Indian J Med Res 150, November 2019, pp 425-428
DOI: 10.4103/ijmr.IJMR_1920_19

Quick Response Code:

Editorial

Diabetes mellitus, vitamin D & osteoporosis: Insights

Globally, diabetes affects around 415 million people, and its prevalence is likely to increase to 640 million by 2040[1]. The current estimates of prevalence of diabetes in India are 8.8 per cent with wide regional variations related to rural or urban dwellings[2]. The prevalence of diabetes within India, during 15 yr of assessments, was 4.3 per cent in Bihar, 4.5 per cent in Meghalaya and further higher in the southern Indian States[2]. Urban areas have a 2-3 times higher prevalence than the rural areas. An interesting observation in the urban areas is higher risk of diabetes among the low socio-economic groups than the affluent counterparts[2]. There is increasing awareness about common problems of bone health *i.e.,* vitamin D deficiency (VDD) and osteoporosis. The interrelation between bone health and diabetes is an emerging new area for clinicians.

VDD was considered to be rare among Indians. However, studies indicated that hypovitaminosis D was not unusual among healthy indoor subjects[3-5]. Skin complexion, poor sun exposure among indoor workers and vegetarian food explain the VDD among indoors despite sunny climate[6,7]. Calcium intake, crucial for bone health, is also deficient by upto 30 per cent in urban and tribal areas[8]. Osteoporosis is characterized by reduced bone mass and altered bone microarchitecture, resulting in decreased bone strength and an increased risk of fractures. One in three women and one in five men experience an osteoporotic fracture in their lifetime[9]. With increasing life expectancy, osteoporosis is likely to be a major health concern in India[10,11]. The prevalence of osteoporosis based on bone mineral density (BMD) was 22 per cent at femoral neck and 39 per cent at lumbar spine in 1560 postmenopausal women in rural south India[10], whereas 'DeVOS' study observed 17.1 per cent prevalence of osteoporosis among north Indian females of more than 50 yr age[11].

Fragility fractures are common in type 1 and type 2 diabetes. The incidence of hip fractures in patients with type 1 diabetes mellitus (T1DM) is six-fold higher than that in general population. Similarly, hip fractures are 2.5-fold higher in type 2 diabetes mellitus (T2DM)[12]. Cross-sectional studies on Indian population have estimated 20-35 per cent prevalence of osteoporosis in patients with T2DM, with females affected two times more than the males[13]. Hip fractures are more common with diabetes when compared to vertebral fractures[14]. Patients with T2DM have a higher risk of fractures than the non-diabetic population for a given BMD. Microarchitectural abnormalities of bone predispose patients with diabetes to fragility fractures. These abnormalities are difficult to measure and are often independent of BMD. Bone fragility is, therefore, an underestimated problem in diabetic patients. Bone turnover markers are relatively low in patients with diabetes, and the actual fracture rates in diabetic population are higher than those predicted by fracture risk assessment tool (FRAX).

The pathogenesis of osteoporosis in T1DM involves decreased peak bone mass due to deficiency of insulin and insulin-like growth factors, leading to inhibition of osteoblast growth, inactivation of p27 (responsible for osteoblastogenesis) and poor collagen synthesis[15]. Collagen type 1 alpha 1 (COL1A1) gene and vitamin D receptor gene polymorphisms are other contributors to decreased BMD in T1DM[16,17]. Besides, T1DM can be associated with other predisposing conditions such as Graves' disease, celiac disease, amenorrhoea, delayed puberty and eating disorders[17]. A complex pathophysiological interaction exists between T2DM and bone health due to several factors including the direct effect of T2DM on bone metabolism and strength, indirect effects of antidiabetic medication-induced altered bone metabolism, and

This editorial is published on the occasion of the World Diabetes Day - November 14, 2019.

retinopathy and neuropathy associated increased risk for falls and hence, subsequent fractures. The bone changes in T2DM are linked with obesity and hyperglycaemia which activate interleukin-6 (IL-6) and osteoclast-mediated resorption, accumulation of advanced glycation end products on collagen, reduced cross linking of collagen and glycosuria, leading to hypercalciuria and decreased total body calcium[17]. Serum osteoprotegerin, which binds to RANKL (receptor activator of nuclear factor kappa B ligand), is elevated in patients with diabetes, thus leading to suppression of bone remodelling. Wnt β-catenin pathway inactivation is another factor for reduced bone mass in diabetes[18].

Though it is reasonable to screen diabetic patients for osteoporosis, the diagnostic criteria for osteoporosis in diabetes are challenging. The World Health Organization defines osteoporosis as a BMD score of −2.5 or less[19]. With fractures occurring at higher BMD, there is a need to assess other parameters reflecting bone microarchitecture quality in diabetes[19,20]. Trabecular bone score determined from the pixel grey analysis of dual-energy X-ray absorptiometry (DXA) images is a novel method to assess bone microarchitecture which may help to identify the patients at risk of fractures but with normal BMD[20]. Other methods for assessing bone health include microarchitecture analysis by quantitative computed tomography (CT), high-resolution peripheral quantitative CT, high-resolution magnetic resonance imaging (MRI) and micro-CT and hip structural analysis using DXA. Among various drugs used in the management of diabetes, thiazolidinediones (TZDs) are associated with increased risk of fractures[21]. TZDs stimulate nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ), induce differentiation of multipotent mesenchymal stem cells into adipocytes, channelling away from bone osteoblast precursors, and also increase osteoblast apoptosis. Incretin-based drugs [glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] might exert potentially beneficial effects on bone by direct or indirect action on thyroid C-cells producing calcitonin, that suppresses bone resorption[22]. There has been concern regarding increased fracture risk associated with use of sodium-glucose transport protein 2 (SGLT2) inhibitors in diabetes[23]. However, the subject awaits further studies related to bone microarchitecture, bone resorption markers and changes in calcium and phosphate homeostasis, circulating fibroblast growth factor 23 (FGF23), parathyroid hormone and 1,25-dihydroxyvitamin D.

Initial observational studies indicated an inverse correlation between serum vitamin D status and prevalence of diabetes, and also a possible association between poor vitamin D status and increased progression from pre-diabetes to diabetes. The worsening of glycaemic control in diabetic patients during winter was also attributed to lowering of vitamin D levels during those months. Till recently, these notions were driving clinicians to consider routine supplementation of vitamin D to patients with diabetes mellitus. Two recent independent double-blinded randomized controlled trials have shown no beneficial role of vitamin D supplementation in glycaemic outcomes including prevention of diabetes[24,25]. Similarly, Wallace *et al*[26], showed absence of any effect of vitamin D supplementation on insulin resistance, beta cell dysfunction and glycaemic control in diabetic patients. Thus, it seems vitamin D has no major-independent role in glycaemic control among patients with diabetes.

General management principles of osteoporosis in diabetes include good glycaemic control, prevention of hypoglycaemia and falls and exercise programmes to improve overall muscle and bone strength. The Institute of Medicine recommends that all adults receive vitamin D at a dose of 600 IU/day in the age bracket of 51-70 yr and 800 IU/day for those more than 70 yr[27]. The recommendations for elemental calcium are 1200 mg for all females above 50 yr and males above 70 yr and 1000 mg for males in the age range of 51-70 yr[27]. A meta-analysis of 81 randomized trials showed no beneficial effect of vitamin D supplementation in the prevention of fractures or falls in adults or clinically meaningful effects on BMD[28]. Currently, there are no separate guidelines for the initiation of anti-osteoporosis medications in diabetes. The available evidences support the use of both anti-resorptive and anabolic agents in these patients with bisphosphonates being the first-choice[29]. Denosumab can be employed in those with impaired renal function. However, the potential benefit of these agents in patients at high-risk for fractures with near-normal BMD and normal or low bone turnover markers is unproven. The advent of new molecules such as sclerostin antibodies which can improve the bone microstructure and strength might help improve diabetes associated fragility.

The skeletal control of energy metabolism is another upcoming area in bone health and diabetes. Undercarboxylated form of osteocalcin (OC) improves glucose metabolism through multiple mechanisms including increase in pancreatic beta cell proliferation, insulin secretion, insulin sensitive glucose utilization and energy expenditure[30]. Reciprocally, the action of insulin on osteoblastic receptors activates osteoclastic activity and increased undercarboxylated OC, resulting in a feed forward loop[30].

Thus, the area of bone health in DM requires in-depth research in multiple areas such as alteration in bone quality, methods to investigate perturbed bone microarchitecture, diagnostic criteria for osteoporosis and choice of anti-osteoporotic medicines for best bone health. Further, there is a need to monitor the effect of antidiabetic medicines including pioglitazones, newer GLP analogues and SGLT2 inhibitors on the parameters of bone quality and strength to identify the effect of these medicines on bone health in diabetes.

***Conflicts of Interest*:** None.

Ravinder Goswami[1,*] & Abilash Nair[2]
[1]Department of Endocrinology & Metabolism,
All India Institute of Medical Sciences,
New Delhi 110 029 &
[2]Department of Endocrinology & Metabolism,
Government Medical College,
Thiruvananthapuram 695 011, Kerala, India
[*]*For correspondence*:
gosravinder@hotmail.com

Received October 31, 2019

References

1. International Diabetes Federation. *IDF Diabetes Atlas*, 8th ed.; 2017. Available from: *https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html*, accessed on November 19, 2019.
2. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, *et al*. Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol* 2017; *5* : 585-96.
3. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. *Am J Clin Nutr* 2000; *72* : 472-5.
4. Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, *et al.* Vitamin D and bone mineral density status of healthy schoolchildren in Northern India. *Am J Clin Nutr* 2005; *82* : 477-82.
5. Ray D, Goswami R, Gupta N, Tomar N, Singh N, Sreenivas V. Predisposition to vitamin D deficiency osteomalacia and rickets in females is linked to their 25(OH)D and calcium intake rather than vitamin D receptor gene polymorphism. *Clin Endocrinol* (*Oxf*) 2009; *71* : 334-40.
6. Saha S, Goswami R, Ramakrishnan L, Vishnubhatla S, Mahtab S, Kar P, *et al.* Vitamin D and calcium supplementation, skeletal muscle strength and serum testosterone in young healthy adult males: Randomized control trial. *Clin Endocrinol* (*Oxf*) 2018; *88* : 217-26.
7. Goswami R, Saha S, Sreenivas V, Singh N, Lakshmy R. Vitamin D-binding protein, vitamin D status and serum bioavailable 25(OH)D of young Asian Indian males working in outdoor and indoor environments. *J Bone Miner Metab* 2017; *35* : 177-84.
8. Harinarayan CV, Akhila H. Modern India and the tale of twin nutrient deficiency-calcium and vitamin D-nutrition trend data 50 years-retrospect, introspect, and prospect. *Front Endocrinol* (*Lausanne*) 2019; *10* : 493.
9. Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med* 2016; *374* : 254-62.
10. Binu AJ, Cherian KE, Kapoor N, Jebasingh FK, Asha HS, Paul TV. Bone Health after fifth decade in rural ambulatory South Indian postmenopausal women. *Indian J Community Med* 2019; *44* : 205-8.
11. Marwaha RK, Tandon N, Gupta Y, Bhadra K, Narang A, Mani K, *et al*. The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS). *Arch Osteoporos* 2012; *7* : 201-7.
12. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: The Nurses' Health Study. *Diabetes Care* 2006; *29* : 1573-8.
13. Sharma B, Singh H, Chodhary P, Saran S, Mathur SK. Osteoporosis in otherwise healthy patients with type 2 diabetes: A prospective gender based comparative study. *Indian J Endocrinol Metab* 2017; *21* : 535-9.
14. Ahmed LA, Joakimsen RM, Berntsen GK, Fønnebø V, Schirmer H. Diabetes mellitus and the risk of non-vertebral fractures: The Tromsø study. *Osteoporos Int* 2006; *17* : 495-500.
15. Nyman JS, Even JL, Jo CH, Herbert EG, Murry MR, Cockrell GE, *et al.* Increasing duration of type 1 diabetes perturbs the strength-structure relationship and increases brittleness of bone. *Bone* 2011; *48* : 733-40.
16. Hampson G, Evans C, Petitt RJ, Evans WD, Woodhead SJ, Peters JR, *et al*. Bone mineral density, collagen type 1 alpha 1 genotypes and bone turnover in premenopausal women with diabetes mellitus. *Diabetologia* 1998; *41* : 1314-20.
17. Jackuliak P, Payer J. Osteoporosis, fractures, and diabetes. *Int J Endocrinol* 2014; *2014* : 820615.
18. Gaudio A, Privitera F, Battaglia K, Torrisi V, Sidoti MH, Pulvirenti I, *et al*. Sclerostin levels associated with inhibition

of the Wnt/β-catenin signaling and reduced bone turnover in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2012; *97* : 3744-50.

19. Leslie WD, Aubry-Rozier B, Lamy O, Hans D; Manitoba Bone Density Program. Trabecular bone score and diabetes-related fracture risk. *J Clin Endocrinol Metab* 2013; *98* : 602-9.
20. Yamamoto M, Yamauchi M, Sugimoto T. Prevalent vertebral fracture is dominantly associated with spinal microstructural deterioration rather than bone mineral density in patients with type 2 diabetes mellitus. *PLoS One* 2019; *14* : e0222571.
21. Liao HW, Saver JL, Wu YL, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: A systematic review and meta-analysis. *BMJ Open* 2017; *7* : e013927.
22. Yang J, Huang C, Wu S, Xu Y, Cai T, Chai S, *et al.* The effects of dipeptidyl peptidase-4 inhibitors on bone fracture among patients with type 2 diabetes mellitus: A network meta-analysis of randomized controlled trials. *PLoS One* 2017; *12* : e0187537.
23. Azharuddin M, Adil M, Ghosh P, Sharma M. Sodium-glucose cotransporter 2 inhibitors and fracture risk in patients with type 2 diabetes mellitus: A systematic literature review and Bayesian network meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 2018; *146* : 180-90.
24. Angellotti E, D'Alessio D, Dawson-Hughes B, Nelson J, Cohen RM, Gastaldelli A, *et al*. Vitamin D supplementation in patients with type 2 diabetes: The vitamin D for established type 2 diabetes (DDM2) study. *J Endocr Soc* 2018; *2* : 310-21.
25. Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, Aroda VR, *et al.* Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 2019; *381* : 520-30.
26. Wallace HJ, Holmes L, Ennis CN, Cardwell CR, Woodside JV, Young IS, *et al*. Effect of vitamin D3 supplementation on insulin resistance and β-cell function in prediabetes: A double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2019; *110* : 1138-47.
27. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al*. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab* 2011; *96* : 53-8.
28. Bolland MJ, Grey A, Avenell A. Effects of Vitamin D supplementation on musculoskeletal health: A systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 2018; *6* : 847-58.
29. Ferrari SL, Abrahamsen B, Napoli N, Akesson K, Chandran M, Eastell R, *et al*. Diagnosis and management of bone fragility in diabetes: An emerging challenge. *Osteoporos Int* 2018; *29* : 2585-96.
30. Liu JM, Rosen CJ, Ducy P, Kousteni S, Karsenty G. Regulation of glucose handling by the skeleton: Insights from mouse and human studies. *Diabetes* 2016; *65* : 3225-32.