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 lifestyle 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.

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 preproinsulin 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