Diabetes and Osteoporosis

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About the Author

Dr. Timothy O'Leary received his medical degree from Queen's University, Kingston, Ontario in 1981. He trained in Internal Medicine in Toronto followed by an Endocrinology residency in the Ottawa/Kingston Program. He was an Assistant Professor at the University of Ottawa from 1985 to 2014 with a special interest in disorders of bone and mineral metabolism. Dr. O'Leary is currently in private endocrine practice with LMC Healthcare Ottawa.

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Introduction

As part of our care of patients with diabetes, we monitor target organs for damage. We routinely screen for microvascular and macrovascular complications. In my opinion, the awareness of bones as a target organ of diabetes will improve the care that we provide to patients. Patients with both Type 1 (T1DM) and Type 2 (T2DM) are at increased risk of fractures. This will become a larger issue in the future as the prevalence of diabetes is rising and individuals with diabetes are living longer. In addition to skeletal factors, diabetes and its complications can increase fractures by increasing the patient's propensity to fall. This can be due to neuropathy, visual impairment and hypoglycemia. However, there are some differences between the characteristics of bone disease between patients with T1DM and T2DM.

T1DM Diabetes and Fractures

Patients with T1DM have an increased risk of almost all types of fractures starting in childhood. Beginning at age 40, both men and women with T1DM have an increased hip fracture risk.[1] Studies show a 4-6-fold increase in hip fractures compared to age-matched non-diabetic controls.[2] This very high incidence of hip fractures is particular to T1DM and is not well understood. While bone mineral density (BMD) is slightly lower in T1DM, this is not sufficient to explain the much higher risk of fractures. This suggests that there are bone quality issues in addition to the lower bone density. Risk factors for fractures in patient with T1DM include longer duration of diabetes, female sex, poor glycemic control, and microvascular complications.[2] Furthermore, T1DM patients have increased morbidity and mortality from their fractures.[9]

T2DM and Fractures

With T2DM, the duration of diabetes is a very important factor for fractures. Patients with prediabetes are not at a higher risk of fracture. By 10 years of diabetes, there is a 40% increase in the risk of hip fracture.[3] Paradoxically, BMD is higher in patients with Type 2 diabetes.[4] This indicates a bone quality issue. It also means that uncorrected BMD or FRAX will underestimate fracture risk.[11] Risk factors for fractures in patients with T2DM include older age, lower BMD, lower body mass index (BMI) and diabetic complications.[3] Insulin use is also a risk factor for

fractures but it may just be a surrogate for other risks like duration of diabetes, complications, and hypoglycemia. Insulin is anabolic for the bone and increases density.

Is BMD Measurement Predictive of Fractures in T2DM?

BMD by dual energy x-ray absorptiometry DEXA at the hip and at the lumbar spine is our standard way of assessing fracture risk. However, we have stated that T2DM patients have higher bone densities but have more fractures.[11] Individuals with T1DM have lower bone densities but their fracture risk is higher than predicted from their bone density. BMD is useful for assessing fracture risk in patients with diabetes, but a correction to properly estimate the must be applied. If one subtracts 0.05 from the T-score of patients with more than 10 years of diabetes, the risk is better approximated.[2] For example, a T-score of -2.0 in a patient with T2DM would have the fracture risk of a T-score of -2.5 in a person without diabetes. This correction can be used with T1DM but there is less supporting data. Some DEXA machines can provide a Trabecular Bone Score in addition to BMD. This is a measurement of bone texture at the lumbar spine. Trabecular Bone Score averages lower in patient with T2DM and is more predictive of fracture risk.[13]

Is FRAX a Useful Tool for Patients With T2DM?

Similar to BMD, the FRAX underestimates fracture risk in patient with diabetes.[14] The FRAX calculator is available online here at no charge. One inputs patient information and receives the 10-year risk of major fractures and hip fractures. In general, a risk for major fracture of ≥20% or hip fracture of ≥3% indicates the need for osteoporosis drug therapy. Unfortunately, the free version does not provide a check box for diabetes. Various corrections have been advocated. One can subtract 0.5 from the T-score, check the box for rheumatoid arthritis or check the box for secondary osteoporosis.[15] In general, these adjustments should only be done for patients with a 10-year history of diabetes.[12] The latest version of FRAX (www.FraxPlus.org) does allow corrections of the risk by the presence of diabetes and the duration of diabetes. If the DEXA machine you use provides a Trabecular Bone Score, you can add this in to FraxPlus for a more accurate prediction of risk. The use of FraxPlus does require a fee.

Bone Quality and Diabetes

The traditional method of assessing bone quality was a bone biopsy to demonstrate microarchitecture and turnover. This is difficult for the patient and doctor, and not commonly done in clinical practice. Some advanced centres have High Resolution Peripheral Quantitative Computer Tomography. This is a small CT scanner that can examine an arm or a leg and provides resolution down to 60 microns. Studies show more cortical porosity in patients with T1DM and T2DM.[5] These microscopic holes weaken the bone. They may represent microvascular disease of the bone. These cortical pores are more common in diabetics with microvascular disease in the eyes and kidneys. Another mechanism for reduction in bone quality is advanced glycation end products (AGE's). This process is utilized with hemoglobin A1c (HbA1c) measurement. Proteins become glycated with exposure to glucose. When AGE's form on the T1DM collagen fibers, the bone becomes weaker and less flexible. The osteoclasts are less able to metabolize the bone. Bone resorption and bone formation decrease leading to a low turnover state; bone strength decreases.

The Effect of Diabetes Medication on BMD and Fractures

Several classes of medications for diabetes have been shown to affect BMD and fractures **(Table 1)**. Some studies with metformin show a lower risk of fractures while others suggest that it is neutral.[7] Sulphonylureas and insulin may slightly increase the risk of fractures but this could be due to hypoglycemia and falls as these agents do not decrease BMD. Thiazolidinediones (rosiglitazone and pioglitazone) have the most clearly documented negative effects on bone.[7] As PPAR gamma agonists, thiazolidinediones favour mesenchymal stem cell differentiation into adipocytes rather than osteoblasts.[6] DPP-4 and GLP-1 agonists appear to be neutral for bone.[2] The skeletal effects of SGLT-2 inhibitors are less clear and evolving. Some studies with canagliflozin (CANVAS) suggest a decrease in hip BMD and increased fractures.[2] However, a large meta-analysis and post-marketing surveillance trials have failed to show increased fractures in patients on SGLT-2 inhibitors.[8] The benefits of SGLT-2 inhibitors generally outweigh the risks to the skeleton.

Medication	BMD	Fracture Risk
Metformin	Neutral or increase	Neutral or decrease
Sulphonylureas	Neutral	Neutral or Increase
Insulin	Neutral	Neutral or Increase
Thiazolidinediones	Decrease	Increase
DPP-4 Inhibitors	Neutral or increase	Neutral or decrease
GLP-1 Agonists	Neutral or increase	Neutral or decrease
SGLT-2 Inhibitors	Neutral or decrease	Neutral

Table 1. The effect of medications for T2DM on BMD and fractures; courtesy of Timothy John O'Leary, MD, FRCPC

Does Improving HbA1c Decrease Fractures?

Improving HbA1c most likely decreases fractures, but this is difficult to study. The Accord Trial, which compared a standard control group with a mean A1c of 7.5%, with an intensive control group with an HbA1c of 6.5% did not show a difference in fractures over the four years of the trial.[19] However, both arms were under fairly good control. Epidemiological studies suggest that fracture risk increases when the HbA1c exceeds 8.5%.[19] We have many reasons for attempting to achieve good diabetic control and it should also improve bone health.

How Should We Treat Osteoporosis in Diabetic Patients?

In general, we should follow the same guidelines as we do for patients without diabetes. We are unlikely to see prospective randomized controlled trials of osteoporosis medications in patients with diabetes that are large enough and long enough to demonstrate a fracture reduction. Subgroup analysis of diabetic patients in studies of osteoporosis medications show trends of BMD and fractures to suggest a similar response to nondiabetics. In the FIT study, women were randomized to alendronate or placebo for three years. Diabetic women assigned to alendronate had a similar increase in spine and hip density as non-diabetic women on alendronate.[16] There is observational data showing that diabetic patients receiving raloxifene or bisphosphonates have a similar reduction in fracture to non-diabetic patients on these medications.[17] The FREEDOM Trial of denosumab showed improvement in BMD and fewer fractures in the subgroup with T2DM.[18]

Summary

Patients with both T1DM and T2DM are at increased risk of fractures. Hip fracture incidence is particularly high in patients with T1DM. The fracture risk exceeds the prediction from BMD and FRAX for both T1DM and T2DM, suggesting bone quality issues. Leading theories about the cause of the bone quality issues include increased cortical porosity and advanced glycolation end products. Aside from thiazolidinediones (rosiglitazone and pioglitazone), treatments for diabetes do not have a major effect on fractures. BMD and FRAX are useful for assessing fracture risk although corrections need to be applied to prevent underestimation of fracture risk. Diabetes patients can be treated with the medications approved for osteoporosis in patients without diabetes.

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