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PEDIATRIC TYPE 2 AND MONOGENIC DIABETES (O PINHAS-HAMIEL, SECTION EDITOR)

Impact of Type 2 Diabetes Mellitus and Antidiabetic Medications on Bone Metabolism

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Abstract

Purpose of Review This review focuses on the complex interactions between hyperglycemia and bone fragility and the effects of antidiabetic medications on bone metabolism.

Recent Findings Type 2 diabetes (T2D) is associated with increased risk of bone fracture even in those with increased or normal bone mineral density (BMD). The pathophysiology of diabetic bone disease is not completely understood, but it is thought to be multifactorial and associated with complex cross talk among factors such as AGEs, IGF-1, enteric hormones, and pro-inflammatory cytokines. Treatment for T2D may have an impact on bone metabolism.

Summary Diabetic bone disease should be considered a serious complication of long-standing T2D.

Keywords Type 2 diabetes · Osteoporosis · Bone remodeling · Fracture

Introduction

Type 2 diabetes mellitus (T2D) is a major health problem and one of the most prevalent chronic diseases. In 2019, 463 million people (9.3% of adults 20–79 years old) were living with T2D worldwide. The estimated number of people (20–79 years) living with T2D has increased by 62% over the past 10 years [1]. Moreover, the increasing prevalence of childhood obesity is a worldwide problem [2]. The prevalence of T2D has more than doubled in children and adolescents in the past 10 years [3].

Diabetes and its complications are a major cause of morbidity and mortality and result in increased economic burden. T2D can affect many different organ systems in the body and, over time, can lead to serious complications including nephropathy, neuropathy, retinopathy, and cardiovascular disease. Recently, the increased risk of fragility fractures has been recognized as an important complication in diabetics; although, paradoxically, the bone mineral density (BMD) in those with T2D is higher than in non-diabetic subjects [4].

In this review, we described the complex interactions between hyperglycemia and bone and the effects of antidiabetic medications on bone metabolism.

Bone Mineral Density and the Prevalence of Fractures in Type 2 Diabetes

Although the prevalence of T2D in children and adolescents has increased dramatically in past decades, there have been few reports on bone metabolism in pediatric patients with T2D. In a study by Lee et al. [5], the BMD of the lumbar spine and total body in adolescents with new T2D was not different compared to obese controls without T2D, but the BMD of the femoral neck was significantly lower than in controls. In adults, a meta-analysis reported that patients with T2D had approximately 25–50% higher BMD in the lumbar spine and hip, but not in the forearm compared to normal controls after adjustment for BMI [6]. However, a recent review article reported that thirteen studies in adults demonstrated decreased BMD in those with T2D, while eight other studies found no difference in BMD in those with T2D compared to normal controls [7].

It has been observed that T2D negatively affects bone strength despite increased or normal BMD. In the Rotterdam Study, 6655 men and women with T2D (aged ≥ 55 years) had

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an increased risk of non-vertebral fractures compared with subjects without T2D (HR 1.33), although they had a higher BMD [8]. In the Health, Aging and Body Composition Study, T2D was associated with accelerated bone loss at the hip, and a high risk of fractures was observed (relative risk 1.64; 95% CI 1.07–2.51) after adjustment for hip BMD and additional risk factors for fracture [9]. A large meta-analysis of case-control and cohort studies confirmed an increased relative risk (RR) for hip fracture of 1.4- to 1.7-fold in both men and women with T2D compared to subjects without diabetes [10, 11]. In a recent meta-analysis of 21 independent observational studies involving 82,293 hip fracture events among 6,995,272 participants, subjects with T2D had an increased risk of hip fractures (RR 1.34; 95% CI 1.19–1.51) [12]. Moreover, fractures of the wrist and foot were more prevalent in patients with T2D than in subjects without it [8, 13].

Hip fractures are the most extensively studied fracture type in patients with T2D, and most studies reported that patients with T2D have a higher risk of hip fracture than subjects without T2D. However, vertebral fractures are quite difficult to evaluate in large observational studies and reports of the association between T2D and vertebral fracture have been contradictory. In a meta-analysis of 738,018 individuals, patients with T2D had a higher incidence of vertebral fracture compared with subjects without T2D (OR 1.55, 95% CI 1.04–2.31) [14]. Another study in an Asian population (982 postmenopausal women aged 47–108 years, 18.9% with T2D) reported that women with T2D were at similar risk for vertebral fractures compared with subjects without T2D (OR 0.74, 95% CI 0.32–1.74), after adjustment for age, BMI, BMD, and previous fractures [15]. These discrepant observations may be attributable to differences in study design, ethnicity, sample size, and variable methods of vertebral fracture ascertainment.

Overall, fracture risk is almost two times higher in patients with T2D compared with subjects without T2D, even though patients with T2D have an increased or normal BMD. In pediatric patients, the BMD of the femoral neck is reduced compared with normal obese controls. This might be the mechanism underlying the association of T2DM with the risk of hip fracture.

Pathogenesis of Bone Fragility in Type 2 Diabetes

Patients with T2D have normal or increased BMD, so this increased risk is probably due to abnormalities in bone material strength and biomechanical quality. Bone mass is determined by the balance between osteoblast and osteoclast activity, which is orchestrated by osteocytes in reaction to endocrine and mechanical stimuli. Bone marrow mesenchymal stem cells are differentiated into osteoblasts, osteocytes, adipocytes, and chondrocytes. Osteoblasts produce bone matrix proteins, including type I collagen. Osteoblasts are involved in cross talk with osteoclasts through cytokines and the extracellular matrix. The interaction between osteoblast and osteoclast activity leads to osteoclast formation, differentiation, and apoptosis [16]. Recent studies demonstrated that hyperglycemia may directly or indirectly influence osteoblasts and osteoclasts as well as osteocytes [17]. The pathogenesis underlying bone fragility in T2D are complex and multifactorial, including accumulation of advanced glycation end products (AGEs) in the collagen fibers, insulin-like growth factor-1 (IGF-1), incretin hormones like glucose-dependent insulinotropic peptide (GIP), sclerostin, chronic inflammation with increases in pro-inflammatory cytokines, and bone microangiopathy with reduction in vascular flow and increased bone fragility [4].

Hyperglycemia and Advanced Glycation End Products

Hyperglycemia may act through non-enzymatic pathways and induce the formation of AGEs [18]. The AGEs in patients with T2D accumulate in bone as a result of hyperglycemia and increased levels of oxidative stress [19]. AGEs not only significantly inhibit osteoblast proliferation, but also induce osteoblast apoptosis. Moreover, AGEs suppress osteoblastic differentiation and mineralization, accompanied by enhanced expression of the receptor for AGEs (RAGE) [20, 21]. AGEs induce production of reactive oxygen species (ROS), which plays an important role in many of the complications associated with T2D, and increased oxidative stress has a negative impact on bone formation by modulating osteoblast differentiation and survival [22]. The AGE-RAGE interaction mediates generation of ROS and vascular inflammation results in the development and progression of microangiopathy [23]. Microangiopathy leads to abnormal blood flow and may be associated with altered bone remodeling due to changes in vascular endothelial growth factor signaling or increased accumulation of AGEs [24].

Bone matrix consists of mainly type I collagen and minerals, and smaller quantities of non-collagenous proteins. AGEs can contribute to reduced bone formation by inhibiting the synthesis of type I collagen and results in reduced bone strength. Tang et al. [25] reported that accumulation of AGEs in human cancellous bone can increase the stiffness of the collagen network and reduce its ductility.

Pentosidine, which is the most studied AGE, is increased in patients with T2D compared to non-diabetic controls [26]. Elevation of serum pentosidine is associated with an increase in prevalence of vertebral fracture in older adults (70–79 years) and postmenopausal women with T2D, irrespective of BMD [27, 28]. These studies supported the notion that accumulation of AGEs in response to hyperglycemia plays a pivotal role in both bone material properties and bone turnover, which results in bone fragility in patients with T2D.

Apart from the indirect effects of hyperglycemia on osteoblastic differentiation and activity through the formation of

AGEs, hyperglycemia directly affects the differentiation and function of osteoblasts. Deng et al. [29] reported that hyperglycemia inhibits the differentiation of mesenchymal stem cells (MSCs) to osteoblasts, and that the proliferation and osteogenic differentiation of MSCs are associated with glycemic control. High glucose is associated with a shift in the differentiation of MSCs toward adipogenesis, rather than toward osteoblasts [30]. This adipogenic conversion of MSCs is mediated through ROS production [31]. The peroxisome proliferator-activated receptor gamma (PPARγ), which consists of two isoforms in humans (PPARγ1 and PPARγ2), is a master regulator of adipogenesis. In bone, PPARγ2 plays an important role in regulating the differentiation of MSCs toward osteoblasts and adipocytes [32]. Levels of PPARγ were found to be positively correlated with increased BMI in obese patients [33]. Therefore, activation of PPARγ2 in patients with T2D may disturb the delicate balance between bone marrow adipocytes and osteoblasts and results in decreased osteogenesis by inhibiting the differentiation of MSCs into osteoblasts [34].

Low Turnover Marker

Most studies, but not all, reported that bone turnover markers are reduced in patients with T2D compared to non-diabetic controls [35, 36]. Osteocalcin, which is the most abundant osteoblast-specific marker, is a key determinant of bone formation [37]. Observational studies demonstrated that patients with T2D have lower plasma osteocalcin levels compared to non-diabetic individuals [38, 39]. A recent meta-analysis based on 47 studies evaluating bone turnover markers in diabetes reported that osteocalcin, C-terminal telopeptide of type I collagen (CTX), N-terminal telopeptide of type I collagen (NTX), and procollagen type 1 amino-terminal propeptide (P1NP) levels tended to be lower or significantly lower in patients with diabetes than in controls [35]. Furthermore, Wang et al. [40] reported that bone formation markers including osteocalcin and P1NP were inversely correlated with HbA1c.

Sclerostin is produced by osteocytes and is a potent inhibitor of bone formation through inhibition of the Wnt/β-catenin signaling pathway. Wnt/β-catenin signaling pathway activation promotes osteoblast cell lineages and suppresses osteoclastogenesis by inducing osteoprotegerin [41]. Gaudio et al. [42] reported that elevated serum sclerostin level is associated with a significant reduction in serum β-catenin levels. They suggested that increased sclerostin has a causative effect in impairing the functionality of Wnt signaling in patients with T2D [42]. In a meta-analysis, sclerostin levels were higher in patients with T2D than in healthy controls [43]. Furthermore, sclerostin levels were negatively correlated with P1NP levels in patients with T2D [44]. In a cross-sectional study, increased sclerostin levels were associated with an increased risk of vertebral fractures in patients with T2D after adjusting for BMD [45]. Taken together, these findings suggest that low bone turnover in patients with T2D is associated with bone fragility, and may increase the risk of fracture.

Insulin-Like Growth Factor-1

IGF-1 is an anabolic hormone that directly influences bone cells and potentially contributes to bone fragility. IGF-1 increases osteoblast proliferation and inhibition of matrix collagen degradation by decreasing collagenase 3 transcription [46]. IGF-1-deficient mice exhibited delayed mineralization, reduced chondrocyte proliferation, and increased chondrocyte apoptosis [47]. IGF-1 levels were lower in postmenopausal women with T2D compared to age-matched controls, and decreased serum IGF-1 levels were inversely associated with vertebral fractures in these patients [48]. Several experimental studies demonstrated that the stimulatory actions of IGF-1 on osteoblasts are blunted by increased AGEs [49, 50]. Therefore, reduced IGF-1 levels may be associated with bone abnormalities.

Enteric Hormones: Glucose-Dependent Insulinotropic Peptide and Glucagon-Like Peptide 1

GIP and glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) are gastrointestinal hormones released by K cells in the duodenum and proximal jejunum and from L cells located in the distal ileum and colon, respectively. The serum GIP and GLP-1 levels start to rise after nutrient ingestion and reach a peak after about an hour [51]. The bioactivity of both GIP and GLP-1 is limited by rapid degradation and inactivation by the enzyme, dipeptidyl peptidase-4 (DPP-4) [52]. GLP-1 increases the number of osteoblasts and promotes the expression of genes related to bone formation such as Runx2 [53, 54]. Patients with T2D have a decreased incretin response with impaired GLP-1 production after nutrient ingestion [55]. GLP-1 receptors are also expressed on bone marrow stromal cells and osteoblastic precursor cells [56]. Therefore, incretins may be associated with control of bone mass and bone quality, so impaired GIP and GLP-1 could contribute to bone fragility in T2D [57]. However, further studies are needed to investigate the role of incretins in bone health.

Pro-Inflammatory Cytokines

Chronic inflammation may be a link between bone abnormalities and fracture risk in T2D. Serum pro-inflammatory cytokines including interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and high-sensitivity C-reactive protein are upregulated in T2D patients with bone fractures, which are associated with reduced osteoblast viability [58, 59]. Moreover, TNF-α promotes the apoptosis of osteoblast cells in the presence of high glucose and stimulates osteoclastogenesis [59, 60].

Another study showed that pro-inflammatory cytokines stimulate the production of ROS, which affects differentiation and survival of osteoclasts and osteoblasts [61].

Effects of Antidiabetic Drugs on Bone Metabolism

Many antidiabetic medications have recently become available for patients with T2D. Many studies have reported that these antidiabetic drugs, including insulin, metformin, and thiazolidinediones, can have positive, negative, and neutral effects on fracture risk [62]. All of these studies were conducted in adults with T2D, and to date, there have been no studies conducted in children and adolescents with T2D.

Insulin

Insulin has an anabolic effect on bone regeneration by stimulating osteoblast proliferation and differentiation based on experimental studies [63, 64]. However, in human observational studies, insulin treatment was associated with increased fracture risk in patients with T2D [65, 66]. Losada-Grande et al. [67] reported that insulin treatment is associated with an increased risk of fracture (hazard ratio 1.38, 95% CI 1.06–1.80) patients with early-stage T2D. However, insulin is often the last option for treatment in those with T2D. Thus, patients who initiate insulin treatment are more likely to already have greater complications such as microvascular disease or peripheral neuropathy as well as a more severe disease progression. Insulin treatment could affect fracture incidence due to increased risk of hypoglycemia, which may lead to falls.

Metformin

Metformin is a first-line drug in the treatment of T2D and is thought to improve insulin sensitivity. Metformin has been found to affect bone metabolism by activation of AMP-activated protein kinase in bone marrow progenitor cells and osteoblasts in vitro [68, 69]. In a recent meta-analysis, metformin treatment in patients with T2D was associated with a reduced risk of fracture (RR 0.86, 95% CI 0.75, 0.99) [70]. In A Diabetes Outcome Progression Trial (ADOPT), patients treated with metformin had a lower incidence of fracture than those treated with thiazolidinedione (TZD) [71]. Interestingly, there were no differences in the incidence of fractures in men with T2D taking different antidiabetic medications in the ADOPT study. Clinical studies assessing the association between different antidiabetic drugs and fracture risk have shown that metformin use has a positive or neutral effect on bone health [72–74].

Thiazolidinedione

Thiazolidinedione (TZD) improves insulin sensitivity and its action primarily activates PPARγ. In an experimental study, TZD had a detrimental effect on bone metabolism by suppressing bone formation and stimulating bone resorption [75]. Treatment with TZDs such as rosiglitazone and pioglitazone was associated with a 45% increased risk of fractures in ten randomized controlled trials [76]. A recent meta-analysis included 22 randomized controlled trials (RCT) with over 25,000 patients. This meta-analysis demonstrated that women treated with TZD had significantly increased risk of fractures (OR = 1.94; 95% CI: 1.60–2.35), but there was no effect in men (OR = 1.02; 95% CI: 0.83–1.27) [77]. For women, both rosiglitazone and pioglitazone were associated with increased fracture risk. TZD treatment was also associated with reduced BMD in the lumbar spine and femoral neck and hip. However, there was no significant difference in fracture risk based on TZD treatment duration [77]. These findings suggest that TZD treatment has a negative effect on bone metabolism, and women with T2D treated with these medications have an increased risk of fracture. TZD use should be avoided in women, especially after menopause.

Sulfonylureas

Sulfonylureas increase insulin secretion by binding to an adenosine triphosphate (ATP)–dependent K^+ channel on the cell membrane of pancreatic beta cells. In an experimental study, glimepiride, which is a second-generation sulfonylurea, enhanced osteoblastic differentiation under hyperglycemic conditions through the phosphoinositide 3-kinase (PI3K)/Akt/eNOS pathway [78]. However, there have been relatively few studies on the effect of sulfonylureas on bone metabolism in patients with T2D. In the ADOPT study, patients taking a sulfonylurea (glyburide) had a similar incidence of fracture compared to those taking metformin, but a lower incidence than those taking rosiglitazone [71]. Sulfonylurea treatment was associated with an increased risk of fracture in a meta-analysis of 11 studies evaluating the effect of sulfonylureas on fracture risk (OR 1.14; 95% CI, 1.08–1.19) [79]. However, this may be due to the fact that sulfonylurea-induced hypoglycemia increases the risk of falls.

GLP-1 Receptor Agonists and DPP-4 Inhibitors

GLP-1 receptor agonists comprise a new class of incretin-based therapy. GLP-1 receptor agonists reduce hyperglycemia by increasing insulin secretion and decreasing glucagon secretion, with a low risk of hypoglycemia [80]. Data on the effect of GLP-1 receptor agonists and fracture risk in humans is sparse. Mabilleau et al. [81] reported that GLP-1 receptor agonist treatment was not associated with fracture risk

compared with the use of other antidiabetic medications in a meta-analysis. However, a network meta-analysis of 54 RCTs with 49,602 participants indicated that GLP-1 receptor agonists were associated with a decreased risk of fractures compared with other antidiabetic treatments or no treatment in patients with T2D [82]. Data from these studies should be interpreted carefully because most studies were short in duration.

DPP-4 inhibitors increase active incretin hormone levels by inhibiting plasma DPP-4 activity. Clinical evidence supporting the effects of DPP-4 inhibitors on fracture risk is also conflicting. A meta-analysis of 28 RCTs with a duration of at least 6 months demonstrated that DPP-4 inhibitors reduced the risk of bone fracture by 40% compared with controls or other antidiabetic drugs [83]. In a retrospective study from Germany, the use of DPP-4 inhibitors was associated with a significant decrease in fracture risk in both men and women (HR 0.67; 95% CI 0.54–0.84) [84]. However, a recent UK cohort study reported that the long-term use of DPP-4 inhibitors (duration; 4.0–8.5 years) was not associated with increased fracture risk compared with other antidiabetic treatments (HR 0.99; 95% CI 0.93–1.06) [85]. An analysis of 62 RCTs showed that the risk of fracture was not different between patients taking DPP-4 inhibitors and controls (RR 0.95; 95% CI, 0.83–1.10) [86].

Taken together, these findings suggest that GLP-1 receptor agonists and DPP-4 inhibitors seem to have a positive or neutral effect on bone health, but further RCTs with a longer treatment duration are required to further evaluate the effects of these drugs.

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the latest class of oral medications for T2D and improve glycemic control by inhibiting proximal renal tubular reabsorption of glucose [87]. Canagliflozin, empagliflozin and dapagliflozin have been approved by the US Food and Drug Administration (FDA). SGLT2 inhibitors may have negative effects on bone metabolism by altering calcium and phosphate homeostasis [88]. Blau et al. [89] reported that serum phosphate, fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH) levels increase, whereas active vitamin D level decreases after canagliflozin administration in healthy adults. These results suggest that SGLT2 inhibitors may lead to increased risk of bone fracture. In the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial, the rate of all fractures was higher in patients taking canagliflozin compared with controls (HR 1.26; 95% CI, 1.04 to 1.52) [90]. However, in a recent meta-analysis of 30 RCTs including 23,372 patients with T2D, the incidence of bone fractures was not significantly different between patients taking SGLT2 inhibitors and those taking a placebo (OR 0.86; 95% CI 0.70–1.06) [91]. Clinical data for SGLT2 inhibitors is limited, and further studies are needed to clarify the bone effects of these medications.

Conclusion

Patients with T2D are at increased risk of bone fracture, even those with increased or normal BMD. Diabetic bone disease should be considered a serious complication of long-standing T2D. The pathophysiology of diabetic bone disease is not completely understood, but is apparently multifactorial, associated with complex cross talk among factors such as AGEs, IGF-1, enteric hormones, and pro-inflammatory cytokines. Antidiabetic treatment may have an impact on bone metabolism. In particular, adolescence is a critical period of peak bone mass, so T2D may affect bone density and increase susceptibility to fractures in adolescents. However, there have been few reports on the effects of hyperglycemia on bone development and homeostasis in children and adolescents. Further research on the mechanisms underlying diabetic bone disease and the effects of antidiabetic medications on bone metabolism is necessary.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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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