

Increased Bone Fragility in Diabetes Mellitus

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In 2021, 537 million, or one in ten, adults were living with diabetes mellitus. Diabetes increases bone fragility. However, the most commonly available absolute fracture risk calculators, like FRAX®, do not include diabetes as a clinical risk factor for fracture and may also underestimate fracture risk in type 2 diabetes where bone mineral density (BMD) is either increased or normal. Together with a lack of awareness of this increased fracture risk by clinicians, osteoporosis may be neglected as an important comorbidity of diabetes. The causes of bone fragility differ between type 1 and type 2 diabetes, and patients with type 1 diabetes have a higher fracture risk and lower BMD. Changes in bone microarchitecture tend to parallel changes in areal BMD except for trabecular bone score (TBS), which is reduced in both type 1 and type 2 diabetes (1). Obesity, chronic low-grade inflammation, changes in bone quality with accumulation of advanced glycation end products (AGEs), microvascular complications and an increased falls risk all contribute to the increased fracture risk.

In this regard the paper by Curtis et al. in the current issue of JBMR is very helpful in quantifying fracture risk in type 1 and type 2 diabetes and the effects of clinical, heel estimated BMD (eBMD) and biochemical risk factors (2). The investigators utilised the UK Biobank to study 498,949 women and men aged 40-69 years, of whom 1,836 had type 1 diabetes and 20,551 had type 2 diabetes. Patients with type 1 diabetes were on average 7 years younger than those with type 2 diabetes (55 vs 62 years). In their fully adjusted models, incorporating eBMD, fat mass, CRP and eGFR, type 1 and 2 diabetes were both associated with a significantly increased fracture risk. For type 1 diabetes the risk increase was almost three-fold (2.93) compared with a more modest risk increase for type 2 diabetes (1.25), which was similar by sex. Comorbidities and complications of diabetes were more common in type 1 than in type 2 diabetes. Duration of diabetes was important in determining fracture risk in type 2 diabetes with fracture risk only increasing after 5 years, indicating why earlier studies with a shorter duration of type 2 diabetes may not have identified an increase in fracture risk. Obesity was also a modifying factor in type 2 diabetes so that only overweight or obese individuals had an increase in fracture risk. Any type of microvascular complication was associated with increased fracture risk irrespective of the type of diabetes. Fracture risks were particularly elevated for participants with neuropathy and glomerular disorders, which increased fracture risks by two- or three-fold. The effect of diabetes on eBMD differed by sex and diabetes type. Type 1 diabetes was negatively associated with heel eBMD, more strongly in men than women (after adjustment for fat mass). On the other hand, type 2 diabetes was positively associated with heel eBMD in both women and men, with stronger associations observed in women (after adjustment for fat mass). Importantly, the increased risk of fracture with type 1 diabetes persisted even after eBMD adjustment.

The strength of this study is that with over 500,000 participants, the UK Biobank affords high statistical power to allow for comprehensive analyses and subgroup assessments, to study the association between diabetes and fractures. In this Biobank, diabetes is one of the most prevalent chronic noncommunicable conditions, with 22,387 cases reported at baseline (from 2006 to 2010) with a predicted 40,000 incident cases by 2023. These estimates of increased fracture risk in both type 1 and type 2 diabetes are therefore robust.

The clinical implications of these findings are important and clarify that fracture risk is modestly increased in type 2 diabetes as well as in type 1 diabetes. Currently, type 1 diabetes is one of the “secondary osteoporosis” options as an input variable into FRAX®, the most used

fracture risk calculator internationally. This assumes a BMD-dependent effect on increasing fracture while the current study also provides clear evidence for BMD-independent effects. These effects may be incurred by changes in bone quality related to diabetes duration, and accumulation of AGEs, akin to premature bone ageing. In support of this hypothesis, a bone biopsy study identified greater concentrations of an AGE, pentosidine crosslinks, in both cortical and trabecular bone from patients with type 2 diabetes compared with bone from a normal glucose tolerance group while fluorescent AGE cross-link density was also increased (3). Bone pentosidine content in patients with impaired glucose tolerance did not differ from those with normal glucose tolerance and was lower than in type 2 diabetes. Bone tissue AGEs increased with worsening glycemic control assessed by HbA1c. This indicates the greater AGE content observed in type 2 diabetes occurs with progressive diabetes and with worsening control. Cortical bone from patients with type 2 diabetes was stiffer and harder than that from normal individuals, increasing fragility.

Another clinical implication is that diabetes control should be optimised to avoid microvascular complications, particularly neuropathy and glomerular disorders, which increased fracture risk irrespective of the type of diabetes. Part of this increase in fracture risk may be mediated by falls, so patients with microvascular complications of diabetes may benefit from a falls risk assessment and prevention strategies.

The public health implications are that type 2 diabetes should now be included with type 1 diabetes in the next iteration of FRAX®, FRAX2®, reflecting both BMD dependent and independent effects on fracture risk. Currently suggested corrections to FRAX® to account for the increased fracture risk with type 2 diabetes have included substituting the risk factor of rheumatoid arthritis or increasing the patient's age by 10 years (4). BMD independent effects can be assessed clinically by measuring TBS and assessing diabetes control with a glycated hemoglobin measurement. The clinical role of pentosidine measurements has not been defined.

The current evidence that type 2 diabetes as well as type 1 diabetes is associated with fracture risk means that bone health should be assessed in all patients with diabetes. It also sharpens the focus on improving diabetes control to reduce microvascular complications and bone quality, both of which contribute to fracture risk in diabetes. Osteoporosis should no longer be neglected as an important comorbidity of diabetes.

References:

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UNCORRECTED MANUSCRIPT