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BONE AND DIABETES (A SCHWARTZ AND P VESTERGAARD, SECTION EDITORS)

Glycemic Control and Bone in Diabetes

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Abstract

Purpose of Review This review summarizes recent developments on the effects of glycemic control and diabetes on bone health. We discuss the foundational cellular mechanisms through which diabetes and impaired glucose control impact bone biology, and how these processes contribute to bone fragility in diabetes.

Recent Findings Glucose is important for osteoblast differentiation and energy consumption of mature osteoblasts. The role of insulin is less clear, but insulin receptor deletion in mouse osteoblasts reduces bone formation. Epidemiologically, type 1 (T1D) and type 2 diabetes (T2D) associate with increased fracture risk, which is greater among people with T1D. Accumulation of cortical bone micro-pores, micro-vascular complications, and AGEs likely contribute to diabetes-related bone fragility. The effects of youth-onset T2D on peak bone mass attainment and subsequent skeletal fragility are of particular concern.

Summary Further research is needed to understand the effects of hyperglycemia on skeletal health through the lifecycle, including the related factors of inflammation and microvascular damage.

Keywords Diabetes · Dysglycemia · Bone · Fracture · Osteoblast · Osteoclast

Introduction

Bone modeling and remodeling across the lifecycle is accomplished through the delicately coordinated action of osteoblasts and osteoclasts. These cell lineages differ in metabolic requirements and regulation. Advances in our understanding of the effects of glucose and insulin on osteoblasts and osteoclasts in cell and animal models bring us closer to revealing the pathophysiologic effects of impaired insulin signaling and glycemic control on bone metabolism in diabetes. However, these findings have not been translated to studies demonstrating the effect of dysglycemia on bone health in people with diabetes. The inability to sustain normal physiologic levels of glucose and insulin is associated with other health complications, such as obesity, inflammation, and microvascular damage that also affect bone health. Adding further ambiguity, the epidemiology and presentation of bone fragility in different forms of diabetes, namely type 1 diabetes (T1D) and type 2 diabetes (T2D), show different patterns of bone fragility. Presently, there are substantial knowledge gaps in our understanding of the effects of glycemic control on bone fragility in diabetes.

Studies of bone health in people with diabetes have used a variety of methods to capture the properties of bone fragility. Bone fragility is determined by numerous densitometric, qualitative, and morphological properties, including density, macro- and micro-architecture, collagen cross-linking, micro-repair properties, and bone turnover. Most commonly, dual-energy x-ray absorptiometry (DXA) is used clinically to measure areal bone mineral density (aBMD) at multiple body sites (lumbar spine, hip, forearm, and total body) that vary in composition of cortical and trabecular bone. Additional DXA-derived measures, specifically hip structural analysis [1],

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describe the geometry and structural strength of bones. Trabecular bone score (TBS) estimates bone quality from lumbar spine DXA scans using a texture-based gray-level analysis [2]. More detailed measures of microstructure and strength require research techniques such as high resolution peripheral quantitative computed tomography (HR-pQCT) that estimates volumetric BMD and structure of cortical and trabecular bone, including cortical porosity and finite element–derived measures of failure load and stiffness, at remarkable resolution (‹ 58 μm) [3]. Reference point indentation [4], a technique that measures the bone's compliance to a given strain *in vivo*, has also been used to estimate bone material strength in the context of diabetes.

This summary reviews recent developments on the effects of glucose and insulin on bone cells and the effects of diabetes on bone health in youth and adults.

The Cellular Basis of Bone Complications in Diabetes

Metabolic Features of Osteoblasts and Osteoclasts

Recent studies with state-of-the-art technology have provided unprecedented details about osteoblast metabolism that offer insights into the effect of diabetes on bone metabolism. The use of Seahorse technology to measure metabolic fluxes in real time has shown that osteoblast differentiation is coupled with increased glucose consumption and lactate production [5, 6•]. The Seahorse technology quantifies key metabolic processes such as mitochondrial respiration and glycolysis in live cells grown in a multi-well plate. Specifically, the Seahorse XF analyzer measures oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in real time both at basal conditions and following automatic addition and mixing of specific compounds. Although ECAR is often used as a surrogate for the lactate production rate from glucose, OCR generally does not distinguish the contribution of different energy substrates to mitochondrial respiration unless specific interventions such as chemical inhibitors are used to block the use of certain substrates.

Stable-isotope tracing with ^{13}C-glucose confirmed the dominant fate of glucose to be lactate both in osteoblast cultures and in the cortical bone of the mouse [6•]. Compared to the Seahorse technology, the tracing method can be used both in vitro and in vivo to quantify specific substrate contributions to either energy production or biosynthesis. The preference for lactate production from glucose under aerobic conditions, commonly known as aerobic glycolysis or the Warburg effect, was estimated to fulfill ~80% of the energy needs in mature osteoblasts differentiated in vitro from neonatal murine calvarial cells. Genetic deletion of Glut1, the main glucose transporter in osteoblasts, reduced bone formation in the mouse, whereas overexpression of Glut1 in osteoblasts increased bone mass [7].

In addition to glucose, fatty acids have been implicated in energy production in osteoblasts. Specifically, biodistribution studies with radiolabeled fatty acid tracers detected a notable uptake by bone. Moreover, osteoblast-specific deletion of carnitine palmitoyltransferase 2 (Cpt2), an obligate enzyme for fatty acid oxidation, reduced bone formation in female mice [8•]. Interestingly, disruption of fatty acid oxidation in those mice increased glucose uptake in bone, thus highlighting the plasticity of fuel utilization by osteoblasts.

Osteoblast metabolism is highly attuned to extracellular signals. Wnt signaling through Lrp5, a potent osteogenic mechanism, was shown to stimulate aerobic glycolysis via direct modulation of glycolytic enzymes during osteoblast differentiation [9•]. In a subsequent study, genetic deletion of Glut1 eliminated the bone-inducing effect of Wnt overexpression, providing functional evidence that glycolysis is integral to bone formation [10]. Additional studies have indicated that Wnt also promotes glutamine oxidation not only for energy production but also to enhance protein synthesis capacity in osteoblasts [11]. Furthermore, deletion of Lrp5 in bone reduced fatty acid oxidation by osteoblasts, leading to increased plasma lipids and overall adiposity, whereas mice expressing a gain-of-function Lrp5 mutant allele exhibited the opposite phenotype [12]. Thus, Wnt-Lrp5 signaling stimulates fuel metabolism of multiple substrates to activate bone formation. Similarly, teriparatide, the main bone anabolic drug to date, has been shown to boost glucose metabolism in osteoblasts to support bone formation activity [13]. More recently, nitric oxide (NO) was reported to stimulate bone anabolism via increased osteoblast glycolysis [14]. This is potentially significant as NO supplements have been documented to improve bone formation and prevent ovariectomy-induced osteoporosis in mice [15].

In contrast to osteoblasts which are of mesenchymal origin, osteoclasts are descendants of hematopoietic stem cells and exhibit a different metabolic profile. Both aerobic glycolysis and oxidative phosphorylation (OXPHOS) increase during osteoclast differentiation in vitro [16, 17]. Extracellular flux measurements detected a marked increase in ATP production from OXPHOS versus glycolysis, supporting mitochondrial respiration as the main energy source in osteoclasts [16]. Interestingly, genetic deletion of Glut1, the predominant glucose transporter in macrophage progenitors, resulted in a modest reduction of osteoclasts only in female mice. This finding suggests sex-dependent flexibility in the use of energy substrates by osteoclasts. In addition to glucose, glutamine supports osteoclast differentiation in vitro [18•]. The increased dependence on OXPHOS in osteoclasts is consistent with robust mitochondrial biogenesis triggered by Rankl signaling during osteoclastogenesis [19, 20]. Genetic studies in the mouse have confirmed a critical role of mitochondria in

osteoclasts as deletion of the mitochondrial transcription factor A (Tfam) in mature osteoclasts reduced intracellular ATP levels and accelerated apoptosis of osteoclasts [21]. Disruption of mitochondrial complex I by deletion of Ndufs4 in the macrophage progenitors diminished osteoclastogenesis, resulting in osteopetrosis in the mouse [22•].

Insulin Signaling and Hyperglycemia

Insulin signaling begins by binding to its receptor present on the plasma membrane of the target cells [23, 24]. Binding of the receptor leads to activation of its tyrosine kinase activity which in turn phosphorylates multiple intracellular substrates including the IRS proteins and leads to activation of distinct signaling cascades, chiefly PI3K3/AKT and Shc/RAS/MAP kinase pathways. Further downstream, insulin is known to stimulate metabolic enzymes involved in glycogen synthesis in the muscle, and those for lipid synthesis in adipose tissue, chiefly through changes in phosphorylation. In addition, insulin action via the PI3K/Akt axis phosphorylates FoxO transcription factors, resulting in their exclusion from the nucleus. For example, insulin stimulates mitochondria biogenesis and electron transport chain (ETC) activity in the liver via regulation of the transcription factor FoxO1 [25]. Thus, insulin signaling controls cellular metabolism through both direct phosphorylation of enzymes and transcriptional regulation.

Much remains to be learned about the metabolic effect of insulin on bone cells. An early study reported stimulation of glucose uptake in neonatal rat calvarial bone sections by physiological levels of insulin [26]. However, a more recent study found no effect of insulin on glucose uptake in either osteoblast cultures or bone in vivo [7]. Regardless, deletion of insulin receptor (IR) in osteoblasts reduces bone formation [27, 28]. In one study, insulin signaling was proposed to suppress twist 2, a known inhibitor of Runx2 activity [27]. Another study demonstrated that insulin signaling in osteoblasts suppressed the expression of Opg, a known inhibitor of osteoclastogenesis, thus favoring bone resorption [28]. Both studies reported that mice lacking IR in osteoblasts exhibited a defect in whole-body glucose handling due to reduced insulin secretion, presumably due to insufficient osteocalcin (OC) signaling. However, recent reports have challenged the hormonal function of OC as two independent OC knockout mice did not exhibit a metabolic phenotype [29, 30]. In keeping with the bone anabolic function of insulin, deletion of FoxO1, 3 and 4 in osteoprogenitors resulted in high bone mass in the mouse due to increased osteoblast number and bone formation [31]. However, deletion of the FoxOs did not prevent the adverse effect on osteoblasts and bone formation in a mouse T1D model induced by streptozotocin (STZ), indicating yet undefined mechanisms underlying impaired bone formation in T1D [32•]. Overall, it remains unclear whether and how insulin signaling modulates cellular metabolism in osteoblasts to stimulate bone formation.

Aside from impaired insulin signaling, hyperglycemia also adversely affects bone accrual and quality. Non-enzymatic glycation of bone type I collagen leading to accumulation of advanced glycation end products (AGEs) has been implicated in compromising bone biomechanical properties in T2D [33]. Hyperglycemia also triggers numerous intracellular changes responsible for diabetic complications. Extensive studies of the cardiovascular system have identified mitochondrial superoxide overproduction as a central mediator of hyperglycemia, which in turn activates multiple pathogenic events including increased polyol pathway flux, increased protein modification through the hexosamine pathway, production of intracellular AGEs, and activation of PKC pathway [34]. Interestingly, hyperglycemia has been reported to increase oxidative inhibition of guanylate cyclase activity; pharmacological activation of cGMP synthesis reversed oxidative stress and restores osteoblast activity in T1D mice [35•]. However, future studies are warranted to elucidate fully the mechanism for hyperglycemia to impact bone cells and diabetic osteopenia.

Type 1 Diabetes and Bone Health

T1D is an incurable disease characterized by failure of the insulin-producing pancreatic beta-cells. The mechanisms underlying the development of T1D remain incompletely understood but are known to include both genetic and environmental factors. The time to progression from stage 1 T1D (autoimmunity without hyperglycemia) to stage 3 T1D (autoimmunity with symptomatic hyperglycemia) is highly variable, with some individuals living for months to years with mild asymptomatic hyperglycemia. Once diagnosed, T1D is treated with lifelong daily insulin administration. Excellent glycemic control is attainable with modern insulin pump and glucose sensor technology. However, T1D self-care remains arduous, and a variety of individual and socio-economic factors have been associated with failure to achieve glycemic targets [36]. The wide heterogeneity in T1D progression and management amongst people living with T1D, coupled with the inter-relatedness of insulin status and blood glucose levels, have made it difficult to parse out the relative impacts of hyperglycemia, insulin deficiency, and other concomitant metabolic factors on skeletal health. There have also been profound advancements in the medical management of T1D from the discovery of insulin in 1921, to the adoption of intensive diabetes treatment in the 1990s, to the approval of the first hybrid closed-loop insulin pump in 2016 [37], that complicate the assessment of exposure to hyperglycemia over the lifespan of an individual or cohorts of individuals with T1D.

Fracture in T1D

Numerous studies in diverse populations of children and adults have shown that people with T1D have an increased risk of fracture that is greater in magnitude than what is observed for T2D [38, 39]. Notably, the risk of hip fracture has consistently been shown to be increased out of proportion to other skeletal sites [40•, 41]. Contemporary epidemiologic studies have yielded mixed results regarding the relationship between hyperglycemia and fracture risk in T1D populations. Meta-analyses of T1D-related fracture studies have not systematically evaluated the relationships between hyperglycemia and fracture risk due to variability in the inclusion and ascertainment of glycemic control measures across studies. A study performed on > 30,000 people with T1D in The Health Improvement Network (UK) reported that each 1% (11 mmol/mol) greater mean hemoglobin A1c (HbA1c) was associated with an increased fracture risk of 5% (males) and 11% (females) [42••]. In a matched case-control study of children and young adults in the Diabetes Prospective Follow-up Study (Germany), higher HbA1c was associated with a prevalent fracture in females and pre-pubertal males [43]. Higher HbA1c was also associated with greater odds of fragility fracture in older adults with long-standing diabetes followed by the Canadian Study of Longevity in Type 1 Diabetes [44]. By contrast, other studies conducted in adults with T1D from the T1D Exchange Clinic Registry (USA) and Freemantle Diabetes Study (Australia) found no difference in mean HbA1c between participants with and without fractures [45, 46]. The frequency and severity of hypoglycemia is a potential confounder in the association between hyperglycemia and fracture risk, as a history of severe hypoglycemia has also been reported to be a risk factor for fracture [43, 47].

Bone Density and Quality in T1D

Mounting evidence suggests that the skeletal fragility observed in people with T1D is multi-factorial and the product of both impaired bone density and bone quality. Greater HbA1c has been associated with lower aBMD by DXA cross-sectionally [48, 49] and diminished bone accrual [50] in children with T1D. Other studies have found no associations between glycemic control and bone density in youth with T1D [51, 52]. The assessment of bone quality is less standardized than for bone density and interpretation of findings in T1D cohorts has been challenging due to differences in imaging modalities and techniques. Studies utilizing HR-pQCT have shown that individuals with higher HbA1c have more pronounced deficits in trabecular and cortical bone microarchitectural and strength elements, although the specific deficits vary across studies [53•, 54••, 55•]. A single study using hip structural analysis reported deficits in hip geometry and estimated bone strength in adolescent females with higher HbA1c [1]. TBS was not found to be associated with HbA1c in recent studies of adults with T1D [56, 57].

The mechanisms linking hyperglycemia to skeletal fragility in T1D are incompletely understood and appear likely to include both direct and indirect adverse effects on skeletal metabolism. Hyperglycemia is toxic to osteoblast function [58], and markers of bone formation are commonly found to be inversely associated with HbA1c in both children and adults [49, 59•]. Long-term exposure to hyperglycemia leads to the development of microvascular disease including retinopathy, neuropathy, and nephropathy. Several studies have reported that the development of a diabetes-related microvascular disease is associated with the presence of skeletal deficits, and in some cases statistically significant deficits compared to controls were only seen in the subset of T1D subjects with microvascular disease [60•, 61]. It is not yet known if this association is driven by a direct negative effect of microvascular disease on bone, or if the presence of microvascular disease is a marker of greater overall hyperglycemia exposure. Clinical studies of AGEs in T1D cohorts are limited. Serum pentosidine, a fluorescent AGE, was found to be associated with a prevalent fracture in an adult cohort with T1D [62]. Another small study found that AGE concentrations were higher in bone samples at fracture sites of subjects with T1D compared to healthy controls, although it is not clear if AGE concentration contributed to bone fragility [63].

To date, there have been no published studies of interventions to improve glycemic control on primary bone health outcomes in populations with T1D. Likewise, bone health assessments are not commonly included as secondary outcomes in trials to improve glycemic control. It therefore remains unknown if improving glycemic control to levels closer to that of people without diabetes, which is now attainable for some individuals, will be sufficient to prevent the development of T1D-related skeletal fragility.

Type 2 Diabetes and Bone Health

T2D is a complex metabolic health condition impacting nearly one in ten adults in the USA [64]. Of particular concern is the growing prevalence of pre-diabetes, since upwards of one in three adults and one in five youth are suspected to have pre-diabetes, with many being unaware of their increased risk for developing T2D. Impaired glucose control resulting from insulin resistance, reduced insulin production and increased gluconeogenesis are the main features of T2D, contributing to the development of co-morbidities impacting most body systems. The most common complications of T2D include kidney disease, vision disability, and cardiovascular disease, and the skeletal system is also impacted.

Fracture in T2D

As noted above, a recent systematic review and meta-analysis of observational studies found an increased risk for fracture among people with diabetes but that the relative risk for both hip and non-vertebral fractures was greater in T1D compared to that in T2D [40•]. In both forms of diabetes, fracture risk was heightened in younger individuals (<65 years of age), and in T2D only, longer duration of diabetes and use of exogenous insulin for glucose regulation were associated with increased risk. Consistent with these findings, a study by Ha et al. leveraged data from a population-based cohort of >6.5 million people from the Korean National Health Insurance Service to assess associations between diabetes and fracture [39]. They observed increased fracture incidence in people with both T1D and T2D, and that people with T1D had a greater risk for fracture in all skeletal regions compared to those with T2D. A recent meta-analysis by Hidayat et al. underscores the contribution of glycemic control in diabetes-related fracture [65]. Glycemic dysregulation, measured via HbA1c, was associated with an increased risk for fracture. However, this association was non-linear, such that the association was significant at HbA1c values >8.0%. In contrast, hypoglycemia resulting from anti-diabetes medication such as insulin can also lead to fracture due to a greater propensity for falls.

Bone Density and Quality in T2D

Whereas T1D typically involves low aBMD as a result of insulin deficiency [66], T2D is typically accompanied by normal or even increased aBMD [67–70]. For this reason, standard clinical measures of BMD from DXA tend to underestimate fracture risk in people with T2D [69]. Recent advancements in DXA-based imaging, such as TBS, have provided insight into the potential role of bone quality in diabetes-related bone fragility. Studies in adults with T2D report lower TBS values compared to non-diabetic controls [2, 71, 72]. An important consideration in interpreting TBS results in the setting of T2D is potential confounding attributed to body size and overlaying soft tissue. The TBS algorithm accounts for BMI, but might not entirely resolve confounding attributed to excess abdominal soft tissue [73]. The potential confounding of TBS values from overlaying soft tissue is particularly concerning from a clinical standpoint, since TBS has been recommended for use in people with long-term or poorly controlled diabetes [74]. Weight loss from diet, physical activity, pharmacologic intervention, and/or bariatric surgery is often a treatment goal in people with T2D, so the extent to which excess abdominal fat and changes in body composition impact TBS measures require further investigation.

Studies of cortical and trabecular bone morphology and estimated strength from HR-pQCT in people with T2D have yielded somewhat inconsistent findings [3, 75, 76]. These studies varied with respect to disease progression and overall health status of study participants which likely contributed to differences in results across studies. The most consistent effects of T2D on bone micro-structure involve accumulation and expansion of cortical bone micro-pores, which are associated with fractures in people with diabetes [3, 77–80]. An exploratory five-year longitudinal study of 20 women with T2D and 12 controls observed similar increases in cortical porosity among groups, but the women with T2D and a history of fracture had significantly greater declines in bone stiffness and failure load, measures of bone strength derived by finite element analysis [78]. These authors suggested that the cortical pore expansion may occur early in the disease and that differences in the size, shape, and distribution of micro-pores in cortical bone may contribute to bone fragility in T2D. Glycemic control is one potential contributor to cortical bone structural deficits in T2D [81, 82]. de Ward et al. reported deficits in cortical bone morphology, including greater cortical porosity, lower volumetric BMD, and lower thickness, in adults with T2D that had an HbA1c >7.0% while adjusting for relevant confounders [81]. As most studies of bone microstructural characteristics have been cross-sectional, additional longitudinal studies are required to further understand the contribution of cortical porosity and other aspects of bone microarchitecture on diabetes-related bone fragility.

Accumulation of AGEs contributes to diabetes-related complications, including bone fragility [71]. Pentosidine and carboxy-methyl-lysine (CML) have been associated with bone structural deficits and increased risk for fracture and bone deficits in healthy and diabetic populations [80, 83–85]. Most recently, Dhaliwal *et al.* utilized data from the Health, Aging, and Body Composition (Health ABC) cohort of older adults, approximately 74 years of age, to assess associations between CML and incident and prevalent vertebral fractures [86••]. T2D status was associated with increased CML concentrations, which were subsequently associated with increased fracture incidence independent of BMD. Farr and colleagues were among the first to report compromised bone material strength assessed by reference point indentation in adults with T2D *in vivo* [87]. More recent studies have confirmed these earlier findings that T2D is associated with reduced bone material strength and that factors such as AGEs, cortical porosity, and microvascular complications of diabetes might contribute [88].

Bone Health in Other Forms of Diabetes

T2D has long been considered an adult-onset condition, but epidemiological data over the past several decades highlights concerning trends in youth-onset T2D [89]. Youth-onset T2D is of particular concern given the rise in cases observed from

2020-2022 during the COVID-19 pandemic [90]. This concern is further compounded by the fact that youth-onset T2D is a more insidious disease compared to diabetes in adulthood [91, 92]. Despite the strong evidence supporting a detrimental effect of T2D on bone health in adulthood, bone outcomes have not been extensively studied in children and adolescents with T2D. Studies in younger individuals mainly focus on the association of subclinical indictors of T2D progression, such as obesity, insulin resistance, and cardiometabolic risk factors associated with metabolic syndrome with measures of bone health [93]. One of the first studies of youth-onset T2D examined total body BMD Z-scores (adjusted for height Z-score) between youth with healthy weight, obesity, and T2D (with obesity) [94••]. The association between T2D status and BMD was moderated by age, such that younger individuals with T2D had greater BMD compared to those with obesity, but adolescents and young adults with T2D had lower BMD compared to those with obesity. Prominent limitations of this study include the cross-sectional design and assessment of bone health only by total body BMD from DXA. Trabecular bone micro-architectural deficits have been reported in late-adolescent females around the age of peak bone mass (about 19 years of age) [95], but these features of bone quality have not yet been studied in the setting of youth-onset T2D. Longitudinal studies are needed to investigate the effects of youth onset T2D on development of peak bone mass and strength.

Secondary forms of diabetes can occur because of complications or endocrinopathies accompanying other chronic diseases (e.g., pancreatitis, Cushing's syndrome) and/or clinical interventions (e.g., glucocorticoids, radiation therapy) [96]. Cystic fibrosis (CF), for example, results in a unique form of diabetes, which is among the most common non-pulmonary complications of CF [97]. Bone fragility is also common in CF [97]. CF Foundation Patient Registry data indicate that prior diagnosis of CF-related diabetes is among the strongest predictors of whether or not a patient with CF is screened for bone disease [98], but few studies have evaluated the diabetes-bone connection in the setting of CF. Mathiesen *et al.* recently compared bone density and biomarkers of bone metabolism between adults with CF ages 18–53 years with and without diabetes [99]. They reported marginally lower femoral BMD as well as lower bone turnover in people with CF-related diabetes compared to those with normal glucose control. In the era of new therapies for the treatment of CF, further investigation of non-pulmonary complications of CF such as diabetes and bone disease is needed in this population.

Conclusion

Recent research into cellular metabolism has revealed the important role of glucose in osteoblast differentiation and energy consumption of mature osteoblasts and insulin signaling in energy metabolism. Further research is needed to illuminate how these findings relate to patterns of bone fragility in patients with diabetes. The risk of hip fracture is elevated in individuals with T1D, and compromised bone strength is associated with elevated HbA1c. Fracture risk is also elevated in T2D, but not to the same degree as in T1D. Alterations in the size and distribution of micro-pores in cortical bone and reduced bone strength are major contributors to bone fragility in T2D. The increasing prevalence of youth-onset T2D is particularly concerning, given the aggressive development of other complications, yet limited information about their bone health is currently available. Further research is needed to understand the effects of hyperglycemia on both the developing and aging skeleton, including the related factors of inflammation and microvascular damage.

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Compliance with Ethical Standards

Conflict of Interest The authors do not have existing conflicts of Interest.

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