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REVIEW

Impact of diabetes and its treatments on skeletal diseases

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Abstract **Diabetes mellitus is an enormous menace to public health globally. This chronic disease of metabolism will adversely affect the skeleton if not controlled. Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are associated with an increased risk of osteoporosis and fragility fractures. Bone mineral density is reduced in T1DM, whereas patients with T2DM have normal or slightly higher bone density, suggesting impaired bone quality is involved. Detrimental effects of T1DM on the skeleton are more severe than T2DM, probably because of the lack of osteo-anabolic effects of insulin and other pancreatic hormones. In both T1DM and T2DM, low bone quality could be caused by various means, including but not limited to hyperglycemia, accumulation of advanced glycosylation end products (AGEs), decreased serum levels of osteocalcin and parathyroid hormone. Risk for osteoarthritis is also elevated in diabetic population. How diabetes accelerates the deterioration of cartilage remains largely unknown. Hyperglycemia and glucose derived AGEs could contribute to the development of osteoarthritis. Moreover, it is recognized that oral antidiabetic medicines affect bone metabolism and turnover as well. Insulin is shown to have anabolic effects on bone and hyperinsulinemia may help to explain the slightly higher bone density in patients with T2DM. Thiazolidinediones can promote bone loss and osteoporotic fractures by suppressing osteoblastogenesis and enhancing osteoclastogenesis. Metformin favors bone formation by stimulating osteoblast differentiation and protecting them against diabetic conditions such as hyperglycemia. Better knowledge of how diabetic conditions and its treatments influence skeletal tissues is in great need in view of the growing and aging population of patients with diabetes mellitus.**

Keywords diabetes; bone; osteoporosis; osteoarthritis

Introduction of diabetes

Diabetes mellitus (DM) is a group of chronic diseases characterized by high blood glucose levels. It is estimated that more than 347 million people worldwide currently have diabetes [1] and many more people are estimated to become diabetic soon. This emerging global epidemic of diabetes is in large part due to rapid increases in obesity and lack of physical activity. The burden of diabetes is skyrocketing globally, particularly in developing countries. It is estimated that 80% of diabetes-caused deaths occur in low- and middle-income countries. Diabetes results from defects in the body's ability to produce and/or use insulin efficiently. There are mainly three types of diabetes. Type 1 diabetes mellitus (T1DM) is characterized by the lack or insufficient production of insulin by the pancreas and requires daily administration of insulin. Type 2 diabetes mellitus (T2DM) is characterized by the body's inability to use insulin efficiently and T2DM comprises 90% of diabetic population around the world. Besides life style management, the treatment of T2DM includes oral medications and insulin administration as well. The third type of diabetes is gestational diabetes which affects women during pregnancy. Overtime, diabetic condition will cause serious complications, namely severe damages in tissue like the heart, blood vessels, eyes, kidneys, and nerves. It has also been increasingly recognized that diabetes adversely affects bone health. In this review, the authors will briefly discuss the impact of diabetes and its pharmacological treatments on skeletal tissues.

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Diabetes and osteoporotic fracture

Bone is highly dynamic tissue that undergoes constant

remodeling. Both quantity and quality of the bone are maintained by mainly three cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts are bone-forming cells responsible for new bone creation, which are differentiated from mesenchymal progenitor cells [2–4]. Osteoclasts are bone-resorbing cells responsible for old bone removal, which are differentiated from hematopoietic progenitor cells [2–4]. Osteocytes, the most abundant cells in the bone matrix, have also been found to contribute to bone remodeling through regulation of both osteoblast and osteoclast activity [5–7]. The balance between bone resorption by osteoclasts and bone formation by osteoblasts is critical for skeletal homeostasis and osteoporosis occurs when old bone removal outpaces new bone formation [2–4]. The bone loss during osteoporosis will cause the bone to become brittle and fragile. Globally, osteoporotic fractures are a leading cause of morbidity and an enormous medical and economic burden, especially in developed countries [8]. Enhanced understanding of bone biology and risk factors for osteoporosis are of great clinical significance.

The wide spread chronic disorder of DM adversely affects multiple organ systems including bones. One of the serious skeletal complications in bones is osteoporotic fractures due to weakened bone strength. Both T1DM and T2DM patients have a higher risk of sustaining osteoporotic fractures compared to non-diabetic subjects [9–12] and fracture risk in patients with T1DM is more severe than that in patients with T2DM [13]. Bone strength is determined by a composite of both bone mass and bone quality. As a measurement of bone mass, bone mineral density (BMD) is affected differently by T1DM and T2DM. Majority of the available data suggest that patients with T1DM display lower BMD and this is attributed to reduced bone formation during skeletal growth in children and adolescents [14,15]. By contrast, based on two meta-analyses, adults with T2DM have normal or slightly higher BMD values in spite of increased fracture risk [12,16], suggesting that patients with T2DM might have poor bone quality that is not reflected by BMD measurements. Although significant advance has been made in assessment of bone quality using combination of non-invasive imaging techniques, mechanical property testing, and compositional measurements [17], reliable and sensitive biomarkers of bone quality for early detection of skeletal diseases are lacking. In patients with advanced diabetes mellitus, the propensity for falls is increased as a result of neuropathy, particularly impaired vision [18–22] and this also increases the risk for osteoporotic fractures in diabetic population which already presents compromised bone mass and/or bone quality [18–22].

The mechanisms underlying the low bone strength in patients with advanced DM are not fully understood. The distinct reduction of peak bone mass in young patients with T1DM, even shortly after the onset of diabetes mellitus, has led to the hypothesis that insulin has anabolic effects on bones [14,15,23]. Impaired bone formation has been proposed as a major contributing factor for the low accrual of peak bone mass observed in T1DM patients. Support for osteo-anabolic effects of insulin comes from animal studies and clinical data and will be discussed in better detail later in the review. Hyperinsulinemia observed in T2DM patients may contribute to the high BMD values. However, since insulin resistance is a key feature of T2DM, hyperinsulinemia may encounter low insulin sensitivity in bone cells. Therefore, differences in skeletal effects between T1DM and T2DM cannot be fully explained by the "insulinopenia" hypothesis [14,15]. As reviewed by Hamann *et al.*, in addition to insulin, pancreatic β cells fail to produce other osteo-anabolic factors, such as islet amyloid polypeptide (also known as amylin) and preptin in T1DM patients [15]. Lack of production of these peptides likely contributes to low bone formation in T1DM patients as well [15].

As mentioned previously, while having an increased risk of bone fragility, patients with T2DM present no reduction in BMD than non-diabetic individuals, suggesting that compromised bone quality is involved. Several factors have been suggested to affect bone quality under diabetic conditions (Fig. 1). For both T1DM and T2DM, higher than normal blood glucose level (hyperglycemia) is the main characteristic of the disease and hyperglycemia may have multiple adverse effects on bone metabolism in patients with poorly controlled T1DM and T2DM. Accumulating evidence suggests that mesenchymal stem cells (MSCs) are affected adversely by hyperglycemia and compromised MSCs differentiation and function may result in low bone turnover and formation. In cultured human bone marrow-derived MSCs, high concentrations of glucose inhibited osteoblast differentiation while increased MSC-derived adipocytes [24]. Moreover, hyperglycemic condition caused reduced growth and altered the differentiation potential to favor the adipocyte lineage in human MSCs [25]. Also, MSCs isolated from diabetic rats lost their capability to react to fibrin matrices [26]. Hyperglycemia may exert its detrimental effects on bone cells by increasing oxidative stress which is a key component in etiology of diabetic complications [27–29]. In estrogen deficient mice, oxidative stress increased production of TNFα which contributes to bone loss [30]. As thoroughly reviewed by Manolagas [31], reactive oxygen species (ROS) has significant impact on generation and survival of bone cells. For example, it is documented that ROS not only attenuates osteoblastogenesis and but also stimulates apoptosis in osteoblasts [31]. Hyperglycemia also leads to elevated levels of advanced glycation end products (AGE) such as pentosidine. In bones isolated from diabetic rats, increase in pentosidine content coincided with impaired bone mechanical properties despite no reduction in BMD values, suggesting that overglycosylation due to hyperglycemia may contribute to reduced bone quality [32]. In human osteoblasts, pentosidine caused a significant reduction in bone turnover markers and hampered the formation of bone nodules indicating compromised functionality of osteoblasts [33]. In

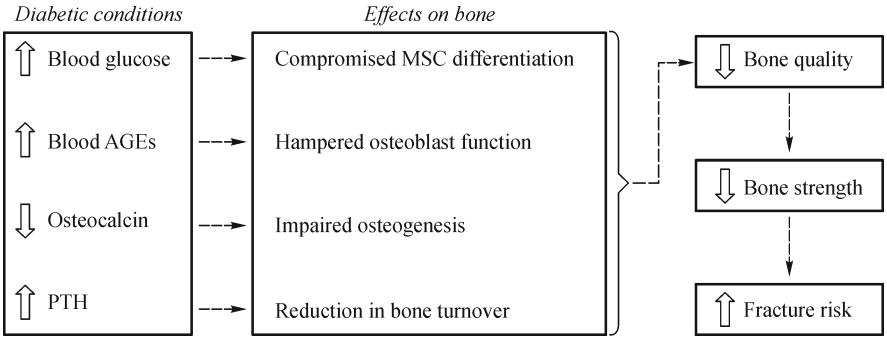

Fig. 1 Possible mechanisms through which diabetic conditions increase the risk of osteoporotic fractures. Diabetic conditions common among both T1DM and T2DM patients can exert detrimental effects on skeletal tissue which will compromise bone quality. The impaired bone quality will reduce bone strength and therefore increase osteoporotic fracture risk. In addition to the above depicted factors, the lack of insulin and other bone anabolic hormones from the pancreas also contribute to impaired osteogenesis and decreased bone mass observed in T1DM patients. AGEs, advanced glycosylation end products; PTH, parathyroid hormone; MSC, mesenchymal stem cell; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

a study with functioning older men and women, higher pentosidine levels in urine was found to be a risk factor for fractures in adults with T2DM and may account in part for the lowered bone strength [34]. These results strongly support the concept that detrimental effects of DM are mediated, at least in part by AGE.

As a hormone secreted specifically by osteoblast, osteocalcin has been implicated to serve as a functional link between bone metabolism and glucose homeostasis [35–39]. Activation of insulin receptor in osteoblast induces osteocalcin production which in turn increases β-cell proliferation, insulin secretion, insulin sensitivity, and energy expenditure [39,40]. Revealed by mouse genetics model, osteocalcin also targets testes to regulate male fertility and testosterone production in Leydig cells [38,41]. The secreted testosterone has been long known to regulate bone mass accrual and bone remodeling [38,41]. In a recent review by Hamann *et al.*, a model for possible mechanisms for impaired bone formation in T1DM was presented with osteocalcin as a center piece [15]. In this model of vicious cycle, destruction of pancreatic β cells in patients with T1DM prevents secretion of insulin and other osteo-anabolic factors. The lack of insulin and other pancreatic hormones decreases proliferation and differentiation of MSCs into osteoblasts. Less osteoblasts will compromise bone formation. Moreover, reduced insulin secretion in patients with T1DM prevents stimulation of osteoblasts to produce sufficient osteocalcin. In turn, low osteocalcin levels will aggravate the shortage of insulin. Similarly, osteocalcin acts on the testes to stimulate production of testosterone, an osteogenic factor. The reduced osteocalcin activity will lower circulating testosterone level which may contribute to increased fracture risk. Accumulating evidence also suggests that osteocalcin may also contribute to compromised bone formation in patients with T2PM. In postmenopausal women, reduced serum osteocalcin concentrations were associated with elevated blood glucose, increased waist circumference, and presence of T2DM [42]. In another study, serum undercarboxylated osteocalcin level was inversely associated with plasma glucose level and fat mass in men with T2DM [43]. Determined by a continuous glucose monitoring in patients with T2DM, serum osteocalcin levels were also negatively correlated with fasting plasma glucose, HbA1c, and 24 h mean blood glucose [44]. Moreover, in a study to examine risk factors of vertebral fractures in 248 Japanese men with T2DM, serum osteocalcin/bone-specific alkaline phosphatase ratio was inversely associated with presence of vertebral fractures, suggesting that reduction in OC/BAP ratio is a predictor of vertebral fracture risk in men with T2DM [45]. Taken together, the above data strongly suggest that osteocalcin has promising potential to serve as a biomarker and even therapeutic target for osteoporotic fractures in patients with both T1DM and T2DM.

Another factor worth mentioning is parathyroid hormone (PTH). Bone turnover, which is a major component of bone quality [46], is dynamically regulated by PTH. In postmenopausal women, oral glucose load induced hyperglycemia and significantly reduced serum PTH levels [47]. Also, impaired PTH secretion was found to be responsible for the low bone turnover in hemodialyzed patients with T2DM [48] and increased incidence of vertebral fractures were reported in hemodialysis patients with T2DM [49]. In a prospective study in Austria, reduced PTH levels and hyperglycemia were shown to independently contribute to lower bone turnover in elderly nursing home patients with T2DM [50]. Furthermore, in adynamic bone from individuals with DM, expression level of PTH/PTH-related protein receptor was less than 1/3 of normal bone [51]. This may help to explain why female rats with uncontrolled T1DM failed to respond to intermittent PTH treatment [52]. These findings suggest that not only impaired PTH secretion but also reduced sensitivity to PTH stimulation in osteoblasts may contribute to low bone

turnover under diabetic conditions. More research is needed to ascertain the pathophysiology of lowered PTH secretion under diabetic conditions.

Taken together, the detrimental effects of diabetic condition compromise bone strength and enhance risk for bone fractures. Increased understanding of osteoporotic fractures under diabetic condition is in great need in view of the growing and aging population of patients with DM.

Diabetes and osteoarthritis

Osteoarthritis (OA) occurs when the cartilage at the joints deteriorates over time and is the leading cause of disability among adults in the United States. More than 10% of the US adult population suffered from clinical OA in 2005 and OA was the fourth most common cause of hospitalization in 2009 [53]. Several epidemiological and experimental data suggest that diabetes could be an important risk factor for OA [54]. Based on data from 2008 to 2010 US National Health Interview Survey, among adults with diagnosed DM, 48.1% (9.6 million) also have arthritis and the prevalence ratio of arthritis among arthritic adults with versus without diabetes (95% CI) was: 1.44 (1.35–1.52) [55]. How diabetic condition accelerates the deterioration of cartilage during OA development remains largely unknown. There is accumulating evidence suggesting that the higher than normal level of blood glucose and glucose derived AGE could contribute to damage of cartilage tissues (Fig. 2). In streptozotocin-induced diabetic mice model, diabetic conditions increased chondrocyte apoptosis and osteoclastogenesis that accelerate the loss of cartilage [56]. Regain of normal glycemic control by insulin treatment reversed these effects [56]. In cultured normal and OA human chondrocytes, exposure to high glucose mobilized the chondrocyte catabolic program which may promote articular cartilage degradation and facilitate OA development and/or progression [57]. Moreover, in a longitudinal cohort study, even increased fasting serum glucose concentration below the arbitrary "diabetic range" of serum glucose levels was associated with adverse structural changes at the knee in women [58]. In cultured human articular cartilage, increased AGE levels resulted in increased stiffness of the collagen network and this increased stiffness may compromise the ability of human articular cartilage to resist damage [59]. Elevated AGE levels also reduced the maintenance and repair capacity of human articular cartilage and may contribute to the development of OA [60]. In a canine model of experimental OA, enhanced cartilage AGE levels by ribose injections led to increased OA severity as measured by increased collagen damage and enhanced release of proteoglycans [61]. Activation of receptor for AGE in human articular chondrocytes stimulated production of MMP-13 which contributes to the cartilage degradation and joint damage [62]. In addition, in human OA chondrocytes, AGE treatment also stimulated expression of matrix metalloproteinase-1, -3, and -13, and TNF-α [63], augmented inflammatory responses by increasing PGE2 and NO levels [64], and induced expression of interleukin-6 and interleukin-8 [65]. In summary, more research is needed to ascertain the mechanisms through which diabetic condition exerts its detrimental effects on development and progression of OA in order to develop better therapeutic interventions. There is also great interest in studying the relationship between diabetic condition and rheumatoid arthritis. Since rheumatoid arthritis affects the lining of the joints but not bone tissue at the beginning stage of the disease, it is beyond the scope of this review.

Impact of diabetic treatments on bone

Insulin

Insulin treatment is the primary means of blood glucose management in patients with T1DM. Some type 2 diabetic patients receive insulin administration as well. The distinct osteopenia and osteoporosis observed in type 1 diabetic patients has led to the hypothesis that insulin serves as a bone anabolic factor [23]. Much evidence obtained from animal models supports for a direct bone anabolic effect of insulin with most convincing data coming from "loss of function" analysis of vital insulin signaling components. Insulin receptor substrates (IRS) are essential for insulin/IGF-1 receptor signaling. Mice lacking the *IRS-1* gene showed severe osteopenia with reductions in osteoblast and osteoclast number and function, resulting in decreased bone turnover [66]. In mice lacking *IRS-2* gene, osteopenia with decreased bone formation and increased bone resorption was exhibited indicating that IRS-2 is essential to maintain predominance of bone formation over bone resorption [67]. Moreover,

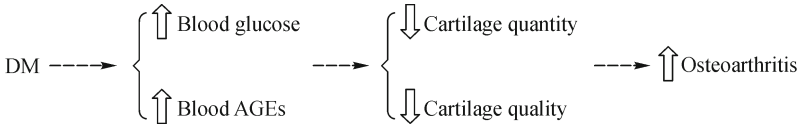

Fig. 2 Diabetic conditions increase the risk of osteoarthritis. Diabetic conditions such as elevated blood glucose and blood AGEs levels have been suggested to compromise not only the quantity but also the quality of the cartilage tissues. This will increase the risk of developing osteoarthritis. DM, diabetes mellitus; AGEs, advanced glycosylation end products.

disruption of Akt1, a major downstream target of IRS in mouse bone cells led to low-turnover osteopenia caused by dysfunctions of osteoblasts and osteoclasts, supporting that Akt1 plays a crucial role in promoting the differentiation and survival of osteoblasts and osteoclasts to maintain bone mass and turnover [68]. Human data support the concept that insulinopenia in T1DM may impair osteoblast function. A large study conducted in a group of children and young adults with T1DM showed that biochemical markers of bone formation and bone turnover such as procollagen type I propeptides, alkaline phosphatase, osteocalcin were lower in diabetic patients when compared to healthy controls [69]. Moreover, consistent with the insulinopenia hypothesis are the positive skeletal effects of intensive insulin therapy on bone metabolism over the course of 7 years [70]. In this study, 62 patients with T1DM and low BMD were started on intensive insulin therapy and followed for 7 years. Insulin treatment was associated with the stabilization of BMD at all sites, as well as a significant decrease in bone resorption determined by serum activity of tartrate-resistant acid phosphatase [70]. Available data suggest that insulin has anabolic effects on bone and plays an important role in regulating bone metabolism and turnover. Insulin treatment in diabetic patients could help to prevent the development and progression of osteopenia/osteoporosis. Also, given the anabolic effects of insulin on bone, hyperinsulinemia observed in some patients with T2DM may contribute to the higher BMD observed than non-diabetic individuals.

Thiazolidinediones

Thiazolidinediones (TZDs) such as troglitazone, rosiglitazone, pioglitazone, and netoglitazone are synthetic peroxisome proliferator-activated receptor γ (PPARγ) agonists and have proved to be effective to enhance insulin sensitivity in treatment of T2DM [71–74]. However, increasing data from both animal studies and clinical analysis indicate that treatment of TZDs is associated with a higher osteo-fracture risk. Mice treated with TZDs *in vivo* showed decreased bone mineral content, bone formation, and trabecular bone volume [75–77]. A four-year follow-up data in older adults with T2DM indicated that TZDs treatment is associated with greater bone loss in female diabetic patients [78]. Moreover, in A Diabetes Outcome Progression Trial, four years of rosiglitazone treatment significantly increased the incidence of fractures in both pre- and post-menopausal women with T2DM [79]. In a retrospective cohort study, TZDs were associated with an increased risk of fracture in diabetic women, particularly at ages above 65 years [80]. Even in healthy postmenopausal women, a short-term treatment (14 weeks) of rosiglitazone exerted detrimental effects on bone formation and decreased bone density [81]. The detrimental effect of TZDs on bones in male diabetic patients is less conclusive and is only reported in isolated study [82]. As agonist of PPARγ, TZDs exert detrimental effects on bone through PPARγ-activated signaling pathways. The most convincing evidence of the function of PPARγ comes from analysis of transgenic mouse models. Homozygous PPARγ-deficient embryonic stem cells failed to differentiate into adipocytes, but spontaneously differentiated into osteoblasts. These defects were restored by reintroduction of the PPARγ gene [83]. Also, PPARγ insufficiency increased bone mass by stimulating osteoblastogenesis from bone marrow progenitors [83]. When overexpressed specifically in osteoblasts, PPARγ decreased bone formation and bone mineral density in male mice and accelerated estrogen-deficiency-related bone loss in female mice [84]. Moreover, when PPARγ was deleted in osteoclasts but not in osteoblasts, mice showed impaired osteoclast differentiation and developed osteopetrosis characterized by increased bone mass indicating that PPARγ-mediated signaling plays a key role in promoting osteoclast differentiation and bone resorption [85]. Consistently, activation of PPAR*γ* by TZDs inhibited osteoblast differentiation while promoted adipocyte differentiation [77,86,87] and activation of PPARγ by rosiglitazone enhanced osteoclast differentiation in a receptor-dependent manner [85]. Besides data obtained from cell and animal models, a recent clinical study in diabetic patients showed that markers of osteoblast activity and bone formation, PINP (procollagen type I N-propeptide) and bone alkaline phosphatase were decreased in both women and men treated with rosiglitazone and markers of osteoclast activity and bone resorption, CTX-I (C-terminal telopeptide for type I collagen) were increased by 6.1% in the rosiglitazone-treated women but not men [88]. Taken together, the above results suggest that suppressed bone formation (inhibited oesteoblastogenesis) and elevated bone resorption (enhanced osteoclastogenesis) are two important mechanisms through which TZDs contribute to bone loss and higher fracture risk in diabetic patients. However, other mechanisms may also mediate the effects of TZDs on skeletal tissue. For example, TZDs may negatively impact bone by promoting osteocyte apoptosis [89,90]. It is also suggested that TZDs may also function indirectly by activation of PPARγ in other tissue such as the hypothalamus-pituitary-gonad axis to regulate bone mass and quality indirectly [91].

Metformin

As an insulin sensitizer, patients with T2DM are frequently treated with oral anti-diabetic drug, metformin. In type 2 diabetic patients, metformin treatment has been associated with a decreased risk of bone fracture [92]. In rat marrow mesenchymal stem cells culture, metformin inhibited adipocyte differentiation and promoted osteoblast differentiation [93]. In primary culture of osteoblasts obtained from rat calvaria, metformin increased trabecular bone nodule formation [94]. Metformin was also shown to improve bone mass and quality compromised by bilateral ovariectomy in rats [95]. Both *in vitro* and *in vivo*, metformin administration increased alkaline phosphatase activity, type I collagen

Table 1 Effects of diabetic treatments on bones

Treatments	Effects on bone
Insulin (+)	Stabilization of BMD and decrease in bone resorption; Prevention of osteopenia/osteoporosis
Thiazolidinediones (–)	Suppressed bone formation (inhibited oesteoblastogenesis) Elevated bone resorption (enhanced osteoclastogenesis)
Metformin (+)	Elevated bone formation (enhanced oesteoblastogenesis) Suppressed bone resorption (inhibited osteoclastogenesis) Protection of osteoblasts against hyperglycemia

"+"symbol indicates a beneficial effect; "–" symbol indicates a detrimental effect.
BMD: bone mineral density.

synthesis, osteocalcin expression, and extracellular calcium deposition of bone marrow progenitor cells [96]. Furthermore, metformin stimulated bone lesion regeneration in control and diabetic rats [96]. The mechanisms of osteogenic effects of metformin have been investigated in various models. In human osteoblast-like Saos-2 cells, metformin suppressed Wnt/β-catenin signaling to favor cell differentiation [97]. Metformin also stimulated osteoblast differentiation through the transactivation of Runx2 in mouse calvaria-derived progenitor cells [98]. It is also suggested that metformin may regulate osteoblastic and adipogenic differentiation through inhibition of PPARγ [93]. Metformin displayed protective effects on osteoblasts against the deleterious effects of high glucose [99] and AGEs [100], although the mechanism remains unclear. In the case of osteoclast, metformin reduced receptor activator of nuclear factor-κB ligand and stimulated osteoprotegerin expression in osteoblasts, subsequently inhibited osteoclast differentiation and reduced osteoclast number to prevent bone loss [101,102]. Taken together, metformin has a beneficial role in bone formation/quality by stimulating osteoblast differentiation and protecting them against diabetic conditions such as hyperglycemia. However, most data mentioned above are derived from cellular or rodent models. More research in human subjects is warranted to validate its effect clinically.

In summary, the above mentioned pharmacological treatments for diabetic patients could have important effects on skeletal tissue (Table 1). This needs to be taken into consideration when selecting medicines for diabetic patients with high risk of skeletal complications. Also, research to investigate the impacts of other antidiabetic medicines and combination effects of multiple treatments on bones is lacking.

Conclusions

In this review, authors briefly summarize the impact of diabetic conditions and its treatments on the skeleton. Diabetes mellitus and skeletal diseases like osteoporotic fractures and osteoarthritis are two of the most important causes of mortality and morbidity in older individuals. The risk of both osteoporotic fractures and osteoarthritis is increased in diabetic patients. Although substantial progress has been made in the field, the mechanisms underlying the detrimental effects of diabetes are still not fully understood. Control and treatment of diabetic conditions are key elements in management of osteoporosis and osteoarthritis in patients with T1DM and T2DM. More research is needed in many areas. For example, the knowledge derived from cell cultures and animal models needs to be validated in humans. The contribution of osteocytes, the most abundant bone cells to skeletal health under diabetic conditions remains unknown. Also, reliable and sensitive biomarkers of bone quality for early detection of skeletal diseases are demanded clinically and a group of biomarkers are very likely required to ensure that the analysis is sufficiently sophisticated. As mentioned above, factors like osteocalcin could serve as one of them. Moreover, in the battle against skeletal diseases in diabetic patients, prevention is of great clinical significance. Clinical trials included cohorts of African, Indian, Polynesian, Hispanic, Arabian, and Chinese peoples documented that exercise improved insulin action in high-risk populations [103]. Although pharmacological interventions were also effective for reversing metabolic syndrome, life style management including exercise and diet seems to be the most efficacious strategy to prevent progression to metabolic diseases like T2DM [104,105]. It is also reported that certain exercise regimen is effective in improving BMD in populations with high-risk of osteoporosis [106,107]. Therefore, prevention plan which likely combines exercise, diet and pharmacological interventions in high-risk patients is very likely to yield beneficial outcomes and more research in this area is warranted.

Conflict of interest Authors declare no conflict of interest.

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