Diabetes and Bone

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Based on the 2014 National Diabetes Statistics Report, 29.1 million people (9.3% of population) have diabetes mellitus (DM) within the United States.[1] The same year, a report on the prevalence of osteoporosis in the United States estimated that 54 million adults greater than the age of 50 years are affected by low bone mass.[2] Diabetes has emerged as an important risk factor for osteoporosis in the last 10 years.[3] The staggering numbers of people affected by both these conditions begs a need to evaluate the possibility of a cause-and-effect relationship between these disorders, and to determine if the bone disease can be considered a complication of diabetes. Recent advancements in the management of diabetes, especially type 1 diabetes (DM1), have resulted in increased patient longevity, which in turn has brought into clinical focus disease-related comorbidities that were previously not a concern.

BONE MINERAL DENSITY

DM1

Bone growth in children occurs by a process called modeling where osteoblasts lay down the bone and osteoclasts shape the bone.[4] It has been postulated that in children with prepubertal onset of DM1, the decreased bone formation and inadequate accrual of peak bone mass are major contributing factors for low bone mass, reduced bone strength and osteoporosis later in life.[5] Most studies show that bone mineral density (BMD) when it is measured by dual energy X-ray absorptiometry (DEXA) is decreased in patients with DM1 with approximately 50% of diabetics having low bone mass for their age.[6] The decrease in BMD seem to be age and gender dependent in children with DM1 having 0.5-1.5 lower Z-score than age-matched controls, and men of all ages exhibiting a higher risk for low bone mass.[6] A decrease in BMD does not appear to be related to glycemic control, age of onset or duration of diabetes.[6]

Many hormones, including gonadal steroids, insulin, growth hormone, growth factors and cytokines control bone modeling, and disruption in these hormones can lead to low bone mass for age.[6,7] Insulin has an anabolic effect on bone and is thought to play both a direct and an indirect role in stimulation of osteoblasts,[7] and patients with DM1 may lack this effect due to insulin deficiency. Intensive insulin therapy has shown to stabilize BMD.[8] Amylin, the other hormone secreted by beta cells, has been found to increase osteoblast and chondrocyte proliferation, as well as to suppress osteoclastic activity. Amylin is decreased in patients with DM1.[7] Another contributing factor to decreased BMD is the lower body mass index typical of patients with DM1.[8] Thinner individuals are denied the benefits that mechanical loading and the actions that adipocytokines have on increasing BMD.[8]

Type 2 Diabetes Mellitus

Meta-analysis of observational studies comparing patients with type 2 diabetes mellitus (DM2) and nondiabetic controls shows that diabetics have increased BMD with a pooled mean difference of 0.04 (95% CI: 0.02-0.05) that is not gender related.[9] The BMD was higher at the femoral neck, at the total hip and the spine, with no difference in forearm BMD.[9] Neither race nor gender has been shown to be contributing factors for higher BMD in patients with DM2 over controls.[10] It is easy to postulate that higher BMD may be due to higher weight in patients with DM2, however, not all studies support the positive correlation between higher BMD and weight.[11] A positive correlation between higher hemoglobin A1C (HbA1C) has been observed in many studies, suggesting that poor glycemic control may be contributing factor to an increase in BMD.[9,12] Studies evaluating an age-related change in BMD among patients with DM2 have shown conflicting results with some studies observing lower rates of BMD loss,[13] whereas others reporting higher rates of BMD decline in poorly controlled DM2 when diabetes is associated with glycosuria, hypercalciuria and secondary hyperparathyroidism.[12]

FRACTURE RISK

DM1

Patients with DM1 have a 6.9-fold increased incidence of hip fractures,[14] and combined analysis estimates a 1-2–fold increase of fracture at any skeletal site.[6,7]

DM2

Despite increased BMD in patients with DM2, the risk for fragility fractures is also increased, and fractures occur at a T-score that is 0.6 higher than that of controls.[5]

Postmenopausal women with diabetes exhibit a 20% increased risk for all type of fractures.[15] Men with diabetes also have an increased risk for all type of fractures: odds ratio (OR) = 1.57 ($P = 0.01$).[16] In the recent meta-analysis, the relative risk (RR) for hip fracture among patients with DM2 was 1.34 (95% CI: 1.19-1.51) with the pooled female-to-male RR of 1.09 (95% CI: 0.93-1.28)[17]; thus confirming data from older meta-analysis showing that older patients with diabetes have an increased risk for hip fractures (RR = 1.7) and any clinical fractures (RR = 1.2).[18] Data assessing vertebral fracture risk is less abundant. In the Japanese population, DM2 was found to be an independent risk factor for vertebral fractures among women (OR = 1.9) and in men (OR = 4.7).[19]

RISK FACTORS

Several disease-related characteristics have been shown to be risk factors for fractures in both the types of diabetes.

Diabetic complications are associated with a greater than 10-fold increased RR of fracture among both men and women with DM1.[3]

Long-standing poorly controlled diabetes ultimately results in comorbidities that may contribute to an increased risk of fracture. It is well known that uncontrolled diabetes leads to microvascular complications such as neuropathy, retinopathy and nephropathy.[7] These microvascular complications can compromise blood flow to the bone, further decreasing bone density and effecting bone quality.[20] Risk for falling (perhaps due to hypoglycemia, neuropathy, dementia, poor muscle mass quality, obesity or vitamin D deficiency or both) is increased in the diabetic population, potentially increasing the risk for fractures.[20,21] Duration of diabetes (over 10 years for hip fractures in DM2) and presence of long-term complications (especially retinopathy) have been shown to increase risk for fractures in patients with diabetes.[23,12,22,23] Diabetic nephropathy affects bone health through multiple mechanisms. Decreased renal function impairs the kidney's ability to convert Vitamin D to its active form 1,25-dihydroxycholecalciferol. Over time, this leads to secondary hyperparathyroidism, tertiary hyperparathyroidism and increased bone turnover. In later stages of diabetic nephropathy, uremia can lead to uremic osteodystrophy.[20] Individuals with DM1 are also at a greater risk of celiac disease.[24] Celiac disease contributes to decreased nutritional absorption that ultimately affects bone health.[20] Having multiple diabetes-associated complications can lead to immobilization and ultimately "disuse" osteoporosis.[20] The Diabetes Control and Complications Trial showed a 35-60% decrease in microvascular complications with intensive insulin treatment.[25] Insulin stimulates osteoblast proliferation and differentiation, and it should be beneficial for bone strength in patients with DM1[7]; however, some, but not all, population-based studies in patients with DM2 found that being on insulin increased the risk for fractures.[12,22]

Despite patients with DM2 having higher BMD with higher body mass index, obese men and women tend to fracture more, suggesting that higher weight is not protective and may be an independent risk for fractures. In age, race and BMD-adjusted models in MrOS study of older overweight or obese men with DM2 compared with those of normal weight, the hazard ratio for non–spine fracture was 1.04 (95% CI: 0.87-1.25) for overweight, 1.29 (95% CI: 1.00-1.67) for obese and 1.94 (95% CI: 1.25-3.02) for morbidly obese men.[26] In the GLOW study, obesity increased risk for ankle and lower leg fractures among women older than 55 years with DM2.[27] Perhaps obesity, especially in the diabetic population, leads to overall deconditioning, a decrease in muscle mass quality, an increase risk for falls, worsening glycemic control and overall increased risk for fractures.

It is also interesting to note that thiazolidinediones and peroxisome proliferator-activated receptor γ agonists stimulate pluripotent mesenchymal stem cells to differentiate into adipocytes rather than osteoblasts.[19] Meta-analysis of studies in patients with DM2 treated with thiazolidinediones showed an increased risk for overall fractures in women (OR = 2.23), but not in men.[28]

The relationship between glycemic control and risk for fractures is less clear. As mentioned before, studies show that higher HbA1C positively correlated with the increase in BMD in patients with DM2, but despite that, some studies show that HbA1C > 7.5% is associated with an increased risk for fractures,[29] however, others did not support this finding.[30] More data are needed to establish how hyperglycemia influences fracture risk.

MECHANISMS FOR THE INCREASED RISK FOR FRACTURES IN PATIENTS WITH DIABETES

Studies have shown that the main culprit in bone fragility in patients with DM1 appears to be decreased osteoblast activity and differentiation. Differentiation is impaired as these patients fail to maintain a pluripotent stem cell population for osteoblast differentiation.[3] Multiple studies show that markers of bone resorption and formation are suppressed in DM2 population as well.[6] From the few histomorphometric studies in patients with DM2, it seems that there is an imbalance between suppressed bone formation and disproportionate milder reduction in bone resorption.[22] Multiple proteins and enzymes play a role in this process. The 2 important genes associated with osteoblast differentiation are Run