REVIEW

Diabetic Skeletal Health and Potential Benefits of Exercise

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ABSTRACT

Bone tissue undergoes continual remodeling through resorption and formation. The balance between these 2 activities is critical to optimizing bone mineral density (BMD) and the biomechanical integrity of the tissue, thereby reducing fractures. There is increasing evidence that diabetes negatively alters the cellular activity of bone tissue and reduces bone quality resulting in an increased risk of fractures. The mechanisms by which diabetes impacts bone are not completely understood; however, insulin, hyperglycemia, and glycation appear to influence skeletal regulation. This review will explore the influence of diabetes mellitus on bone as well as examine the potential methods by which exercise can serve as a nonpharmacological method to optimize bone health in persons with diabetes. *Journal of Clinical Exercise Physiology*. 2019;8(3):108–114.

Keywords: osteoporosis, glycation, bone quality, fracture

INTRODUCTION

Osteoporosis is a metabolic condition resulting in a loss of bone mineral density (BMD), increasing bone fragility, leading to an increased risk of fracture. Nearly 54 million men and women over the age of 50 in the United States have osteoporosis or low bone mass (1). The National Osteoporosis Foundation reports that 50% of women and 20% of men will incur an osteoporotic related fracture in their lifetime; thus, the economic burden is significant. In a study examining hospitalizations and associated expenses between the years 2000 and 2011 in women 55 and older, it was determined that osteoporotic fractures (OFs) resulted in a greater number of hospitalizations compared to myocardial infarction (MI), stroke, and breast cancer (2). Additionally, OF generated the greatest health care expenditures at $5.1 billion. These data are quite concerning and require an examination as to potential contributing factors. More recently, evidence of elevated fracture risk in those with diabetes has generated increased interest in examining the connection between diabetes and skeletal health.

The Centers for Disease Control and Prevention estimate more than 100 million Americans have diabetes (30.3 million) or are considered prediabetic (84.1 million), with an incidence of 1.5 million new cases per year (3). The overwhelming prevalence of diabetes has resulted in an extensive economic burden estimated at $327 billion in 2017. Diabetes mellitus (DM) is a condition in which the body is unable to appropriately manage blood glucose due to either insufficient insulin production (typically Type 1 DM [T1DM]) or cellular insulin resistance (Type 2 DM [T2DM]). Diabetes results in progressive and extensive damage and can lead to several comorbidities. In addition to commonly recognized diabetic complications such as retinopathy, nephropathy, neuropathy, stroke, coronary artery disease, and peripheral vascular disease, diabetes appears to negatively influence bone (4). Studies have reported elevated fracture risk with diabetes. For instance, Valderrabano and Linares (5) provide a thorough review of studies evaluating fracture risk in T1DM (8 studies) and T2DM (7 studies). Each of these studies reported an increased risk of fracture in diabetic populations compared to controls, with elevated risk of hip fracture being of particular concern. Interestingly, Weber et al. (6) examined fracture incidence across the lifespan (0–89 years) in T1DM as part of The Health Improvement Network study. They reported that fracture risk was elevated at all age

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Conflicts of Interest and Source of Funding: None.

categories compared to nondiabetics, with peak fracture rates occurring between the age of 60–69 for males and 40–49 in females. The Fracture Risk Assessment score (FRAX) is a common tool used to assess the likelihood of incurring an OF by assessing a variety of variables such as age, smoking status, family history, and BMD. Recently, however, the FRAX was reported to underestimate fracture risk in those with DM, suggesting that including diabetes as a variable to the FRAX could improve the prediction accuracy of the tool (7).

Fracture risk associated with diabetes can vary substantially, however, as the result of numerous factors such as the type of diabetes, length of diagnosis, and disease management. Thus, understanding the possible mechanisms by which diabetes may influence bone, which is quite complex, is important. Additionally, research examining bone in those with diabetes is novel, and there is still much more to learn. The following review will explore some of the potential effects DM has on the microenvironment of bone and subsequent negative consequences to bone health. Furthermore, exercise as a potential mechanism to mediate some of the negative effects of diabetes and thereby optimize bone physiology, improving skeletal health, will be discussed.

Diabetic Factors Affecting Cellular Differentiation

Bone tissue undergoes constant changes as it responds and adapts to mechanical loading as well as the alterations in the microenvironment. The critical cells involved in the bone remodeling process include osteoclasts, osteoblasts, and osteocytes. The cellular interplay between osteoclast bone resorption and osteoblast bone formation is critical to formulating osteocytes and maintaining a healthy skeleton. As the activity of these 2 cell types becomes uncoupled, with resorption outweighing formation, BMD is compromised (8). Because the etiology of T1DM and T2DM is heterogeneous, the process by which each condition influences skeletal development and maintenance is somewhat distinct. This is quite evident when examining the literature relative to BMD. Bone mineral density is often used as the primary marker of fracture risk. Normal BMD values are often equated with optimal skeletal health. Studies have reported low BMD with T1DM, while BMD in T2DM is more variable across the literature. Bone mineral density is lower, the same, or in many cases higher in T2DM compared to healthy controls (9–12). The discrepancies in BMD between T1DM and T2DM can in part be attributed to insulin.

Insulin is involved in anabolic mechanisms influencing bone metabolism via osteoblast differentiation and activity (13). This is especially problematic since reduced insulin levels with T1DM can potentially limit bone accrual during the critical years of bone growth, resulting in greater susceptibility to osteoporosis (14). Hyperinsulinemia associated with T2DM, in combination with enhanced mechanical loading due to overweight/obesity conditions, stimulate osteoblast proliferation and activity increasing BMD (4). Regardless of BMD status, both T1DM and T2DM demonstrate an increased risk of fracture (5). The discrepancy seen in T2DM, having higher BMD yet increased fracture risk, provides some evidence of altered bone quality with DM influencing the mechanical properties that typically help protect the bone from fractures.

Although BMD, measured via dual energy x-ray absorptiometry, is the most common method for evaluating bone health, it does not provide information on bone quality. Bone mineral density provides information relative to the mineral content of bone, while bone quality relates to aspects of bone geometry/architecture and material properties. According to Donnelly (15):

> … geometric factors include the macroscopic geometry of the whole bone and the microscopic architecture of the trabeculae. Material factors include of the constituent tissue arising from the composition and arrangement of the primary microstructural constituents, collagen and mineral, as well as microdamage and microstructural discontinuities such as microporosity and lamellar boundaries (pp. 2128–9).

These variables are independent of BMD, influencing structural integrity (15,16). Bone quality variables such as bone geometry and architecture can be evaluated via quantitative computed tomography (QCT), high-resolution peripheral QCT (HR-pQCT), and high-resolution magnetic resonance imaging, while methods such as scanning electron microscopy and microindentation testing can evaluate bone material properties. For a complete review of bone quality evaluation methods, see Donnelly (15). Bone quality assessments may prove more beneficial to understanding the influence of diabetes on bone health.

Examining the microenvironment of bone has provided some insight regarding potential variables that influence bone at the cellular level. Elevated blood glucose appears to induce mechanisms that negatively affect bone quality. One such mechanism involves the alteration in osteoblast differentiation from mesenchymal stem cells (MSCs). Mesenchymal stem cells are pluripotent cells that can give rise to a variety of cell types including osteoblasts and adipocytes (17). Runt-related transcription factor 2 (RUNX2) and peroxisome proliferator-activated receptor γ (PPARγ) regulate MSC differentiation. Runt-related transcription factor 2 favors osteogenesis and osteoblast formation, while PPARγ promotes adipogenesis. High glucose levels appear to reduce RUNX2 and promote PPARγ, which results in increased bone adiposity reducing bone quality (17,18).

Osteoblast status may also be influenced by advanced glycation end products (AGEs). Advanced glycation end products are a commonly produced byproduct of the hyperglycemic environment seen with DM as the result of the nonenzymatic reduction of sugars with protein or fat, known as glycation. Advanced glycation end products, in conjunction with an inflammatory environment, are thought to create osteoblast dysfunction and increase osteoclastogenesis (13). In vivo, AGEs induce apoptosis of osteoblasts, which could disrupt normal skeletal regulation (19). Furthermore,

AGEs have a deleterious effect on the function of protein structures such as collagen. Advanced glycation end products appear to induce mechanical changes in bone via glycosylation of Type 1 collagen, resulting in nonenzymatic cross-links. Collagen is critical to the integrity of bone, as it is a major component of the bone matrix providing ductility and tensile strength (20,21). According to Saito and Marumo (20):

> A trend towards increased loss in bone quality in terms of impaired enzymatic cross-link formation and/or an increase in AGEs cross-links in type 1 and 2 diabetes may lead to accelerated increase of bone fragility, which is independent of BMD (p. 209).

Biomechanical Integrity of Diabetic Bone

The altered microenvironment with DM appears to influence the cellular activity of bone, thereby having the potential to impact bone integrity. Assessing the biomechanical properties of bone is challenging due to the invasive nature of testing previously available. Thus, the majority of research has used animal models. In a study by Reddy et al. (22), the femur and tibia of diabetic-induced and nondiabetic control rats were excised and tested using a 3-point bending test. Using a standard load-deformation curve, the researchers evaluated variables of breaking strength (maximum stress applied at fracture), energy absorption capacity to yield point (how much energy can be absorbed without damage; area under the load-deformation curve), toughness (ability to absorb energy during failure), and bending stiffness (represented by the slope of the load-deformation curve). The breaking strength, energy absorption capacity to yield point, and toughness were reduced by 37%, 27%, and 34%, respectively, while bending stiffness was increased 38% in the diabetic group compared to the control group. Similarly, Saito et al. (23) reported that diabetic rats demonstrated reduced bone mechanical properties, which was attributed in part to impaired enzymatic cross-links. With the advancement of technology, researchers are able to assess bone microarchitecture and bone integrity variables in humans.

High-resolution peripheral QCT allows for the quantification of microstructural parameters of bone. Studies using HR-pQCT technology have provided insight regarding potential structural differences between diabetic and nondiabetic bone. Several, but not all, report increased cortical bone porosity and cortical pore volume (10,24–26). The altered microstructure with DM is thought to influence bone integrity. Patsch et al. (25) reported increased cortical porosity related to deficits in overall bone strength parameters such as stiffness, failure load, and cortical load fraction. Similarly, Farr et al. (10) discovered reduced bone material strength, as determined by in vivo microindentation testing, in T2DM compared to nondiabetic individuals despite no significant differences in BMD between DM and non-DM individuals. Using a handheld microindentation instrument, a force was applied by a probe to the midshaft of the anterior aspect of the nondominant tibia and the indentation distance was measured. The researcher indicated the increased cortical porosity via microindentation was associated with reduced bone material strength in T2DM. Even when no differences are present in cortical bone porosity, altered cortical bone biomechanical properties and higher cortical bone AGEs are present in T2DM compared to nondiabetic individuals (27).

Potential Benefits of Exercise

The American Diabetes Association promotes the integration of exercise to aid in the nonpharmacological management of diabetes. Exercise also supports improvement of other health parameters in persons with diabetes, such as cardiovascular fitness and muscular strength (28). The connection between exercise and diabetic bone is not as well understood as other diabetic comorbidities; however, being physically active throughout the lifespan is a widely recognized approach to address optimal bone development during youth and prevention of bone loss during adulthood (29). Exercise can be osteogenic by means of mechanical loading and optimizing the microenvironment. Both variables have the potential to be influential to improving diabetic bone health.

Exercise causes bone to adapt to the stress induced by muscle contraction forces as well as mechanical loading, known as Wolff's law (30). As bone incurs an internal or external load (stress), it undergoes a level of deformation relative to its original length, known as strain. The objective of exercise is to generate a strain on bone to stimulate a subsequent adaptive response via mechanotransduction, improving bone strength for future loading conditions. Mechanotransduction involves the detection of the strain/deformation generated by a mechanical force (internal or external), converting it to a biochemical signal triggering a subsequent effector cell response, ultimately increasing in osteogenesis in the location of the deformation as the result of enhanced osteoblast differentiation (30). When specifically trying to develop an osteogenic exercise prescription, strain magnitude and strain rate are critical variables (31). Concerning strain magnitude, the exercises selected must reach a level of a "minimum effective strain" to induce an adaptive response. Depending on the training status of an individual, untrained/sedentary compared to trained/active, the maximum effective strain may vary, with exercises producing lower strains needed for untrained/sedentary and higher strains needed for trained/active individuals. Additionally, greater strain rates, such as higher velocity dynamic movements, increase the fluid movement within bone, generating a fluid shear stress stimulating the osteogenic response (30,31). This is evident when examining BMD of various athletes. Athletes engaged in sports with higher ground reaction forces generally have higher BMD (32,33). Thus, dynamic weight-bearing exercises, such as walking, running, jumping/plyometrics, and resistance training that introduces novel amounts of muscle and mechanical stress are optimal for generating an adaptive response. Incorporating these types of exercise modalities to improve bone

accrual during youth and reduce losses with aging (29) could serve to counteract the negative impact of DM. More specifically, DM reduces osteoblastgenesis and induces adipogenesis, increasing the lipid accumulation in bone which reduces bone quality. Mechanical stimulation of bone will downregulate PPARγ and result in an increase in the differentiation of osteoblasts and reduce adipogenesis (34–36). Thus, exercise has the potential to mitigate some of the negative factors of DM on bone cellular differentiation; however, more research is needed to support this conclusion.

The microenvironment is also important for supporting optimal bone health. Uncontrolled blood glucose, hyperglycemia, and subsequent AGEs formation appear to be detrimental to the bone microenvironment. Impaired cellular regulation of osteoblasts, as well as the glycation of collagen altering bone biomechanics may be improved with exercise-mediated reductions in blood glucose and AGEs. Both aerobic and resistance exercise help in managing blood glucose and reduce AGEs (37–39). Exercise has also been shown to improve bone quality, strength, and ductility despite no changes in bone geometry (40,41). Improvements in bone quality induced by exercise also can reduce fatigue-induced microcracks (i.e., produced by repeated stress), serving to protect against fracture (41). Further research is needed to determine the association between exercise-induced microenvironment changes in DM and the subsequent impact on bone. The focus of this research should be on bone quality parameters rather than BMD since the two may be distinct in predicting fracture risk with DM.

While there is an extensive amount of research examining the benefits of exercise on DM, the focus has often been on management of the disease, weight loss, and cardiovascular fitness. Few studies have examined the influence on bone health. The studies that have been conducted report mixed results. As part of a 1-year weight-loss intervention study, Schwartz et al. (42) reported BMD losses in participants with T2DM completing the Look AHEAD lifestyle study. The study's intervention included a dietary and an exercise component aimed at inducing weight loss. It is important to note that the exercise intervention included a weekly goal of at least 175 min of moderate intensity aerobic exercise, but resistance exercise was not included. The researchers indicated that the weight loss was associated with BMD losses, which could relate to reduced skeletal loading. Villareal et al. (43) examined the impact of a weight management program combined with exercise on a variety of parameters including BMD. Obese adults completed a 6-month weight management program combined with an aerobic, resistance, or combined aerobic and resistance exercise program. Bone mineral density of the hip decreased 2.6%, 1.1%, and less than 1% in the aerobic, combined, and resistance exercise groups, respectively. The control group, with no weight management nor exercise intervention, increased BMD less than 1%. Therefore, these studies appear to indicate weight management programs can pose a challenge when trying to reduce weight/fat mass while not sacrificing BMD. In contrast, Daley et al. (44) found that, when high-intensity resistance training was included with a weight-loss intervention, BMD was maintained in obese participants with T2DM, while the weight-loss only group lost BMD. Thus, higher skeletal loading via resistance training may be necessary to preserve bone when also addressing the need for weight loss.

Bello et al. (45) used a diverse exercise regimen to examine the benefits of exercise on BMD participants diagnosed as prediabetic or T2DM. The exercise intervention used included 3 moderate-to-vigorous intensity exercise sessions on different days: aerobic exercise (day 1), weight-bearing exercise (day 2), and aquatic exercise (day 3) for a period of 32 weeks. Significant increases in BMD of the Ward's triangle were observed in the exercise group compared to control. Although BMD did not increase significantly in the femoral neck, greater trochanter, total hip, or whole body in the exercise group, losses were not observed as noted in the control group (greater trochanter and whole body).

Exercise Prescription Considerations

While there is very limited research directly assessing exercise intervention protocols on diabetic bone parameters, the research to date seems to indicate that exercise has the potential to positively influence bone in those with DM. Exercise protocols designed to maximize bone accrual and optimize skeletal health should take into consideration the principles associated with mechanotransduction by optimizing strain magnitude and strain rate (46). Strain magnitude is the intensity of the load or the degree of ground reaction forces associated with the exercise mode. For example, walking, running, and jumping induce ground reaction forces of approximately 1–2, 2–3, and 3–4 times body weight, respectively (47,48). Activities inducing higher strain magnitudes, such as higher intensity resistance exercises (>60% 1 repetition maximum) and jumping/plyometrics, are thought to be osteogenic; however, using heavy loads or generating large ground reaction forces may not be safe or appropriate for those beginning an exercise regimen or for individuals with diagnosed osteoporosis. Thus, exercise protocols can manipulate frequency and strain rate to initiate a skeletal response. Greater frequency or increased strain rates via high velocity dynamic movements combined with lower strain magnitudes can also generate an adaptive response (46). As the ability to handle greater loads improves, incorporating exercises that challenge the body resulting in higher strain magnitude can potentially be used safely, depending on the population.

When developing an exercise prescription to address bone health, the presence or absence of diagnosed osteoporosis should influence which modes of exercise are most appropriate. Since osteoporosis increases bone fragility and fracture risk, it is important to note that activities involving heavy loading or high ground reaction forces and twisting, compression, or spinal flexion may need to be avoided. The American College of Sports Medicine provides specific evidence-based recommendations for training frequency, intensity, time, type, volume, and

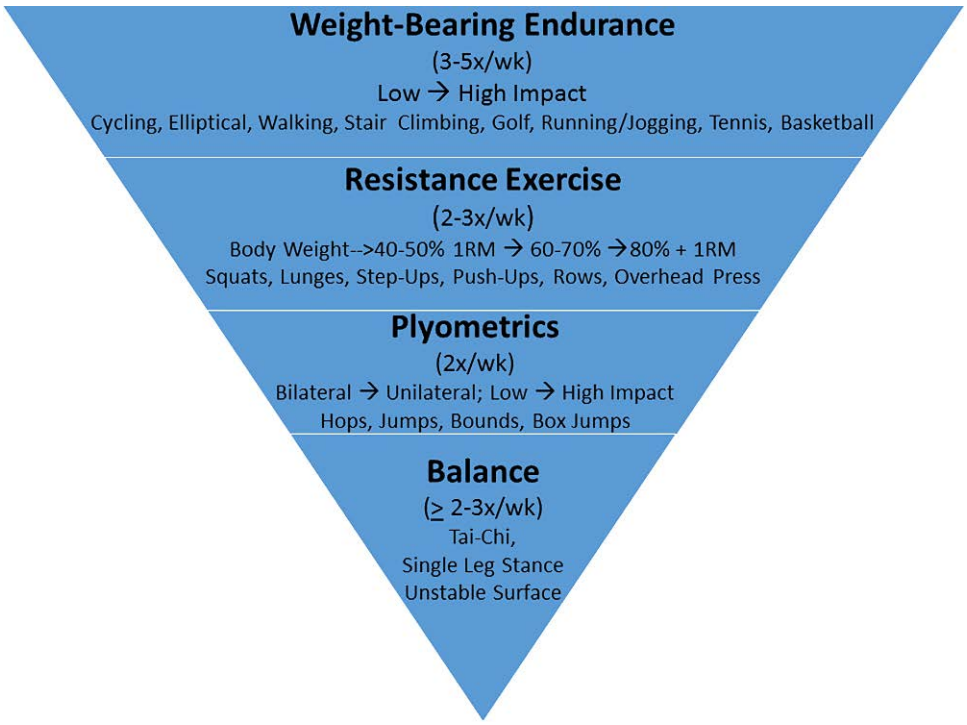

FIGURE 1. Sample recommendations and exercises for a balanced osteogenic exercise prescription including frequency and intensity ranges. RM = repetition maximum.

progression for general fitness as well as frequency, intensity, time, type guidelines for individuals with osteoporosis (49). Additionally, the American College of Sports Medicine position stand "Physical Activity and Bone Health" provides exercise prescription recommendations specifically addressing bone health. Recommendations include weight-bearing endurance activities performed 3–5 times per week and moderate- to high-intensity resistance training targeting major muscle groups 2–3 times per week. In addition to traditional resistance exercises, plyometric training should be incorporated when appropriate to elicit high ground reaction forces at high strain rates.

Additionally, programs should incorporate resistance exercises and plyometrics that load areas at high risk for osteoporotic related BMD loss including the spine, hips, and wrists. For example, squats and jumps load the hips and spine, while overhead press and push-ups (standard or plyometric) load the wrists. Neuromotor or balance activities are encouraged to help reduce fall risk (49,50). Morrison et al. (51) determined fall frequency and fall risk to be higher in patients with T2DM compared to nondiabetic controls. Exercise has been found to positively impact proprioception, strength, and neuromotor control that appear to be compromised with diabetic complications, subsequently reducing fall risk. Exercise programs should progress accordingly, to induce novel stress based on the health and fitness of the client. Figure 1 provides examples of exercises for each recommended mode of activity. As with Figure 1, much like a triangle balanced on its point, so too must exercise prescriptions be balanced, incorporating all the recommended training modalities to optimize outcomes and progress from lower intensities to higher intensities. Ideally, exercise prescriptions targeting bone health need to be of sufficient strain magnitude, include movements that are dynamic in nature, generating a variety of force vectors through the incorporation of multidirectional movement patterns to induce a novel stress, and incorporate faster movements that induce high strain rates (29,52).

Summary

The relationship between DM and bone health is complex, involves numerous variables, and is not fully understood. To date, research has provided some initial indications that insulin status, hyperglycemia, and AGEs are some of the variables that create a microenvironment which alters bone cellular activity, induces bone adiposity, and potentially increases porosity. These variables ultimately compromise bone material properties, subsequently increasing fracture risk. Exercise can serve as a nonpharmacological method to positively modify the microenvironment and cellular activity, thereby improving osteogenesis and bone quality in diabetics. The exercise prescription should include dynamic weight-bearing exercise, optimizing parameters of load intensity, frequency, and rate. Independent of DM, exercise is a recognized method for optimizing bone accrual during youth as well as slowing loss with aging. More research is needed to fully understand the significance of exercise to positively alter skeletal regulation and fracture risk in diabetics. Future studies should examine bone quality and not simply BMD since these variables may be independently impacted by DM.

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