Diabetic Bone Disease – An Indian Snapshot

In addition to the conventional microvascular and macrovascular complications of diabetes mellitus, impairment in bone quality and an increased risk of pathological fractures have been recognized as important non-conventional chronic complication of living with diabetes mellitus. The term diabetic bone disease (DBD) is used interchangeably with diabetic osteopathy to document this complication. The increase in fracture risk among persons living with diabetes (PwD) is a combined result of microarchitectural bone damage, glycation, and alteration of the mechanical properties in bone-related proteins, decrease in bone density, and the increased incidence of falls among PwD. Along with an increased risk of fractures, PwD who suffer fractures also have poorer fracture healing and an increase in mortality following hip fractures.

Fracture Risk Among Persons with Diabetes

Among patients with type 1 diabetes mellitus (T1DM), a meta-analysis of six studies suggested a relative risk (RR) of 1.8 for fracture at any site compared to controls and an RR for 4.4 for hip fractures (RR of 3.67 in men vs. RR of 5.7 among women).[1] Compared to age-, sex-, and body mass index (BMI)-matched controls, patients with T1DM have lower bone mineral density (BMD).[2] The decline in BMD is likely a consequence of reduce insulin action on osteoblasts. Insulin action on osteoblasts promotes mitosis, prevents apoptosis, and reduces the noxious effect of hyperglycemia on bone formation.[3] Hyperglycemia *per se* leads to glycation of key bone proteins, including type 1 collagen and phospholipids, leading to the disruption of osteoblast adhesion to the matrix, thus increasing the fragility of the complex.[4] Bone mineralization is also impaired by hyperglycemia-related reduction in alkaline phosphatase activity [Figure 1]. Additionally, amylin deficiency seen with beta-cell destruction in T1DM further decreases BMD.[5] In this issue, Akhila Bhandarkar and colleagues from Kochi have studied a cohort of 51 young patients with T1DM (mean age 27 years) along with a similar number of controls. They assessed BMD along with body composition and bone turnover markers in both groups. There was no difference in lumbar spine BMD between the groups. There was a decrease in femoral neck BMD among young patients with T1DM compared to controls; however, it did not meet statistical significance due to the relative youth of the cohort and the small sample size.[6]

In contrast, patients with type 2 diabetes mellitus (T2DM) tend to have higher BMD at both the femoral neck and lumbar spine. A meta-analysis of 15 observational studies that included 3,437 patients with T2DM and over 19,000 controls suggested a pooled mean positive difference in BMD of 0.04 g/cm^2 at the femoral neck, 0.06 g/cm^2 at the hip, and 0.06 g/cm^2 at the spine.

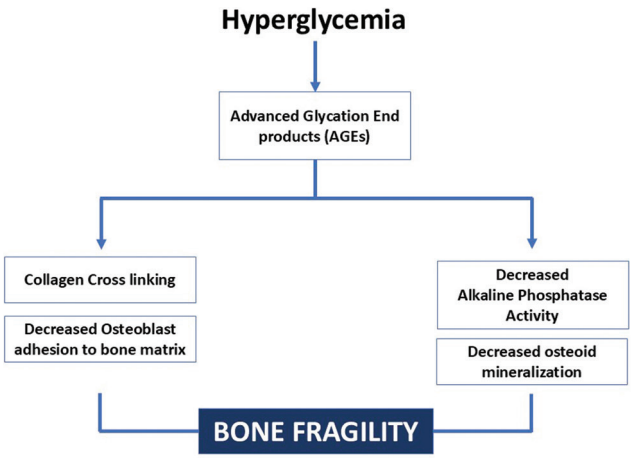

Figure 1: Bone fragility mechanisms induced by hyperglycaemia is common to both type 1 and type 2 diabetes mellitus

Meta-regression of the same data suggested that younger age, higher BMI, and male gender was associated with higher BMD in patients with T2DM.[7] Paradoxically, despite higher BMDs, patients with T2DM also have an increased risk of fractures. The RR of hip fracture among patients with T2DM is estimated to be 2.8 in men and 2.1 among women. The risk of developing a new hip fracture at a T-score of −1.9 in a postmenopausal woman with T2DM is similar to that of a woman without diabetes and a T-Score of −2.5.[8] The presence of chronic complications of T2DM further increases the risk of fractures. In a large Danish cohort, the presence of retinopathy (OR 2.1), neuropathy (OR 1.9), and nephropathy (OR 2.0) was associated with an increased risk of fractures.[9]

In this issue S Kumar and colleagues looked at post-menopausal women with T2DM in another cross-sectional observational study from Varanasi. They divided 62 women in the cohort based on the clinical presence of diabetic neuropathy (DN). Plain radiography and BMD measurements were obtained to assess the presence of vertebral fractures and osteoporosis. As expected, women with DN had longer duration of diabetes ($P < 0.0001$). Only two patients had prevalent vertebral fractures. Significant differences in lumbar spine BMD and T scores were seen and 68% of women with DN had osteoporosis at LS compared to 30% among women without DN (P-0.002). There were no differences in femoral neck BMD and T scores.[10]

Diagnosing Osteoporosis and Fracture Risk Among Patients with Diabetes

Assessing fracture risk using standard T-score cut offs with BMD in patients with T2DM suffers the risk of underestimation.

The higher areal BMD in subjects with T2DM implies that a low percentage of patients with T2DM and fragility fractures will have T-score in the osteoporotic range.[7] Despite BMD measurements systematically underestimating fracture risk it still stratifies fracture risk in older patients with diabetes mellitus.[11] It has been estimated in postmenopausal women with T2DM the T-score associated with hip fracture is 0.5 units higher than in a woman without T2DM. Because of these factors the Indian Society of Bone Mineral Research (ISMBR) and the American Diabetes Association have proposed a T-score of −2.0 should be considered as the cut off for diagnosis and treatment of osteoporosis in patients with T2DM as opposed to the standard −2.5.[12-14]

The fracture risk assessment tool (FRAX) score does not include T2DM as a parameter in its risk assessment of major osteoporotic fractures. T1DM is included among the conditions leading to secondary osteoporosis in the algorithm. Therefore, FRAX would underestimate the ten-year risk of major osteoporotic fracture among patients with T2DM. Two strategies have been employed by experts in the algorithm to improve the prediction of fracture risk in patients with T2DM. The first one is to consider T2DM equivalent to a diagnosis of rheumatoid arthritis in the algorithm, and the second one is to increase the subject's age by 10 years in the presence of T2DM. The newer version of FRAX, called FRAXplus, is likely to incorporate the presence and duration of T2DM in its risk stratification.[15]

Unlike standard areal BMD assessment, trabecular bone score (TBS) at the spine tends to be lower among patients with T2DM and T1DM than controls. Moreover, unlike BMD, TBS was better in those with good glucose control compared to those with poor glucose control.[12] In this issue Tanushi Aggarwal and colleagues from Chandigarh assessed areal BMD and TBS in a cohort of 202 postmenopausal women. Half of the cohort had T2DM. Among the 101 controls, 43 subjects had prediabetes and the remaining 58 had normal glucose tolerance. There was no difference in BMD score at the lumbar spine, neck of femur or forearm in the three groups. In contrast as expected the TBS scores were significantly lower in the women with T2DM when compared to the women with normal glucose tolerance or prediabetes. TBS was also inversely co-related with current HbAic and with duration of diabetes. The paper confirms the superiority of TBS assessment, among Asian women with T2DM in comparison with BMD assessments.[16]

Beyond BMD and TBS this issue also includes an excellent review by Kripa Cherian and colleague of newer dual-energy X-ray absorptiometry techniques including assessment of hip structural analysis and bone strain index in clinical practice. These additional tools they suggest maybe of use in patients with T2DM and obesity.[17]

Therapy in Diabetic Bone Disease

Currently there are no randomized controlled trials directly evaluating efficacy of current anti-osteoporotic therapies in PwD. Clinical evidence regarding efficacy in PwD are provided by the *post hoc* subgroup analysis of trials in osteoporosis. *Post hoc* analysis of the fracture intervention trial (FIT) among post-menopausal women with T2DM suggested similar BMD gains as in women without T2DM with alendronate treatment.[18] Limited evidence currently, available suggests that most anti-osteoporosis drugs have similar efficacy in osteoporotic patients with and without diabetes.

Studies with bone turnover markers in PwD have suggested reduction in both bone formation and resorption. A large meta-analysis involving 66 studies suggested that serum levels of C-terminal cross linked telopeptide (bone resorption marker), osteocalcin and procollagen type 1 amino-terminal propertied (bone formation markers) were found to be lower in PwDs compared to subjects without diabetes. This suggests that DBD is a low turnover disease.[19] This highlights the superiority of bone formation agents in treating diabetic bone disease compared to anti-resorptive treatment. The narrative review by Harsh Durgia and colleagues from Puducherry in this issue summarizes the current knowledge of anabolic agents in treatment of diabetic bone disease.[20]

Beyond the Bone

Beyond bone fragility and fracture risk, other musculoskeletal manifestations of diabetes mellitus (MMDM) are highly prevalent and cause considerable morbidity, pain and significant decline in quality of life. They include syndromes of limited joint mobility due to the fibro-proliferation (diabetic chieroarthopathy, Dupuytren's contracture, adhesive capsulitis and trigger finger), neuropathy related joint disorders (Charcot's arthropathy, carpal tunnel syndrome, diabetic amyotrophy), diabetic muscle infarction, and diffuse idiopathic skeletal hyperostosis (DISH).[21] This issue of the journal also includes a first of its kind community-based study from Kelita George and colleagues from Kochi documenting the prevalence of MMDMs excluding osteoporosis using clinical methods. Almost half of the adults with diabetes (44.8%) had some sort of MMDMs. Osteoarthritis was commonest. Adhesive capsulitis (frozen shoulder) was clinically prevalent in 12% of PwDs.[22]

The six papers on DBD and beyond in this special issue of the journal, I hope, will help focus attention on the unconventional skeletal complications of diabetes and offer a snapshot of the current research on the subject from our country. Hopefully, this will also trigger better studies and interventions that lead to a better quality of life for PwDs in India.

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Access this article online	
Quick Response Code:	Website: https://journals.lww.com/indjem/
	DOI: 10.4103/ijem.ijem_75_25

How to cite this article: Jacob JJ. Diabetic bone disease – An Indian snapshot. Indian J Endocr Metab 2025;29:1-3.