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Vascular deficits contributing to skeletal fragility in type 1 diabetes

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Over 1 million Americans are currently living with T1D and improvements in diabetes management have increased the number of adults with T1D living into later decades of life. This growing population of older adults with diabetes is more susceptible to aging comorbidities, including both vascular disease and osteoporosis. Indeed, adults with T1D have a 2- to 3- fold higher risk of any fracture and up to 7-fold higher risk of hip fracture compared to those without diabetes. Recently, diabetes-related vascular deficits have emerged as potential risks factors for impaired bone blood flow and poor bone health and it has been hypothesized that there is a direct pathophysiologic link between vascular disease and skeletal outcomes in T1D. Indeed, microvascular disease (MVD), one of the most serious consequences of diabetes, has been linked to worse bone microarchitecture in older adults with T1D compared to their counterparts without MVD. The association between the presence of microvascular complications and compromised bone microarchitecture indicates the potential direct deleterious effect of vascular compromise, leading to abnormal skeletal blood flow, altered bone remodeling, and deficits in bone structure. In addition, vascular diabetic complications are characterized by increased vascular calcification, decreased arterial distensibility, and vascular remodeling with increased arterial stiffness and thickness of the vessel walls. These extensive alterations in vascular structure lead to impaired myogenic control and reduced nitric-oxide mediated vasodilation, compromising regulation of blood flow across almost all vascular beds and significantly restricting skeletal muscle blood flow seen in those with T1D. Vascular deficits in T1D may very well extend to bone, compromising skeletal blood flow control, and resulting in reduced blood flow to bone, thus negatively impacting bone health. Indeed, several animal and *ex vivo* human studies report that diabetes induces microvascular damage within bone are strongly correlated with diabetes disease severity and duration. In this review article, we will discuss the contribution of diabetes-induced vascular deficits to bone density, bone microarchitecture, and bone blood flow regulation, and review the potential contribution of vascular disease to skeletal fragility in T1D.

KEYWORDS

T1D, skeletal fragility, microvascular disease, calcification, bone blood flow

Background

The incidence of type 1 diabetes (T1D) is increasing by 2-5% per year worldwide (1, 2) such that over 1 million Americans are currently living with T1D (3). Additionally, advancements in diabetes management have led to an increased number of adults with T1D living into later decades of life (3–6). Unfortunately, this growing population of older adults with diabetes is more susceptible to age-related health problems, including bone loss, osteoporosis, and increased fracture risk. Indeed, adults with T1D have a 2- to 3-fold higher risk of any fracture and up to 7-fold higher risk of hip fracture compared to those without diabetes (7–13). Moreover, those with T1D typically experience worse outcomes and increased complications following a fracture (14, 15). Several factors have been postulated to contribute to skeletal fragility in T1D, however none adequately account for the significantly higher fracture risk. For example, the reduced bone mineral density (BMD) observed in T1D predicts only a 1.4-fold increased risk of hip fracture (16), which is far below the observed 5- to 7-fold higher risk associated with T1D (17). Both diabetes-related vascular disease, as well as poor glycemic control (18), have emerged as potential risk factors for impaired bone health. Higher HbA1c values, which indicate worse glycemic control, are related to increased risk of microvascular disease (MVD) but data on the association between skeletal fragility and HbA1c are equivocal (17, 19–27). Hence, MVD itself may be the primary culprit for bone loss as opposed to glycemic control per se. Notably, most studies report worse bone microarchitecture in T1D adults with MVD (24, 28, 29). Vascular calcifications have also been associated with increased fracture risk (30–34), and thus the high prevalence of macrovascular disease in T1D may also contribute to skeletal fragility. This review article examines the impact of diabetes-induced vascular deficits on bone density and microarchitecture, and discusses the potential influence of MVD on bone blood flow regulation and resulting skeletal fragility in older adults with T1D.

Microvascular disease, diabetes, and vascular damage

Microvascular disease (MVD) affecting small blood vessels represents one of the most serious clinical consequences of diabetes. An overwhelming majority of those with long-term T1D manifest at least one microvascular complication, with retinopathy affecting more than 70% (35), nephropathy present in about 30% (36), and neuropathy impacting up to 90% (37, 38) of older adults with T1D. Glycemic control, which declines in older adults with T1D (39), is inversely associated with risks of nephropathy and neuropathy (39, 40). Moreover, even with strict glycemic control, MVD can still develop, resulting in end-organ compromise (41–43). Although the most well-recognized end-organ targets of MVD in diabetes are the kidney, eye, and nervous system, it is likely that other tissues, such as bone, are also directly impacted. Indeed, several studies have shown greater cortical and trabecular structural deficits and lower bone strength in adults with T1D and MVD compared to their counterparts without MVD (24, 28). The association between the presence of microvascular complications and compromised bone microarchitecture indicates the potential direct deleterious effect of vascular compromise, leading to abnormal skeletal blood flow, altered bone remodeling (44), and deficits in bone structure. Several animal and *ex vivo* human studies report that diabetes induces microvascular damage within bone, including arteriole and capillary rarefaction and apoptosis (45–47), which are strongly correlated with diabetic disease severity and duration (47). In addition, vascular diabetic complications are characterized by decreased arterial distensibility and vascular remodeling with increased arterial stiffness and increased thickness of the vessel walls due to smooth muscle hyperplasia (48–50). Vascular deficits in T1D may very well extend to the bone vasculature, compromising skeletal blood flow regulation, and resulting in reduced blood flow to bone, thus negatively impacting bone health.

Potential alterations in blood flow regulation in diabetes

Similar to other vascular beds, the circulation of bone contains an extensive network of arteries, arterioles and capillaries that provides nutrients, oxygen, and precursor cells critical for all skeletal functions (51). Maintaining skeletal integrity requires appropriate vascular supply and well-regulated blood flow to meet bone metabolic demands. Despite its critical importance, regulation of bone blood flow regulation remains poorly understood, especially in humans and in the context of disease such as diabetes. Broadly, regional regulation of blood flow results in part from a complex interplay of intrinsic local mechanisms of smooth muscle control via vascular myogenic and nitric oxide (NO)-mediated responses.

Vascular myogenic control is crucial for normal hemodynamic function and for maintaining vascular conductance, regulating tissue perfusion, and protecting downstream arterioles and capillaries from damage due to variable perfusion pressure (52–54). In response to changes in local pressure, vascular smooth muscle relaxes (i.e., vasodilation), allowing more blood flow, or contracts (i.e., vasoconstriction), thereby restricting flow. In this way, myogenic responses counter decreases in perfusion pressure with vasodilation and increases in perfusion pressure with vasoconstriction to maintain regional blood flow constant to tissue. However, alterations in vascular structure and function with aging and T1D lead to impaired myogenic vasodilatory responses (55) and heightened vasoconstrictor responses across numerous vascular beds such as muscle, skin (56–58), and retina (59). For example, older adults with T1D and MVD have impaired myogenic vasodilatory response in skeletal muscle (60), which likely contributes to the large deficit in skeletal muscle blood flow (-35%) in this population (61, 62) compared to nondiabetic controls.

Another important regulatory mechanism of blood flow is NO-mediated vasodilation. In response to increased shear stress that acts over a relatively short time (3-5 sec) (63, 64), the endothelium

releases NO that dilates the vessels, allowing for increased flow, and thus playing a pivotal role in maintaining appropriate perfusion of all tissues (63–65). However, aging and T1D are associated with significant reductions in NO production and decreases in NO sensitivity, leading to blood flow reductions across numerous vascular beds. Recent work on long-term diabetes in rats indicates reduced NO-mediated vasodilation in the femoral principal nutrient artery that progresses with disease duration (46). Moreover, in humans with T1D, vasodilatory dysfunction has been identified as an early marker of microvascular complications (66–70). Indeed, structural and functional vascular alterations occur early during diabetes development, long before the manifestation of overt MVD (71–73). Vasodilatory dysfunction is present in over 35% of individuals within 5 years of T1D onset (74, 75), reducing NO-mediated vasodilation by up to 40% across almost all vascular beds (68, 76–78). NO-mediated vasodilation seems to be further impaired by aging in diabetic adults with microvascular complications (79, 80).

Despite the likelihood that the effects of diabetes and MVD on myogenic and NO vascular responses extend to bone in individuals with T1D, this important area of investigation remains largely unexplored. Given the shared pathophysiological mechanisms and the systemic nature of T1D and its associated complications, it is reasonable to hypothesize that the effects of diabetes and MVD likely also influence vascular function and blood flow regulation within the skeletal system.

Link between vascular control, bone blood flow, and bone health

Our understanding of myogenic and NO vascular responses within the bone vasculature and their relative importance for bone health is extremely limited, particularly in the presence of diabetes and MVD. Animal data suggest that arteriolar smooth muscle in bone responds as expected to infused vasodilators and vasoconstrictors, with vasodilators increasing (81) and vasoconstrictors decreasing blood flow to bone (82–88). Moreover, animal studies suggest that NO could be one of the main mediators of blood flow to bone (81, 89–91). However, there have been very few studies investigating these mechanisms in bone in humans. In young healthy adults, our recent preliminary data have shown the presence of myogenic control and NO-mediated vasodilation in tibial bone with distinct mangnitudes and time-courses compared to skeletal muscle. In addition, in another human study of young healthy adults, blockade of endogenous NO formation reduced blood flow to femoral bone marrow as assessed by positron emission tomography (92). Although these initial findings indicate that myogenic and NO vascular responses play an important role in controlling bone blood flow, their specific role in bone blood flow control and their relationship to bone strength and structure, particularly in the presence of diabetes, remain unknown.

There are compelling reasons to suggest that altered regulation of bone blood flow has detrimental effects on skeletal health. Without adequate perfusion to supply oxygen and essential nutrients critical for bone metabolism, nearly all skeletal functions are compromised, including bone formation, maintenance, and repair. Indeed, animal studies demonstrate that regional decreases in bone blood perfusion are associated with localized declines in bone mass (93). Animal work also suggests that if vasodilation is reduced by only ~20-25%, skeletal metaphyseal and bone marrow blood flow are reduced by almost twice as much, simply due to the Poiseuille relationship between flow and vessel diameter (81). Thus, minorly compromised vasodilation can lead to marked reductions in bone blood flow, resulting in insufficient oxygen and nutrient supply for maintaining bone health. Furthermore, in longitudinal clinical studies of aging, reduced large vessel distensibility as assessed by ankle-brachial vascular index is associated with lower extremity bone loss (94). Moreover, reduced skeletal blood flow quantified as reduction in number of bone marrow blood vessels (arteries, arterioles, and capillaries) has been linked to the development of osteoporosis (95). These findings suggest that local reductions in blood flow may directly impact blood flow within bone, thus negatively impacting bone strength.

In the context of T1D and MVD, if the bone vasculature has a diminished ability to regulate blood flow due to compromised vascular myogenic or NO-mediated mechanisms, this would lead to lesser blood flow to bone. (Figure 1) Consequently, this vascular impairment may contribute to skeletal fragility and increased fracture risk in adults with T1D.

Vascular calcifications in diabetes and implications for bone blood flow

Vascular calcification, a hallmark of aging (96, 97), is accelerated in patients with diabetes (98). In fact, atherosclerotic calcification develops 10 years earlier than in those without diabetes and is often present even among asymptomatic older adults with T1D (99). The calcification of the macrovascular conduit arteries affects downstream blood flow regulation and ultimately impacts bone health. Genetically modified mice that mimic human arterial calcification show a slight increase in arterial stiffness and hyperresponsive vascular myogenic constriction (100), particularly with aging, which leads to less efficient control of local blood flow. Furthermore, several animal studies suggest that reduced aortic calcification is associated with greater NO (101–103), while accelerated calcification relates to impaired NO (104, 105). The extensive vascular dysfunction and reduced NO-mediated vasodilation in those with T1D may promote or derive from arterial calcification, leading to disrupted blood flow regulation and restricted critical flow to numerous tissues, likely to bone as well. Hence, it is not surprising that a well-established link exists between vascular disease and osteoporosis.

Several epidemiologic studies of older adults have shown an association between increased arterial calcification and bone loss particularly at the hip and spine using different imaging techniques. One study conducted with community-dwelling men over the age of 65 found that higher abdominal aortic calcification (AAC) scores assessed through lateral thoraco-lumbar radiographs were independently associated with an increased risk of non-spine

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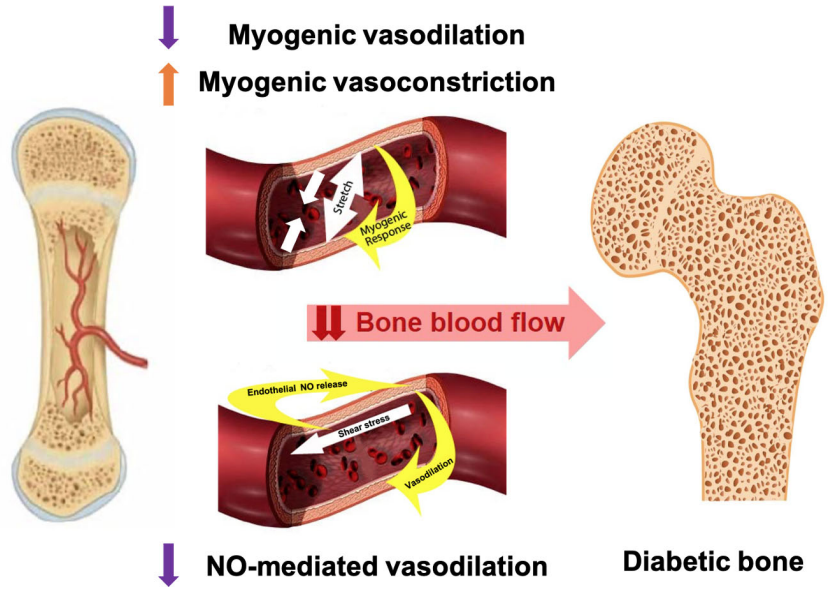

FIGURE 1
Proposed vascular alterations contributing to skeletal fragility in T1D: altered myogenic control and blunted NO-mediated vasodilation may reduce blood flow to one; contributing to bone declines in older adults with T1D.

fractures, particularly hip fractures (HR 1.36, 95%CI: 1.10-1.68) (33). Similarly, a case-cohort study in non-Black women aged 65 years and older found that severe AAC, evaluated from lateral spine radiographs, was associated with a higher risk of vertebral fractures (OR 2.31, 95%CI: 1.24-4.3, p<0.01) (34). Furthermore, a meta-analysis study found a significant association between coronary artery disease (CAD) and low BMD (106), while another meta-analysis demonstrated that vascular calcification was linked to lower lumbar spine and hip BMD levels, as well as an increased risk of developing osteoporosis/osteopenia (107). These studies suggest a negative association between arterial calcification and BMD as measured by dual-energy X-ray absorptiometry (DXA). Of note, DXA may artifactually overestimate BMD in the presence of vascular calcification, particularly at the lumbar spine, and thus the inverse relationship observed between arterial calcification and DXA-BMD is even more striking. These findings have been confirmed by skeletal imaging using 3D modalities such as quantitative computed tomography (QCT), which is not subject to confounding by vascular calcification. One study employing QCT found increased aortic arterial calcification was associated with decreased spine trabecular vBMD in older adults, although no association between cortical vBMD and vascular or valvular calcification was found (108). The emergence of high resolution peripheral quantitative computed tomography (HR-pQCT) allowed not only a better characterization of the tibial and radial bone microarchitecture (109, 110), but also a simultaneous assessment of lower leg arterial calcification (LLAC) in elderly individuals, those with diabetes or chronic kidney disease (111). In a study of patients with end-stage renal disease, moderate-to-severe coronary artery calcification was associated with lower tibial BMD and bone volume as assessed by HR-pQCT (112). Employing HR-pQCT to assess LLAC, a cross-sectional study in older adults found that distal tibia LLAC was correlated with lower trabecular number in male participants, and lower cortical area, lower trabecular number, and higher trabecular spacing in the female participants (113). In another study involving older participants with advanced chronic kidney disease (CKD), the presence of distal tibial LLAC was correlated with worse cortical vBMD, thickness, and porosity (114). Unfortunately, little is known about the impact of vascular calcifications on bone endpoints within diabetic populations.

Taken together, these studies highlight the complex relationship between diabetes, vascular calcification, and bone health. Diabetes is associated with vascular calcification which subsequently alters blood flow control, restricting flow to numerous vascular beds. Furthermore, LLAC is associated with worse bone health, characterized by deficits in both cortical and trabecular bone compartments across different populations, including older adults with CKD. Consequently, the presence of diabetes-associated vascular calcification within the arterial system may directly impact local bone blood flow regulation and bone microarchitecture. More research is necessary to explore the pathophysiology and clinical consequences of vascular calcifications and bone measures in the context of diabetes.

Conclusions

Both osteoporosis and vascular disease are highly prevalent conditions that lead to profound morbidity and mortality in older adults with T1D. Although MVD affecting small blood vessels (e.g., retinopathy, nephropathy, neuropathy) has been implicated in diabetic skeletal fragility, to date, the potential contribution of

bone blood vascularization to bone fragility remains poorly investigated. In this review, we discussed potential vascular mechanisms that may be present in the bone vasculature and may play a direct role in reducing blood flow supply to bone and compromising skeletal integrity in adults with T1D. The characteristics of MVD including vascular remodeling, increased arterial stiffness, as well as vascular calcification negatively impact the complex mechanisms of blood flow regulation such as myogenic and NO-mediated vascular responses. Impairments in these mechanisms have been documented in numerous other tissues in adults with diabetes. These vascular deficits likely extend to the bone vasculature and may lead to compromised blood flow supply to bone, resulting in cortical and trabecular bone deficits and increased fracture risk. Understanding the interplay between vascular disease, blood flow regulation in bone, and osteoporosis in individuals with T1D is an essential step to identify potential therapeutic interventions to improve bone health outcomes in populations with bone loss pathology.

Author contributions

AD: Writing – original draft, Writing – review & editing. BZ: Writing – review & editing. AT: Writing – original draft, Writing – review & editing. MB: Writing – original draft, Writing – review & editing. EY: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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