Type 2 diabetes and fractures: more information is needed

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Received: 16 January 2013 / Accepted: 5 February 2013 / Published online: 24 February 2013
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Keywords Diabetes · Fracture prediction · Bone mineral density · Bone quality

Type 2 diabetes mellitus (T2D) is an exceedingly common chronic metabolic disorder that has an enormous impact on public health. Currently, T2D affects over 366 million adults worldwide and is projected to reach 552 million by 2030 [1]. Until recently, the list of target organs affected by T2D did not include the skeleton. Yet there is now substantial evidence that older adults with T2D have a higher risk of sustaining a hip (RR = 1.7) or any clinical (RR = 1.2) fracture [2], morbidities that have important ramifications given the epidemic rates of this disease. Surprisingly, despite the increased fracture risk, bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is generally higher in those with T2D [3]. In an analysis of three large prospective cohorts, BMD reliably predicted fracture risk in T2D, yet diabetics fractured at a *T* score that was higher by 0.6 than that of controls [4]. Similarly, two recent reports have shown that for a given fracture risk assessment (FRAX) probability, the risk of fracture among individuals with diabetes is higher than the risk in non-diabetics [4, 5]. Thus, although BMD and FRAX are able to predict fractures in T2D, both underestimate the actual fracture risk. This minimization may be partly explained by more frequent trauma, as diabetes is associated with an increased frequency of falls. However, even in studies of diabetes and fracture that control for fall

frequency, diabetes remains independently associated with increased fracture risk [6]. Thus, the paradox of increased fracture risk with high bone density remains unresolved. Because BMD and FRAX are central to fracture prediction, a consequence of this paradox is a lack of suitable methods to predict fracture risk in older adults with T2D.

In this issue of the Journal, Di Somma et al. [7] seek to address this issue by measuring the spinal deformity index (SDI), an index of fracture severity based on lumbar spine X-rays, in a group of 56 male and female T2D patients and 56 male and female controls. Consistent with prior reports, they found that morphometric vertebral fractures were more common in T2D than in controls (46 vs 17 %) and that more of the T2D patients fractured at *T* scores above −2.5 than did the controls (69 vs 10 %). The SDI measurement, a combination of the number of vertebral fractures and of the semiquantitative vertebral deformity scoring system of Genant et al. [8], was higher in T2D than in controls. The study concludes that the SDI measurement might be more useful than BMD for assessment of skeletal health in T2D.

The authors should be commended for carefully examining the spine fracture burden and its characteristics in T2D patients. In particular, their findings are strengthened by the BMI matching between T2D and controls, which eliminates the potentially confounding skeletal effects of obesity. Moreover, the examination of calciotropic indices suggests that, regardless of BMI, vitamin D levels are lower and PTH levels are higher in diabetics. Nevertheless, the study is hampered by certain notable limitations. Importantly, the BMD scores were actually lower in the diabetics at both the lumbar spine and femoral neck, arguing against the point that the SDI measurement is providing fracture risk information that is lacking from BMD alone. Moreover, the study has not addressed the

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question of whether similar data could be more easily obtained with DXA-based vertebral fracture assessment (VFA), a tool associated with wider clinical applicability and less radiation, cost, and inconvenience. Finally, the additional information provided by the SDI measurement in a diabetic patient who has already fractured is unclear. Presumably, once a vertebral fracture has occurred, bone quality can be unambiguously confirmed to be abnormal, regardless of a measure of fracture severity.

The primary contribution of this report is to highlight the need for better methodological approaches to assess bone strength in T2D. Accumulating evidence suggests that specific deficits are present in the diabetic skeleton, which cannot be detected by BMD. Drugs used to control hyperglycemia, especially thiazolidinediones (TZDs), are associated with increases in skeletal fragility [9]. In addition, trabecular bone score (TBS), a new imaging tool, may provide novel information in this regard. This measurement, which quantifies the local variation of gray levels in 2D projection images, is obtained after re-analyzing a DXA scan and accurately predicts fracture risk [10]. In a preliminary report, Leslie and colleagues showed that TBS measures in a large population of diabetics captured most of the diabetes-associated fracture risk and improved fracture prediction when combined with BMD [11]. Other recent reports suggest that deficits in cortical bone, as illustrated by increased intracortical porosity as measured via high-resolution peripheral computed tomography (HR-pQCT), are present in diabetic postmenopausal women who have sustained fragility fractures [12]. Additional skeletal material and dynamic derangements that are similarly undetectable by BMD may further contribute to diabetic skeletal fragility. In the organic bone matrix, accumulation of advanced glycation endproducts (AGEs), a consequence of chronic hyperglycemia, probably leads to abnormally brittle bone [13]. Recent reports also suggest that sclerostin, the inhibitor of the anabolic Wnt-signaling pathway, is increased in T2D in association with a decrease in bone formation [14] and that the inhibition of sclerostin in diabetic rats improves skeletal indices [15]. Further research is needed to investigate these lines of evidence and their utility for diabetic bone strength assessment.

As the incidence of diabetes continues to increase, it is necessary to understand the increased fracture risk in these patients. Use of the SDI could be a potentially relevant way to characterize the nature and severity of these fractures, but additional tools are needed to understand the pathophysiology of bone fragility before fracture occurrence in this growing population. As treatment for T2D improves, affected patients are likely to live longer, and skeletal concerns are likely to be magnified. It is time for skeletal complications to become part of the discussion of

the long-term outlook in T2D to offset serious challenges in this population as they age.

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