominantly cortical made up of approximately 35% trabecular and 65% cortical bone [8]. Through comparison of differences in geometry, volumetric characteristics and microarchitecture across anatomical site mechanisms of pathologies, investigators are attempting to understand the various ways diabetes causes increases in skeletal risk. This review provides an overview of the findings so far on bone microarchitecture in T1DM and the burgeoning research on diabetic complications in individuals with this disease.

Methods of literature assessment

A search of the literature available through pubmed.gov using the terms “bone microarchitecture AND type 1 diabetes”, “bone geometry AND type 1 diabetes”, and “insulin AND bone” was used, along with a review of the references of the papers found through this research. All papers identified assessing the microarchitecture of those with T1DM were included in the review.

Assessment of bone quality in T1DM with QCT and pQCT

The use of several imaging techniques has allowed quantifications of the internal structure and measure of bone strength to ascertain bone integrity to better predict adverse outcomes. These methods include: trabecular bone score (TBS), micro-MRI, quantitative computed tomography (QCT), peripheral QCT, and high resolution- quantitative computed tomography (HR-pQCT), each having advantages in terms of resources and information ascertained [9]. Although these techniques provide tremendous insight, implementation of any of them is costly even in well-funded tertiary care settings.

QCT and pQCT imaging techniques have the ability to provide volumetric BMD, to separately assess cortical and trabecular bone, and to determine bone geometry, advantages over BMD by DXA. However, they do not have sufficient resolution to assess microarchitecture. The pQCT method was used in four case-control [10–13] and two longitudinal studies [14,15]. One additional study used QCT of the lumbar spine [16] (table 1). The average T1DM duration in those studies was 5 years with an average age of 14.4 years, reflecting a young population who had not yet reached peak bone mass with only a few years of T1DM exposure. Although the conclusions across studies were mixed, the trend of results was towards a deleterious effect of the disease on trabecular volumetric BMD. In the two longitudinal studies performed, there were mixed findings likely due to differing time courses. Moyer-Mileur et al's 2004 study found adolescents with T1DM had smaller bones, and this pattern was maintained a year after follow-up [14]. Yet, in a longitudinal study by Bechtold over 5.5-years those with T1DM showed a reduced total, cortical, and trabecular quality at baseline, but no significant differences at follow-up from their peers without diabetes, suggesting only transient impairments in bone metabolism [15].

Further progress in characterizing T1D bone has required new imaging techniques that can assess microarchitecture.

Assessment of bone microarchitecture in T1DM

Historically, the only technique available to assess bone microarchitecture required bone biopsy. More recently, imaging techniques have become available with sufficient resolution to assess microarchitecture and have been used in type 1 diabetes (table 2). HR-pQCT enables a sensitive and specific non-invasive assessment of bone geometry and microarchitecture *in vivo*. This method provides measures of trabecular and cortical volumetric BMD (vBMD), microarchitecture and geometry at the distal radius and tibia providing three-dimensional reconstructions of bone structure with low radiation exposure.

Two studies examining T1D bone microarchitecture have used HR-pQCT. These studies reported trends of higher cortical porosity among those with T1DM than in those with diabetes, however, the most largest difference was seen in trabecular features: trabeculae thickness, trabeculae spacing and trabecular bone volume/total volume ratio [17,18]. The most striking finding was by Shanbhogue et al., who showed differences in bone microarchitecture not between those with and without diabetes, but rather those with T1DM with and without microvascular complication, especially proliferative diabetic retinopathy (PDR) [17].

There were three studies which used methods other than qCT: TBS was calculated at the lumbar spine [19], uCT of biopsies from the iliac crest [20] and microMRI of the proximal tibia [21]. These studies were done in an older cohort who were closer to peak bone accrual and showed stable insulin management and long term hyperglycemic exposure. The mean age of individuals in these studies was 32.5 years with an average T1DM duration of 16.4 years.

In a 2016 paper, Neumann et al demonstrated that TBS of the lumbar spine was more effective in identifying fracture risk than BMD alone [19]. TBS assesses trabecular bone texture of the spine using DXA scans, a measure which correlates with trabecular microarchitecture. Compared to HR-pQCT, TBS has the advantage of being derived from the clinically approved DEXA scan, however, it does not provide a three-dimensional examination of bone structure.

Amongst the other non-pQCT methods, Armas et al, in biopsies from the iliac crest using micro-CT, compared individuals with T1D with and without fracture, but no vascular complications, and those without diabetes [20]. The observed differences were between those with and without fracture rather than compared to those without diabetes across all histomorphometric variables measured (BV/TV, Tb.Th, Tb.N, Tb. Sp, OS/BS, MS/MS, BFR/BS, BFR/BV, Ac. F.), and micro-CT variables (BV/TV, Structure model index, apparent density). In a micro-MRI study, Abdalrahman et al found differences between those with T1DM and without diabetes in the trabecular bone of the lumbar spine, including apparent BV/TV, a lower number of trabeculae, as well as larger spacing between trabeculae [21]. This was on a backdrop of no difference in BMD. This supports the idea that examination of the microarchitecture of the bone gives a better sense of the integrity of the bone.

In summary, population based studies indicate bone microarchitecture of those with T1DM may contribute to increased risk of fracture compared to those with T2DM and to those without diabetes. However, whether this increased risk is derived from defects in the trabecular versus the cortical remains to be concluded. As noted above, most studies investigating bone quality in T1DM were done in individuals who likely have reached peak bone accrual and had an average of approximately 16 years of exposure to hyperglycemia. At this point of duration, early progression to complications may have begun, yet most diabetic complications still have not manifested suggesting it may be early to see the significant changes in bone as well [22–24].

As those with T1DM age and experience the effects of long duration of hyperglycemia, and these two factors may possibly interact to cause skeletal health to decline, further studies are needed in that aging cohort.

Hypoinsulinemia and bone quality

T1DM is characterized by deficiency of pancreatic insulin production, causing decreased or absent insulin levels in the portal system. Exogenous insulin therapy by-passing the portal system cannot reproduce the physiological liver exposure to insulin, resulting in a lower expression of growth hormone receptors on hepatocytes, likely reducing production of IGF1 which contribute to decreased osteoblast stimulation. This would reduce what would be the expected level of bone formation at normal levels of portal insulin. In line with this hypothesis, C-peptide, which is a marker of endogenous insulin production secreted in equimolar concentrations with insulin, has been associated with BMD in non-diabetic post-menopausal women. This was demonstrated by Montalcini et al. in a study of women where those with the lowest concentrations of C-peptide had lower lumbar BMD independent of

age and body mass index. Interestingly, this association was not found in the femur, suggesting a greater effect of insulin on trabecular rather than cortical bone, a site which appears to be more affected in those with T1DM compared to those with T2DM [25]. Murine models also support these findings. Mice specifically lacking insulin receptor in osteoblasts (Ob-IR) show a deficient number of bone forming cells. Since immunoreactivity for insulin receptors is abundant in osteoblasts on the trabecular bone surface, Ob-IR mice accumulate less bone specifically at the trabecular compartment [26]. As suggested by these data the presence of insulin has a differential, significant effect on the individual compartments of bone in those with both types of diabetes and those with normoglycemia.

As demonstrated above, the presence of insulin resistance and hyperinsulinemia both have deleterious effects on bone, yet on different components. It is additionally well-documented that these two conditions are associated with vascular complications. *In vivo* and *in vitro* models, as well as epidemiologic studies, have shown there is an association between skeletal health and vascular health, and recent studies have begun to elucidate the mechanism.

T1DM complications and bone microarchitecture

The association of vascular diabetes complications and decline of skeletal health in those with T1DM has been hypothesized based on large studies of individuals without diabetes [27,28]. The Framingham Heart Study showed that loss in cortical bone is associated with progression of atherosclerotic disease over a 25 year of follow-up period [29]. The role of VEGF in diabetic vascular complications has been well-established, particularly its role in proliferative diabetic retinopathy and nephropathy [30–33]. In addition to angiogenesis, VEGF is a key determinant of bone vascularization regulating osteoblast differentiation, bone repair and post-natal bone homeostasis [34]. *In vivo* models have demonstrated that inhibition of VEGF and its receptors have been shown to impair bone healing by decreasing blood vessel formation in the bone and reducing bone regeneration [35,36].

In a study by Armas et al examining the histomorphometry of the iliac crest of those with and without T1DM, no differences were found between parameters of formation and microarchitecture in the absence of complications, but complications in the presence of T1DM was the differentiating factor for at risk bone microarchitecture [20]. There is now *in vitro* evidence of the secretion of vascular endothelial growth factor (VEGF) by osteoblasts affecting the stimulation of progenitor cells, suggesting an intimate link between diabetic complications and skeletal health [34]. This is directly supported by the STZ animal models from Chakravarthy H et al. and in human studies by Shanbhogue et al as described above [17,37].

Diabetic nephropathy—Over 30% of those with T1DM will develop diabetic nephropathy by 30 years duration. Progression to nephropathy is associated with impaired calcium-phosphorus metabolism, and therefore bone metabolism, primarily renal osteodystrophy. A recent study evaluating renal osteodystrophy in 41 patients with ESRD confirmed the association between diabetes and the renal osteodystrophy, namely adynamic

bone disease [38]. This is characterized by low bone turnover, low bone volume and markedly decreased cellularity, but almost normal mineralization. This manifests in decreased trabecular bone density determined by pQCT and increased cortical bone density compared to patients with high-turnover lesions [39]. As this condition affects mineralization and not overall density, it is not detectable by standard clinical means, contributing to the disproportionate fracture risk in individuals with T1DM. Peripheral resistance to parathyroid hormone (PTH) action and pharmacotherapy PTH over-suppression also occurs secondary to nephropathy potentially leading to adynamic bone disease. The prevalence ranges from 5 to 40% in CKD stages 3–4 and up to 50% in dialysis patients [40]. Diabetic nephropathy comorbidities leading to PTH deficiency, together with the Vitamin D deficiency occurring synergistically propel the individual towards reduced bone turnover and bone fragility [41] [42].

Retinopathy—Diabetic retinopathy is another prevalent microvascular complication affecting almost 90% of those with T1D and is directly related to an excess of VEGF [24–27]. A preliminary mechanistic link between bone and PDR has been presented by Chakravarthy et al. [37] Additionally, this has been supported by Shanbhogue et al's data which describes lower trabecular quality in those with PDR compared to those without [17].

An intimate relationship between bone microvasculature and bone cells mediated by endothelial cells does exist. The proximity of the bone-forming “basic multicellular unit” (BMU) to the microvasculature is critical in maintaining bone anabolism [43]. Moreover, a recent hypothesis by Lim Y et al. suggests alterations in the molecular bone microenvironment involving VEGF and bone morphogenic proteins (BMPs) as a common denominator between diabetic retinopathy and osteopathy [44].

Diabetic neuropathy—Thirty to 70% of individuals with T1DM may be affected by polyneuropathy and autonomic neuropathy [45]. Autonomic neuropathy is caused by the damage of small (Aδ, B and C) nerve fibers and characterized by the imbalance of sympathetic and parasympathetic activities. This results in dysfunction of the alpha- and beta-adrenergic receptors which also regulates bone remodeling by acting on osteoblasts by modulating gene expression and activity [46–48]. This suggests a link between skeletal health and neuropathy in those with T1DM. Yet, it is unclear whether the pattern of neuropathy and effects on bone differ between those with the different types of diabetes. This is supported by evidence from rodent models which shows activation of these adrenoceptors causes impairment in trabecular bone microarchitecture [49,50], bone mass and strength [51].

Macrovascular disease—The leading cause of premature mortality in those with T1DM is cardiovascular disease, particularly among females [52]. Increased levels of hypertension, oxidative stress and inflammation lead even those without diabetes to increased rates of cardiovascular disease (CVD) [53,54]. Those with T1DM have the additional exposures of long-term exposure to the toxic by-products of hyperglycemia, glucose excursions and a higher prevalence of nephropathy, which also contribute to endothelial dysfunction at early ages than in the population without diabetes, leading to increases in morbidity and mortality at younger ages despite a more favorable lipid profile [55–59]. Several studies have

documented an increased risk of cardiac events and mortality in the presence of decreased skeletal health, however, few studies have been done in those with T1DM [27,28,60]. This link has been documented in the Prospective Epidemiological Risk Factors Study which found an increased risk for hip fracture with aortic calcification (adjusted RR: 2.3 95%: [1.1–4.8], $p=0.03$) and in a Swedish population-based case-control in which women without diabetes but with CVD were twice as likely as those to have fractured than those who did not (adjusted odds ratio for hip fracture 2.38 [95CI: 1.92–2.94]) [61,62]. Additionally, yearly rate of vertebral trabecular bone loss evaluated by CT was associated with the rate of change in aortic calcification in post-menopausal women independently from confounding factors such as age, BMI, blood pressure and physical activity. [28]

In vitro data from Arnett et al. supports the epidemiologic studies by demonstrating hypoxia as a major stimulator of bone resorption and osteoclast formation as it causes a significant VEGF response in healthy tissue, and shows a diminished response in tissues with vascular complications. [63] Hypoxia causes acidosis due to increased anaerobic metabolism, reducing pH in bone inhibiting osteoblasts, and enhancing bone resorption by osteoclasts [64]. Also alterations in bone hemodynamics such as vascular calcification and arteriosclerosis, which occur frequently in people with T1DM, have been shown to influence osteoblast activity and bone remodeling [65–67].

Factors including inflammatory cytokines, oxidative stress, vitamin K and vitamin D deficiency, bone morphogenetic proteins (BMPs), osteocalcin and sclerostin have been implicated separately in both the pathogenesis of CVD and bone fragility. As detailed above, there is significant evidence of an interplay of these factors and a potentially synergistic effect of vascular dysfunction and poor skeletal health in promoting a poorer bone microarchitecture among those with T1DM who may experience fractures [68,69] [70].

Conclusion

Some of the increased risk of fracture in those with T1DM has been attributed to the relative decrease in the BMD compared to the general population. However, the small shift in BMD does not explain the 7 fold increase in risk of hip fracture relative to the general population and the five-fold increase relative to those with T2DM. In a review of studies of those with relatively short duration of T1DM in adolescence or middle age examining bone microarchitecture by varying techniques including micro-CT, micro-MRI, pQCT and HR-pQCT, along with association to diabetic vascular complications there is some suggestion that the internal structure of may explain the disproportionate risk. However, further studies on individuals with longer duration T1DM, other types of diabetes and those without diabetes are needed to determine if this exposure has long term effects, or can be ameliorated..

As discussed above T1DM is a disease of insulin deficiency resulting in a reduction in growth hormone action. Unfortunately, there is little evidence that this is entirely rescued by the use of exogenous insulin, as the insulin does not enter the portal system and activate hepatocyte receptors. As described above, the studies which have examined the components of the bone have used a variety of methodologies and assessed several anatomic sites. Overall, the studies suggest there may be a trend towards differences in the trabecular bone

of those with T1DM. However, as most of these studies have been done in those with short duration at relatively young ages it is difficult to determine what may develop, as peak incidence of other diabetic complications is not reached until 30 years duration. This may explain the lack of significant differences found in these studies. Examination of skeletal health in individuals with longer duration with particular focus on the association with complications may give insight on mechanisms aiding in prediction of pathology and best treatment.

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Table 1

Studies of bone volumetric BMD and geometry in those with type 1 diabetes.. Means are presented.

Investigator	Year	Design	Method	Age	Duration	N T1DM	Conclusion	Sites studied
Roe et al [19]	1991	Case-control	QCT	F:12.9 T1DM; 12.9 NDM; M:12.7 T1DM; 12.7 NDM	5.2	48	Ct BMD decreased, no differences in Tb BMD	Lumbar vertebrae
Letten et al [11]	1994	Case-control	pQCT	12.6 T1DM; 12.8 NDM	5.3	42	Lower trabecular Tb vBMD inversely related to HbA1c	Ultra-distal Radius
Moyer-Mileur et al. [17]	2004	Longitudinal 12 months	pQCT/ DXA	14.9 T1DM; 15.0 T2DM	4.2	42	Adolescents with T1D have small bones despite normal growth patterns	Spine DXA/ tibia pQCT
Bechtold et al. [18]	2007	Longitudinal 2–4 years	pQCT	9.87 T1DM; 15.4 NDM	4.3	41	Early stage impairment ameliorated over time	Distal metaphysis and proximal of the diaphysis radius
Heaps et al [12]	2004	Case-control	pQCT/ DXA	F:14.7 T1DM; 14.8 NDM M:14.6 T1DM; 14.5 NDM	5.5*	55	Tb vBMD was inversely related to glycemic control	Spine and FN DXA/ Radius and tibia
Saha et al. [19]	2009	Case-control	pQCT	F: 15.1 T1DM; 15.5 NDM M: 15.2 T1DM; 15.9 NDM	6.8	48	Bone mineral content and cross-sectional area is affected with dominant effect in boys	Radius and tibia
Roggen et al. [20]	2013	Case-control	pQCT	17.9 T1DM; 18.1 T2DM	4.7	56	Smaller bone size in those with T1; Tb was similar.	Distal radius

T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; DXA: Dual X-ray absorptiometry; pQCT: peripheral quantitative computed tomography;

* calculated

Table 2

Studies of bone microarchitecture in those with type 1 diabetes.

Investigator	Year	Design	Method	Age	Duration	N T1DM	Conclusion	Sites studied
Armas et al. [12]	2012	Case-control	uCT biopsy	31 T1DM; 34.1 NDM	15	18	Tb differs between non-fracture T1 and fracturing. Non fracturing T1 not different than controls	Iliac crest
Starup-Linde et al. [67]	2015	Case-control	HR-pQCT/ DXA	24.4 T1DM; 14.6 T2DM	24.4	51	Increased Ct area, bone stiffness lower in tibia T1, radius Ct pore volume lower in T1	Ti
Shanbhogue et al. [10]	2015	Case-control	HR-pQCT/ DXA	45 T1DM; 45.8 T2DM	17	55	Deficiencies of Ct and Tb appear driven by MVD	Ultradistal radius and tibia
Abdalahman et al. [13]	2016	Case-control	Micro-MRI	22.0 T1DM; 21.8 NDM	12.8	30	Deficits in trabecular bone. Among T1D, lower BV/TV with retinopathy	Tibia
Neumann et al. [11]	2016	Case-control	TBS	43.4 T1DM; 42.8 NDM	21.5	119	TBS are lower in inT1D with existing fractures	Lumbar spine
Abdalahman et al. [13]	2016	Case-control	Micro-MRI	22.0 T1DM; 21.8 NDM	12.8	30	Deficits in trabecular bone. Among T1D, lower BV/TV with retinopathy	Tibia

T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; uCT: micro-computed tomography; DXA: Dual X-ray absorptiometry; HR-pQCT: High resolution-peripheral quantitative computed tomography; MRI: Magnetic resonance Imaging; TBS: Trabecular bone score.