Current Osteoporosis Reports (2019) 17:291–300
https://doi.org/10.1007/s11914-019-00526-w

BIOMECHANICS (G NIEBUR AND J WALLACE, SECTION EDITORS)

The Effect of Type 2 Diabetes on Bone Biomechanics

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Published online: 7 August 2019

Abstract

Purpose of Review There is ample evidence that patients with type 2 diabetes (T2D) have increased risk of fracture even though they have normal or high bone mineral density. As a result, poor bone quality is suggested to contribute to skeletal fragility in this population. Thus, our goal was to conduct a comprehensive literature review to understand how bone quality components are altered in T2D and their effects on bone biomechanics and fracture risk.

Recent Findings T2D does affect bone quality via alterations in bone microarchitecture, organic matrix, and cellular behavior. Further, studies indicate that bone biomechanical properties are generally deteriorated in T2D, but there are few reports in patients.

Summary Additional work is needed to better understand molecular and cellular mechanisms that contribute to skeletal fragility in T2D. This knowledge can contribute to the development of improved diagnostic tools and drug targets to for improved quality of life for those with T2D.

Keywords Type 2 diabetes · Bone · Biomechanics · Skeletal fragility · Non-enzymatic glycation · Bone matrix

Introduction

Skeletal fragility is a major complication of type 2 diabetes (T2D). T2D patients experience up to three times increased hip fracture risk compared to non-diabetics [1, 2] despite having normal to high bone mineral density (BMD) [3–5]. Assessment of two-dimensional BMD by dual-energy X-ray absorptiometry is the gold standard to diagnose osteoporosis and accordingly identify low BMD individuals at risk for fracture [6]. However, BMD assessment alone cannot effectively identify diabetic patients prone to fractures. Furthermore, the fracture risk assessment tool (FRAX) that is available and considered a relatively comprehensive algorithm assesses BMD T-score along with other health risk indicators such as age, gender, BMI, previous fracture history, and smoking status, among other characteristics. However, FRAX does not incorporate diabetes (presence, duration, or severity) as a risk factor. Therefore, the primary conventional clinical tools to assess fracture risk are not satisfactory to identify those with T2D at risk for fractures, and consequently, clinicians have difficulty in taking appropriate preventative measures for these patients.

Hence, it is essential to investigate factors independent of BMD to improve upon existing diagnostic tools for this population and to develop drug targets and treatment options for diabetics. Potential non-BMD factors include, but are not limited to, alterations in bone microarchitecture, bone matrix, and bone cell behavior. There is evidence related to all three of these possible mechanisms for increased fracture risk in T2D, although reported studies have several limitations or gaps in the knowledge base.

This review focuses on potential mechanisms contributing to altered mechanical behavior and/or fracture risk in patients with T2D. We conducted a literature search for English language articles in the PubMed database using the following keywords alone or in combination with each other: "diabetes," "bone," "skeletal fragility," "biomechanics," "cortical microarchitecture," "trabecular microarchitecture," "bone matrix," "collagen," "advanced glycation end-products," "AGEs," "bone material strength," "hyperglycemia," "gene expression," "osteoblast," "osteoclast," "non-enzymatic glycation," "hydroxyapatite," "high glucose," "mechanical properties," "cell differentiation," "osteocyte," "bone

This article is part of the Topical Collection on *Biomechanics*

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remodeling," "bone turnover," "bone loss," "inflammation," "anti-diabetic drugs," "thiazolidinediones," "metformin," "GLP-1," "DDP-4," "SGLT2," and "sulfonylureas." We focused on articles published within the last 5 years but included some older studies in topic areas where there was a lack of recent literature. Approximately 100 articles were reviewed on pre-clinical models, ex vivo and in vitro experiments, as well as clinical studies to discuss the effect of type 2 diabetes on bone mechanics and its consequent effect on fracture risk.

Bone Mechanical Properties in Diabetes

Overview of Basic Bone Biomechanics

One of the main functions of bone in the human body is mechanical support and protection. Whole bones fulfill these responsibilities by bearing different types of loads in various combinations including compression, tension, bending, and torsion. As bone is a dynamic tissue, it responds to both external and internal mechanical stimuli [7], which in turn influence bone repair and the overall quality of its tissue. The structure of bone, its type, and magnitude of the applied load affect its response to these forces [8]. Specifically, there are two types of bone: cortical (or compact) bone is more dense while trabecular (or cancellous) bone has more porosity and an intricate network of trabeculae [8]. Both bone types vary greatly in response to forces. Trabecular bone is mostly found in areas that need effective load distribution such as joint regions and vertebral bodies [7]. On the other hand, cortical bone is found in areas requiring strong structural support such as the outer shaft of long bones.

To better understand the mechanical behavior of these two bone types, there are several key mechanical properties that can be assessed from either traditional mechanical tests that incorporate monotonic loading until failure or from recently developed reference point indentation [8]. From a traditional mechanical test, the properties assessed are based on the relationship between applied loads on bone specimens and the resulting deformation in the tissue. From the collected load and deformation data, we can calculate stress (applied force per unit area) and strain (amount of deformation in length divided by original length). As stress and strain are normalized measures of force and displacement, these variables provide information of tissue-level mechanical behavior with confounding variables of geometry already factored into calculations. The stress-strain curve resulting from mechanical testing on bone provides important data about its behavior. The first domain of this curve describes the elastic region in bone. The slope of stress-strain curve in the elastic area determines the elastic modulus, which is a measure of stiffness at the tissue level. All deformations are reversible in this domain (pre-yield properties). However, any deformation beyond the yield point falls is irreversible as it falls in the plastic domain (post-yield properties). The fracture zone is the last domain of the curve, during which microdamage drastically accumulates and the bone fractures. The total area under the whole stress-strain curve represents the mechanical work needed for the bone to fail. From the more recently designed reference point indentation tests, load and deformation data is also used to calculate important variables. In cyclic reference point indentation, the primary properties assessed are various measures of indentation distance into the bone relative to the bone surface [9]. In impact-based reference point indentation, a single measure of bone material strength index is calculated as 100 times the mean of the indentation distance increase from the impact of the probe into bone relative to a polymethylmethacrylate phantom, normalized to the average indentation distance increase [9, 10•].

Mechanical Behavior of Type 2 Diabetic Bone

The ability of bone to resist deformation and fracture is derived from various physical characteristics of the bone tissue on multiple length scales, many of which are independent of bone mineral density [11]. Techniques for ex vivo evaluation of bone material properties depend on the type of bone (cortical/trabecular), shape of the samples, and the orientation of applied loads. Tension, compression, and bending (4-point and 3-point bending) are the traditional methods for measuring bone mechanical properties.

Three-point bending tests on rodent femoral midshafts [12–15], compression tests on rodent vertebral bodies [12, 15], shear loading on rat femoral neck specimens [14], and cyclic reference point indentation on rat femoral mid-diaphysis and canine ribs [15] indicate that there are reductions in whole bone stiffness, yield load, post-yield energy, maximum load, and apparent modulus in T2D bone tissue samples compared to non-diabetic bone [12–15]. Further, a comprehensive study conducted by Acevado et al. showed that T2D rats with hyperglycemia had significantly reduced whole bone biomechanical properties as assessed by three-point bending tests on the ulnae (i.e., reduced modulus, yield strength, and ultimate strength) [16], lower tissue yield strain, ultimate strain, and ductility as assessed by tensile tests, and lower vertebral stiffness as assessed by compression tests [16].

Although there are a few pre-clinical reports as mentioned above, there are limited data about biomechanical properties directly in T2D human bone. To our knowledge, there are currently four reports of bone mechanical properties in bone from patients with T2D [10•, 17•, 18•, 19•]. Although a few studies exist in which bone from humans and animal models was incubated in vitro to simulate high sugar levels [20–23], we focus only on data reported directly in diabetic bone.

Among the two ex vivo studies, one study indicated that cyclic reference point indentation tests conducted on cortical

specimens acquired from the femoral neck of patients undergoing total hip replacement had higher indentation distances in T2D bone than in non-T2D, suggesting deteriorated mechanical behavior [17•]. This same study reported no significant differences in compressive mechanical properties in T2D cancellous bone specimens acquired from the femoral neck [17•]. However, the other more recent study showed that compression tests conducted on male trabecular bone samples from the femoral neck and head resulted in higher elastic modulus, yield stress, and ultimate stress in those with T2D compared to non-diabetics [18•]. Among the two in vivo studies, one study utilized in vivo impact-based reference point indentation and reported that post-menopausal women with T2D have lower bone material strength index in the tibia than control counterparts, even when adjusted for BMI, age, hypertension, and presence of various diabetic complications [10•]. The other study used the same technique and similarly showed a reduction in bone material strength index in post-menopausal women with T2D, which was associated with T2D duration [19•]. These studies all indicate a general deterioration in bone mechanical properties in human diabetic bone. However, as these are the only reports of mechanical properties directly in T2D bone, more work needs to be done utilizing human bone from patients.

Pathogenesis of Skeletal Fragility in Diabetes

Alterations in Bone Microarchitecture

Bone microarchitecture, and more specifically trabecular bone microarchitecture, is one of the major determinants of bone strength. Understanding the effects of both trabecular and cortical bone microarchitecture on bone mechanical properties is important to understand their roles in affecting bone fragility particularly in cases where fracture risk is high and independent of changes in bone density. Bone microarchitecture parameters can be determined for whole animal bone from preclinical studies and ex vivo human cadaveric specimens using microcomputed tomography (microCT) while in vivo assessment can be done by high resolution peripheral quantitative computed tomography (HR-pQCT).

There are several recent pre-clinical studies on cortical bone in diabetes. A recent study using Zucker diabetic fatty rats showed no significant changes in cortical thickness, perimeter, or volumetric BMD, but indicated lower bone volume fraction (BV/TV) and higher cortical porosity in neck and shaft of femur, compared to Zucker Lean controls [24]. However, this study did not assess fracture risk or bone mechanical properties. Another study using hyperphagic Otsuka Long-Evans Tokushima Fatty (OLETF) rats showed greater cortical area and thickness in the femur compared to normoglycemic controls, but no differences in cortical porosity [25]. These OLETF rats also had increased trabecular spacing and decreased connectivity density compared to controls, which corresponded with decreased tensile strength and shear modulus of elasticity [25]. Also, in trabecular bone, one study indicated that University of California, Davis diabetic rats had significantly lower vertebral trabecular bone volume, lower trabecular thickness, and more rod-like trabeculae than control (lean) and obese Sprague-Dawley rats [16]. The study by Dirkes et al., mentioned previously, also assessed trabecular microarchitecture. Within the trabeculae, they found lower trabecular BV/TV, decreased trabecular number, and reduced connectivity density as well as increased trabecular separation in diabetic vs control rats. However, these changes in microarchitecture did not correspond to alterations in whole bone biomechanical properties, which were not different between groups in these rats [25]. Since various rat models were used in these studies, and each reported different parameters, it is difficult to draw a comprehensive conclusion about changes in cortical or trabecular bone microarchitecture based on preclinical studies.

A recent ex vivo study on human cadaveric specimens using microCT on the proximal femoral head showed no change in cortical porosity between T2D patients compared to non-diabetic controls [17•]. Another recent report using ex vivo human trabecular bone specimens reported greater trabecular BV/TV and mineral content in men with T2D compared to non-diabetics. However, this study did not report on any microarchitectural parameters other than BV/TV [18•].

There have been several studies focused on in vivo assessment of cortical and trabecular microarchitecture using HR-pQCT, which has given some insight on bone microarchitecture within patients. However, it should be noted that these data are restricted to peripheral sites only and do not provide measurements in axial regions such as the hip and spine, which are both common fracture sites for fragility fractures in T2D patients. Previous studies using HR-pQCT in diabetics lacked data from type 2 diabetic men, but more recent studies have now included these results. One study found that cortical pore volume is higher in women at the radius compared to men, whereas both cortical porosity and pore volume were higher in men than in women when measured at the tibia [26]. However, the sample size for diabetics was small ($n = 29$ diabetic vs $n = 303$ non-diabetic); duration of diabetes was unknown; the study was unable to distinguish whether participants had type 1 or T2D; and fracture, fracture risk, or BMD T-score was not assessed [26]. In contrast, the Framingham study was conducted on a much larger cohort of men and women ($n = 129$ T2D, $n = 940$ non-diabetic) and recorded patient's history of fracture. This study reported a reduction in cross-sectional area of cortices and cortical BMD, but higher cortical porosity in the peripheral tibia in T2D patients with prior fracture compared to non-diabetics, as well as with increasing duration of diabetes ($\leq$ 5 years, 6–10 years and $\geq$ 10 years). This study reported that there were no differences in

trabecular microarchitecture between groups except for an increase in tibial Tb.N with increasing duration of diabetes [27]. Another study in men and women with T2D ($n = 98$) reported that HbA1c ($\geq$ 7%) was associated with lower cortical BMD, cortical thickness, trabecular separation, and higher cortical porosity at the distal radius, and with lower trabecular thickness and higher trabecular number in the tibia. Further, diabetes duration ($\geq$ 5 years) was significantly associated with higher trabecular number in the radius but not in the tibia [28]. However, differences in microarchitecture due to presence of T2D were not associated with strength at the radius or tibia as assessed by micro-finite element analyses [28].

Overall, findings from pre-clinical studies do not provide any comprehensive conclusion regarding the effect of cortical or trabecular microarchitecture on bone's mechanical properties. Similarly, studies with in vivo measurements in humans also do not have enough information to draw conclusions on the effect of cortical or trabecular microarchitecture on fracture risk at relevant fracture sites. Future studies should focus on gathering more data from ex vivo human specimens as well as in vivo assessment of microarchitecture parameters from both cortical and trabecular bone with adjustments for age, sex, height, ethnicity/race, and location of assessment.

Alterations in Bone Matrix

Bone matrix is a composite material that includes the mineral phase (providing bone with its inherent stiffness) and the organic phase composed primarily of type I collagen (proving bone with its tensile strength, ductility, and toughness). Mineralized collagen fibrils are composed of collagen molecules that are connected to each other through chemical crosslinking by specific enzymes, such as lysine hydroxylase that catalyzes hydroxylation of lysine and lysyl oxidase that catalyzes the crosslinks [29]. These enzymatic crosslinks contribute to improvements in tissue strength. In contrast, non-enzymatic glycation leading to the production of advanced glycation end products (AGEs) within the organic matrix is harmful, as it can lead to a deterioration in bone's overall mechanical properties. AGEs form from a spontaneous biochemical reaction between amino acid residues in the organic matrix and extracellular sugars [30, 31]. This accumulation can stiffen the organic matrix and in turn increase formation of microdamage and deteriorate bone's mechanical integrity [32–34]. A number of AGEs have been identified in bone including pentosidine, carboxymethyllysine, carboxyethyllines, and vesperlysines [35]. Pentosidine is the primary AGE measured in bone, but composes a small percentage of total AGEs and therefore may not be the best indicator of AGEs [36]. Given that the mineral component of bone's matrix (i.e., BMD) is normal or high in T2D, impaired enzymatic cross-linking and/or an increase in non-enzymatic cross-links in the organic matrix may be potential important factors contributing to skeletal fragility in T2D [37–39].

Recently, there have been a few pre-clinical studies on crosslinks and their correlation with various biomechanical properties in diabetic bone. A study conducted on Tallyho mice that exhibit early onset of T2D reported that AGEs were higher in femoral cortical bone than in femurs from control counterparts. This increase in AGEs was associated with higher maximum load and lower post-yield deformation [40]. A study by Poundarik et al. reported that non-enzymatic glycation disrupts bone matrix quality in a diabetic mouse model by impairing collagen's ability to dissipate energy [41]. Hunt et al. compared collagen crosslinking in KK-Ay mice with overt T2D to control littermates and found that T2D mice had increased collagen maturity (as characterized by higher mature enzymatic crosslinks compared to immature crosslinks as well as a greater mineral:matrix ratio) and mineral content, but no increase in pentosidine (an AGE) concentration [42]. It is important to note that rodent models of diabetes have many limitations including having low bone mass or incurring diabetes onset earlier than would be observed in adult humans [43].

To investigate AGEs in human bone, they can be induced in vitro by incubating cadaveric bone specimens at physiologic temperature and pH in a solution composed of Hank's buffer, protease inhibitors, and ribose sugar. Several in vitro studies utilizing incubations in ribose sugar solutions to mimic diabetic conditions suggest that ribose-incubated bone specimens (with higher AGEs) have stiffer collagen and deteriorated stiffness and post-yield mechanical properties compared to vehicle-incubated specimens [41, 44–48] while other studies indicate that bone toughness and AGEs are not related to each other [20, 49, 50]. Further, it is difficult to extrapolate the clinical significance of in vitro studies on bone AGEs. More recent studies have instead focused on assessing crosslinks directly in diabetic bone. A recent study on human bone illustrated that diabetic cortical bone had increased AGEs compared to non-diabetics, and corresponding deteriorations in cyclic reference point indentation properties [17•]. However, this study also indicated that there were no differences in AGE content nor mechanical properties in diabetic trabecular bone compared to non-diabetics [17•]. A study by Willet et al. reported no difference in pentosidine between diabetic and non-diabetic human cortical bone, but the figure in which this data is illustrated suggests that only five diabetic bones were used [51]. However, they report based on measurements from a large group of bone specimens (including those of various ages and those with osteoporosis, cancer, etc.) that pentosidine was not correlated with collagen connectivity, and thus, other components of the organic matrix may have more of an impact on the degradation of bone quality than markers such as pentosidine. Pentosidine indeed composes only a small component of total AGEs and is very poorly correlated with total AGEs [36]. A recent study conducted on men with T2D indicated that cancellous bone from the femoral neck had greater

mineral content and increased pentosidine compared to non-diabetics. The increased pentosidine was associated with decreased post-yield strain and toughness, suggesting that AGEs can increase bone fragility in men with T2D [18•]. Although some studies indicate that AGEs can negatively impact bone matrix quality, there are other non-enzymatic crosslinks that should be evaluated to understand the impact of AGEs on bone, and more importantly in diabetic bone.

Alterations in Cellular Metabolism

The hyperglycemic and inflammatory environments associated with T2D impact osteoblasts, osteoclasts, and osteocytes. Such alterations to cellular metabolism may help explain the compromised bone microarchitecture and diminished bone strength in T2D. Numerous studies indicate that the bone formation markers P1NP and CTX as well as the bone resorption markers RANKL and TRAP5b are lower in T2D, indicating overall lower bone turnover in diabetic bone [52–55].

Osteocytes are the most abundant cells embedded in the bone matrix that orchestrate the bone turnover process. A recent study using a mouse model suggests that high fat-fed diabetic mice have increased osteocyte size and volume, altered topology of the dendritic processes, and an increase in serum sclerostin levels compared to lean controls [56]. Another study on ZDF rats vs lean controls showed that T2D in ZDF rats detrimentally affected trabecular and cortical geometry, which was attributed to low bone formation and high bone resorption [57]. Osteocytes sense mechanical strains through fluid flow shear stress and changes in interstitial hydrostatic pressure. Decreased mechanical strains also induce osteocyte apoptosis, leading to altered remodeling and consequent mechanical behavior [58]. A metabolomics study showed that high glucose inhibits the secretion of citric acid by mechanically stimulated osteocytes. As citrate is essential for calcium binding and hydroxyapatite crystal thickening, the effect of high sugar as in diabetes may affect bone's mechanical behavior via alterations in matrix quality [59]. However, whether these changes similarly occur in human osteocytes remains to be elucidated.

T2D is also associated with an increase in pro-inflammatory cytokines. A recent study conducted in vitro in human osteoblast MG-63 cells indicated an increase in pro-inflammatory cytokines, which was related to a decrease in osteoblast viability and increased apoptosis in presence of high glucose [60]. This result was similarly observed directly in T2D patients with prior fractures compared to non-diabetics and T2D patients without fractures, in which they had increases in various pro-inflammatory cytokines such as IL-1β, IL-6, high-sensitivity C-reactive protein (hsCRP), and TNF-α [60]. Another study similarly showed that cytokine-treated MG-63 cells in presence of high glucose had reduced expression of osteoblast differentiation markers such as ALP, RUNX2, OCN, and OPN, and this result was also detected directly in T2D patients who had an increase in pro-inflammatory cytokines [61]. Impaired osteoblast function is also associated with interactions of AGEs with the receptor for AGEs (RAGE) [62]. RAGE is present in two forms, membrane bound and soluble form (sRAGE). sRAGE can act as an antagonist for molecules interacting with RAGE, thus inhibiting any AGE-RAGE-mediated abnormalities in cells. A recent ex vivo study on T2D patients and age-matched controls showed that serum pentosidine and sRAGE levels in both groups were similar but there was a significant decrease in the potential of peripheral blood mononuclear cells to differentiate towards osteoblasts with only 7.4% of cells showing osteoblast markers in patients with T2D, compared to 86.7% of cells in controls. Impaired osteogenic differentiation was also associated with changes in expression of the RAGE gene (AGER), which had higher gene expression in T2D vs controls (+ 81.8% in T2D vs + 7.7% in controls) [63]. Another study showed that AGEs regulate osteoblast development by activating the Raf/MEK/ERK pathway through interaction with RAGE and induce autophagy, a process that is important for proliferation and function of osteoblasts [64].

Compared to osteoblasts, fewer studies have investigated the effects of hyperglycemia and/or T2D on osteoclasts. A recent ex vivo study on 42 postmenopausal women (21 with T2D and 21 non-T2D) showed a significant increase in osteoclast precursors and reduction in osteoblast precursors in T2D patients vs controls. P1NP (bone formation marker) and TRAP5b (bone resorption marker) levels were significantly decreased in T2D, whereas a negative regulator of bone formation (DKK-1) was increased [53]. Together, these may help explain the decrease in bone formation in T2D patients. An in vitro study showed that high glucose levels suppress RANKL-induced osteoclastogenesis by increasing the expression of a glucose sensor known as liver X receptor β (Lxrβ), but the pathway underlying how Lxrβ suppresses osteoclastogeneis is not known [53]. A similar study showed that high glucose decreases gene expression of Atp6V0d2 and DC-STAMP, which are key players in RANKL-induced osteoclast differentiation, indicating inhibition of RANKL-mediated osteoclastogenesis [65].

Thus, T2D leads to altered bone cell function and matrix repair. Specifically, it can result in altered osteocyte network and osteocytic mechanical responses, increased osteoblast apoptosis and diminished osteoblast differentiation, and decreased osteoclast differentiation.

Effect of Anti-diabetic Drugs on Bone Fracture

Common anti-diabetic drugs include those that increase insulin secretion, insulin-sensitizing drugs, and exogenous insulin. In the case of total insulin deficiency as in type 1 diabetes, the

primary drug utilized is insulin. Insulin generally has an anabolic effect on the bone remodeling process by stimulation of osteoblast proliferation and differentiation [66–68], but insulin treatment of T2D patients results in increased fracture risk [4, 69, 70]. However, it has been suggested that the occurrence of hypoglycemia and subsequent falling are increased in patients treated with insulin, which may have a major effect on the increased fracture risks observed. There are not many randomized controlled trials investigating the effect of insulin in T2D patients and therefore is somewhat difficult to draw any conclusions.

In the case of relative insulin deficiency as in T2D, there are more drug targets available for disease management. Although these treatments have many beneficial results in maintaining overall health, certain side effects may result including deteriorated bone health. The first target drug of choice is typically metformin, a biguanide, which increases insulin sensitivity in T2D. This drug has been shown through in vitro and in vivo studies to promote osteogenesis, which may contribute to increased bone mineral density typically observed in T2D patients [71]. Specifically, metformin promotes differentiation of osteoblasts and leads to an overall improved effect on bone function [72], but adversely affects differentiation of osteoclasts by decreasing RANKL [73]. A few studies indicated that metformin may reduce fracture risk [4, 69], while other studies report that it has no effect on fracture risk [74, 75].

Thiazolidinediones (TZDs) (e.g., pioglitazone, rosiglitazone) can increase the body's sensitivity to insulin [76]. However, there is strong evidence that TZDs have major detrimental side effects including harmful effects on skeletal health. Specifically, use of TZDs impairs function of osteoblasts and promotes osteoclastogenesis [72]. Studies conducted in large patient cohorts have reported the use of TZDs result in bone loss and increased fracture risk in women but not in men [70, 76–80]. Unrelated to bone health, TZDs have the risk of increasing harmful cardiovascular events and therefore are no longer commonly prescribed [81] despite its effectiveness in increasing insulin sensitivity.

Recently new incretin-based drugs such as glucagon-like peptide 1 receptor (GLP-1) agonist, dipeptidyl peptidase-4 (DDP-4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors encourage insulin production. GLP-1 agonist has been shown to improve trabecular bone mass and microarchitecture studies using ovariectomized mice [82–84]. Although there is a report that some GLP-1 agonists reduce bone fracture risk [85], the overwhelming majority of clinical trial data indicate that GLP-1 agonist has no effect on bone fracture risk in adults [86–92]. Studies suggest that DPP-4 inhibitors, which inhibit osteoclastogenesis [93], may decrease fracture risk in T2D patients [94–96]. SGLT2 inhibitors are a newer drug that is effective for glycemic control [97] but can have indirect detrimental effects on bone. Specifically, they stimulate secretion of parathyroid hormone, which influences osteocyte behavior and in turn affects the bone remodeling process. Consequently, SGLT2 inhibitors can adversely affect bone mass and increase fracture risk [97–100]. However, several studies indicate that SGLT2 inhibitors have no effect on fracture risk [101–103].

Sulfonylureas is another class of drugs. Although this drug has been used in patients for more than 50 years, there is barely any clinical data on how it affects bone quality and health, but it has been suggested to decrease bone fracture risk compared to potent drugs such as TZDs [72].

Conclusions

Overall, our literature review indicates several important points regarding the effect of type 2 diabetes (T2D) on bone biomechanics, but there are still some major gaps in the knowledge base regarding this topic. The presence of T2D can deleteriously affect bone biomechanical properties that lead to increased skeletal fragility as shown through pre-clinical models and some recent studies on human diabetic bone, but there are very little data on biomechanical properties of bone directly from T2D patients. T2D affects bone microarchitecture independent of BMD as reported by several ex vivo and in vivo studies. However, there needs to be some clarification by adjusting collected data for potential confounding variables such as sex, height, and location of assessment, which current studies lack. Advanced glycation end-products (AGEs) in the bone matrix impact the overall quality of bone tissue that may contribute to deteriorated bone mechanical properties in T2D. However, the means through which AGEs deteriorate bone mechanical properties is not well understood, and therefore additional studies are needed to identify these intermediate mechanisms. Furthermore, there should be investigation of AGEs other than the commonly measured pentosidine to understand which of these AGEs may have the most deleterious effects on bone. Hyperglycemia characteristic of T2D affects the behavior of major bone cells, which in turn can impact the overall quality of the bone tissue and ultimately affect bone mechanical properties, but we need to better understand how alterations in cell behavior directly contribute towards degraded bone microarchitecture and/or bone biomechanics. Lastly, several anti-diabetic drugs exist that focus on altering bone cell behavior, but some of these drugs have contradicting or no information on how they affect bone mechanical properties and/or fracture risk. A better understanding of molecular and cellular mechanisms as mentioned above has the potential to improve existing drug targets or develop new ones. Furthermore, filling the gaps in knowledge regarding those mechanisms may lead to better diagnostic methods to identify T2D patients at risk for bone fracture.

Acknowledgements Dr. Karim was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award number K01AR069685 and by the American Society for Bone and Mineral Research Rising Star Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Compliance with Ethical Standards

Conflict of Interest Lamya Karim, Taraneh Rezaee, and Rachana Vaidya declare no conflict 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. All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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