World Journal of Surgery and Surgical Research

Review Article
Published: 05 Nov, 2020

The Effects of Type 1 *vs*. Type 2 Diabetes on Bone Metabolism

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Abstract

There is an accumulation of evidence determining an increased risk of fracture in Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). T1D is associated with a low Bone Mineral Density (BMD) determining the decreased bone strength and quality. T2D, paradoxically, presents with a high BMD and increased fracture risk. This formulates the suggestion that both types of diabetes effect bone in their own distinct ways involving issues in underlying bone pathological mechanisms. A decreased Insulin-like Growth Factor-1 (IGF-1) in T1D causes a disparity between bone formation and resorption. T2D presents an increased Advanced Glycation End-Products (AGEs) leading to impaired crosslinking of type 1 collagen and weakening the structural composition of bone. The negative effect of bone by T1D and T2D cannot be defined by one simple mechanism, but by a combination of multiple biological factors. Future research needs to be conducted to discover the chief mechanisms of increased fractures in T1D and T2D, so that preventative measures can be taken to decrease the chance of osteoporotic fractures in diabetic patients.

Introduction

Diabetes Mellitus (DM) is a chronic disease that can lead to an increased risk of cardiovascular damage, renal complications, retinopathy, and neuropathy [1]. Diabetic patients have recently been shown to have altered bone morphology and are associated with increased fracture risk. Type 1 and type 2 diabetes have similar pathologies but exhibit differences in the way their bones respond to the disease.

There are approximately 463 million people living with diabetes worldwide and a projected 700 million will be affected by 2,045 with about 90% accounting for Type 2 Diabetes (T2D) [2]. BMD is the main test to determine osteoporosis and the chance of breaking bone. BMD measures the amount of calcium and other minerals in bone that increase bone strength. Growing research has predominantly shown that T2D presents with a higher BMD and Type 1 Diabetes (T1D) has a lower BMD compared to non-diabetic individuals [1,3-5].

With new research emerging on fracture risk and underlying pathophysiologic mechanisms of both T1D and T2D, it is appropriate to review how both types of diabetes mellitus react in their bone pathology. This perspective provides a concise summary of a comparison between T1D and T2D fracture healing mechanisms through existing evidence describing their bone pathophysiologic mechanisms.

T1D Mechanistic Effects on Bone

Evidence has supported that patients diagnosed with T1D have a lower BMD thus leading to an increased risk of fracture [1,6-8]. BMD has been one of the primary factors in discovering the increased fracture risk in T1D, but the cause is multifactorial and dispersed through several systems.

T1D typically develops at an early age and produces a dramatic change in bone strength and microarchitecture when there is a poor glycemic control and a long duration of disease [8]. Poor metabolic control may alter Growth Hormone (GH) and Insulin-like Growth Factor-1 (IGF-1) leading to alterations in bone size and density. IGF-1 is essential for osteoblast growth and bone mineralization, so with lower IGF-1/GH in T1D patients, it will cause a decrease in bone turnover and might explain the low BMD [8-11]. Some studies have shown impaired osteoblastic bone formation due to low Osteocalcin (OC) and Alkaline Phosphatase (ALP) accompanied with enhanced osteoclast activity (Figure 1) [4,8,11].

The wnt/beta-catenin pathway is essential for osteoblast differentiation and regulation of bone formation. T1D patients may have increased sclerostin and Dkk1 levels, secreted from osteocytes,

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Received Date: *10 Oct 2020*
Accepted Date: *02 Nov 2020*
Published Date: *05 Nov 2020*

Citation:
Moon C, Liu J. The Effects of Type 1 vs. Type 2 Diabetes on Bone Metabolism. World J Surg Surgical Res. 2020; 3: 1258.

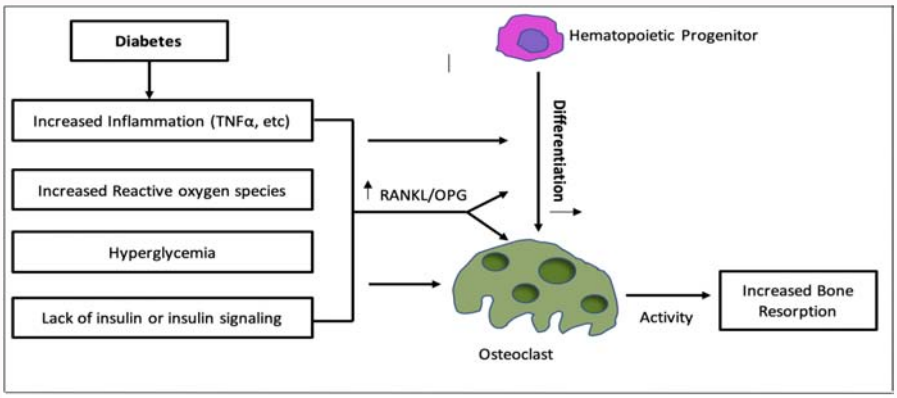

Figure 1: T1D leads to increased inflammation, ROS formation, hyperglycemia, and decreased insulin signaling. This dysregulation causes an increase of RANKL/OPG enhancing the development of osteoclasts. The amplified activity of osteoclasts along with impaired osteoblast function increases the rate of bone resorption.

which act as inhibitors of wnt/beta-catenin signaling. Depression of this pathway results in decreased osteoblastogenesis and bone turnover [11]. Interestingly, Parathyroid Hormone (PTH) has been known to inhibit sclerostin levels allowing for increased bone turnover [7,8]. This suggests that PTH levels are low in T1D and contribute to the increase of sclerostin production [12]. The combination of a low bone turnover rate and increased bone resorption presents T1D patients with weak, old bone causing an increased risk for fracture.

Bone Quality, Structure, and Epidemiology of T1D

T1D typically presents itself at a younger age, and these patients are exposed to the negative effects of insulin deficiency and other chronic complications for a longer period of time [1,6]. Studies using Dual-Energy X-Ray Absorptiometry (DXA) have found a low BMD in T1D patients. A low BMD is suggested to be one of the main causes for weaker bone and increasing the risk of fracture. This is most likely caused by the low bone turnover rate seen in T1D [7,10,13].

Evidence has supported that T1D causes structural changes in bone that can lead to increased fracture risk. A decrease in cortical thickness of bone is seen in T1D and creates a weaker structure for bone [1,13]. Cortical bone accounts for 80% of bone mass providing strength to bone so that it can support and protect the body [14]. Bone in T1D is more vulnerable to non-trauma based fractures without the available strength it needs when the thickness of cortical bone is reduced.

Trabecular Bone Score (TBS) is another component that is significant when assessing the structure and quality of bone and predicts fractures independent of BMD. TBS is also found to be decreased in T1D and alters the microarchitecture of bone causing impaired strength [8,15]. The diagnosis of T1D at a young age has resulted in a reduced height for age and reduced bone length, developing short and narrow bones throughout puberty. Shorter and slender bones in younger children with longer diabetes duration may be associated with reduced bone strength compared to those without T1D [9]. The combination of a decreased BMD and TBS in T1D suggests that there is weakened connectivity of bone, incomplete bone formation, and a higher risk for fractures.

T2D Mechanistic Effects on Bone

Current research on T2D has supported an increased risk of fracture. This evidence presents itself as a paradox since T2D is characterized with a normal to high BMD, leading to the hypothesis that T2D has underlying deficits in bone quality instead of quantity [1,3-5,14,16,17]. Skeletal microarchitecture, bone metabolism, and bone strength abnormalities may be contributing factors in the increased risk of fracture in T2D.

The wnt/beta-catenin pathway is decreased in T2D resulting in a decrease in osteoblastogenesis [18]. The causative agent in lowering osteoblast differentiation is the elevated levels of the glycoprotein sclerostin, similarly seen in T1D [1,4,16,19,20]. In addition to this mechanism, there may also be a decrease multiple bone biomarkers including osteocalcin, alkaline phosphatase, C-Terminal Telopeptide (CTX), Procollagen Type 1 N-Terminal Peptide (P1NP), Runx2 reducing the function and formation of osteoblasts [19-21].

The study by Manavalan et al. presented an increase in subpopulation of immature OC expressing cells containing early CD34 and CD146 markers, suggesting that the pool of circulating osteogenic precursor cells are mostly immature. CD34 and CD146 normally diminish when osteoblasts mature, but the increases of immature cells expressing those markers indicate reduced osteoblast differentiation. These factors cause preferential reduction in bone formation that could lead to an accumulation of older bone consisting of poorer quality [21]. The number of osteoclasts and their function are lower in T2D causing a reduced bone turnover rate complementing the decreased osteoblast function.

Bone Quality, Structure, and Epidemiology of T2D

T2D classically presents an older age of onset most often people over the age of 45, and a higher rate of obesity [3]. T2D is the leading type of diabetes and is starting to develop in younger adults as well. Despite having a normal to high BMD, T2D is unexpectedly associated with an increased risk of fracture suggesting a deficit in bone quality and structure [1,3-5,13,16-21].

Prolonged hyperglycemia and oxidative stress in T2D causes an increase in Advanced Glycated End-Products (AGEs) and deteriorates osteoblast function. Type 1 collagen is the structural composition of bone. When more AGEs accumulate, there is a loss of normal enzymatic cross-linking of collagen leading to brittle bone [4,14,19,22]. AGEs not only alter type 1 collagen cross-linking, but also reduce the expression of pro-osteogenic markers, Runx2 and Osterix, and increase the rate of apoptosis of osteoblasts [20]. The adhesion of osteoblasts to the collagen matrix is impaired leaving a

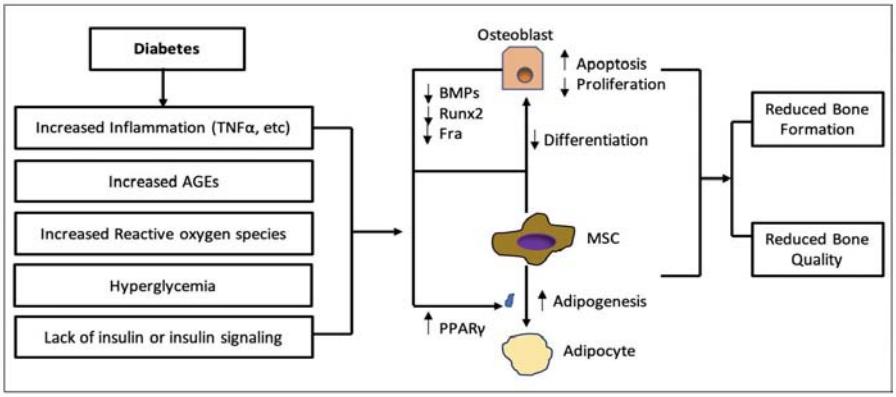

Figure 2: T2D leads to increased ROS formation, hyperglycemia, generation of AGEs, and chronic inflammation. This dysregulation decreases pro-osteoblastic biomarkers lowering osteoblast proliferation. T2D also increases PPARγ causing MSCs to stimulate adipogenesis. These factors reduce bone formation and bone quality.

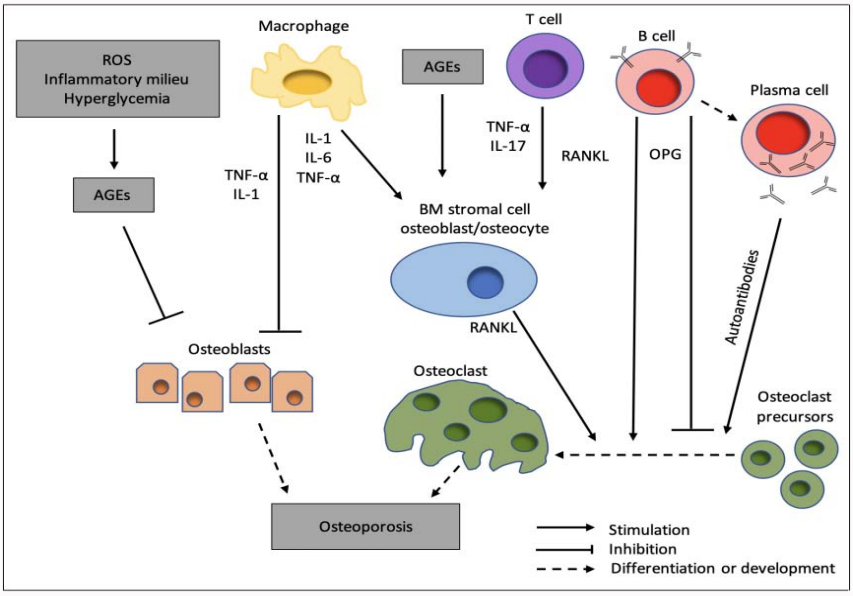

Figure 3: T1D and T2D both contain mechanisms that increase ROS, inflammation, and cause hyperglycemia. These factors from both types of diabetes affect the immune system leading to an increased development of osteoporosis and osteoporotic fractures.

weak bone matrix and lower mineralizing surface values. There is significantly lower bone formation rate, osteoid surface tissue, and osteoblast function that can be explained by increased AGEs in T2D. The accumulation of AGEs reduces biomechanical properties of bone by stiffening the bone collagen and reducing bone strength [17].

AGE affects the vascular system as well by causing AGE-induced apoptosis of Vascular Smooth Muscle Cells (VSMC). The buildup of AGE increases AGE-induced arterial calcification, therefore depressing the vascularization and angiogenesis in bone [1,19]. This is detrimental to the bone and makes it difficult for blood vessels to accumulate in the bone to begin the healing process after an injury. The glycation of bone by AGE and weakened angiogenesis pathway increase the development of crack-like micro damage in bone causing an increased risk of fracture [17,22].

Studies have indicated a change in bone structure in T2D that leads to an increased fracture risk. Peroxisome Proliferator-Activated Receptor Gamma (PPARG) controls adipogenesis in bone marrow and is increased in patients diagnosed with T2D [4,18]. The Free Fatty Acids (FFA) in bone marrow generate Reactive Oxygen Species (ROS) which inhibit osteoblast proliferation by shunting Mesenchymal Stem Cells (MSC) and directing them to differentiate into adipocytes [1,4,19]. Adipocyte accumulation increases the amount of saturated bone marrow lipids compared to unsaturated [23]. Saturated fatty acids in the bone marrow also inhibit osteoblast differentiation and increase production of pro-inflammatory cytokines [1,20]. The high levels of PPARG and AGEs may cause the increased cortical porosity. In addition to a higher cortical porosity in T2D, there is also a lower TBS as well [1,4,8,14,24]. A reduced TBS suggests a lower trabecular number, greater spacing, and lower connectivity in bone (Figure 2) [17]. A higher cortical porosity and decreased TBS are microarchitectural aspects that deteriorate bone to an increased fracture risk and bone fragility [15,25].

Secondary Complications of T1D and T2D on Bone

T1D and T2D both share similar secondary complications that decline skeletal microarchitecture, inhibit bone cell differentiation,

and increase the risk of fractures. DM patients are likely to suffer from chronic kidney disease, cardiovascular disease, neuropathy, and osteoporosis [1]. Many of these secondary diseases will affect bone quality and lead to alterations in bone formation.

Microvascular Disease (MVD) in DM is associated with an accelerated deterioration of cortical bone resulting in a lower cortical thickness and an increased cortical porosity. MVD alters the vascular supply to cortical bone because the blood flow and microvascular density in bone marrow becomes reduced. A loss of strong blood supply to bone makes it difficult to recover from injury and poses a risk to producing tiny breaks in the bone [4,8,13,20,24].

Osteoporosis is another vital comorbidity that destroys bone structure, quality, and mineralization in DM. There is a higher incidence of osteoporosis in postmenopausal women and those with a longer duration of disease that only increases the negative effects on bone [26]. T1D may present with a lower peak bone mass and BMD. This increases the risk of developing osteoporosis creating weaker bones [27]. T2D typically has a higher BMD and contradicts the finding of low BMD in osteoporosis [5]. The higher concentration of AGEs interrupts type 1 collagen crosslinking thereby causing reduced bone strength and influencing the risk of osteoporosis (Figure 3).

The chronic manifestations of peripheral neuropathy and retinopathy play a role in increased fracture risk of DM patients. Neuropathy causes decreased sensation, numbness, and muscle weakness of the upper and lower limbs by damage to the nerves. Diabetic retinopathy damages the blood vessels in the retina leading to partial or complete blindness. Both diseases associated with diabetes increase the chance of falls due to the lack of sensation in the feet and decreased sight making it difficult to walk [28]. Increased fall risk ultimately causes an increased fracture risk specifically in addition to the expression of negative bone effects found in DM [29,30].

Oxidative stress is another major factor causing an impaired healing process of bone. Oxidative stress can possibly cause apoptosis of osteoprogenitor cells in diabetics thereby slowing down bone formation [11]. The adverse properties of DM cause an increase in oxidative stress and ROS which create an imbalance between osteoclast and osteoblast activity. There is also an increase in pro-inflammatory cytokines that can lead to chronic inflammation and bone resorption [4]. ROS can reduce vessel function, once again making it difficult for bone to repair itself with decreased blood flow to bone tissue [20]. Altering the bone remodeling system by oxidative stress will generate weakened bone that is more susceptible to fractures.

BMD in T1D vs. T2D

T1D and T2D have similarities in their bone pathology and secondary comorbidities; however they display some critical differences in their specific causes for an increased fracture risk. One of the major differences between the two types of diabetes mellitus is their BMD. T1D is known to have a lower BMD while T2D typically is associated with a high BMD [1,3-5]. The contradiction of T2D presenting a high BMD and an increased fracture risk is still being studied because of the controversial evidence. This phenomenon suggests that BMD is not the only predictor of fracture risk, but there are other underlying factors that play a role in diabetic fractures [1,3-5,14,16,17].

The role of IGF-1 is critical in bone health and growth. T1D suffers from diminished IGF-1 levels and can account for its low BMD. This is one of the main contributors for decreased bone turnover, cortical thickness, and trabecular bone number in T1D causing an increased risks for osteoporotic fractures [8-11]. Meanwhile, T2D patients typically have a poor diet and may be obese thus triggering persistent hyperglycemia. Hyperglycemic levels initiate increased levels of AGEs resulting in weakened type 1 collagen in T2D. Increased AGEs in addition to amplified oxidative stress and inflammation cause the increased fracture risk seen in T2D despite having a high BMD [4,14,19,22].

Conclusion

Not one factor can be depicted to be the cause for impaired bone healing and increased fracture risk in both types of DM. The influence of multiple systems and enzymes contribute to decreased bone strength and elevated fracture risk. Future studies need to be performed to identify the chief contributing factors of the bone healing process. With this knowledge, there could be a focus on how to prevent osteoporotic fractures in both T1D and T2D.

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