Indian Journal of Orthopaedics (2023) 57:S209–S217
https://doi.org/10.1007/s43465-023-01049-4

REVIEW ARTICLE

Diabetes and Osteoporosis

Trupti Nagendra Prasad[1] · Durairaj Arjunan[1] · Rimesh Pal[1] · Sanjay Kumar Bhadada[1]

Received: 20 October 2023 / Accepted: 7 November 2023 / Published online: 12 December 2023

Abstract
Bone fragility is an emerging complication of diabetes. People with diabetes are at a significantly higher risk of fractures compared to the general population. Bone fragility occurs in diabetes as a result of complex and poorly understood mechanisms occurring at the cellular level contributed by vascular, inflammatory and mechanical derangements. Bone mineral density (BMD) as assessed by DEXA is low in type 1 diabetes. Type 2 diabetes has a high risk of fracture despite a normal to raised BMD. DEXA thus underestimates the fracture risk in diabetes. Data are scare regarding the efficacy of the available therapies in this low bone turnover state.

Keywords Osteoporosis · Bone mineral density · Diabetes mellitus · Bone fragility

Introduction

Diabetes affects nearly 422 million people globally and its prevalence is on rise, likely to reach to 642 million by 2040 [1]. The prevalence of diabetes in India is as high as 7.3% [2]. Diabetes is one of the important cause of secondary osteoporosis. A cross-sectional study of 252 patients with type 2 diabetes mellitus (T2D) in a tertiary care institute in India demonstrated a prevalence of 33% of osteoporosis and 40% of osteopenia [3]. Considering the high prevalence of diabetes, the burden of bone disease in diabetes is also huge. Along with the known micro- and macro-vascular complications of diabetes, bone fragility has emerged as a new complication. Unfortunately, it is often an ignored and undermanaged complication of diabetes. With the ageing population, the prevalence of both diabetes and osteoporosis is expected to increase. Thus, osteoporosis and diabetes are now considered as the dual pandemics.

The pathophysiological mechanism between bone fragility and diabetes is poorly understood. Various factors in diabetes can have an impact on bone homeostasis by impairing the function of osteoclasts, osteoblasts and osteocytes or affecting the structural properties of the bone.

✉ Sanjay Kumar Bhadada
bhadadask@gmail.com

[1] Department of Endocrinology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Epidemiology of Osteoporosis in Diabetes

Patients with diabetes are at an increased risk of fractures compared to general population. Diabetic patients have 0.5 to 2 times increased risk of any osteoporotic fracture compared to control with an odds ratio [OR] = 1.3, 95% CI 1.2–1.5 for T1D and 1.2, 95% CI 1.1–1.3 for T2D. For spine fracture, the OR was significant for type 1 diabetes mellitus (T1D) but not significant for T2D. With regard to hip fracture, the OR was 1.7, 95% CI 1.3–2.2 for T1D, and 1.4, 95% CI 1.2–1.6 for T2D [4]. In a metanalysis, patients with diabetes have a pooled relative risk of hip fractures amongst all the included studies which was 2.07 (95% CI 1.83–2.33) compared to patients without diabetes [5]. In a community-based study in India of 57,117 people with age ≥ 20 years, prevalence of fractures was significantly more in diabetics (4%) compared to non-diabetics (2.5%) [6].

The risk of fracture is more in T1D compared to T2D. According to the IOWA Women's Health study, T1D women have 12 times more probability of sustaining hip fractures than non-diabetic women. In addition, T2D women have 1.7 times chance of having hip fracture compared to non-diabetic women even with a normal bone mineral density (BMD) [7]. The risk of fracture is higher in T1D due to long disease duration and also hip fractures occurs around 15 years earlier compared to control population [8]. The risk is comparatively lower in T2D, but as the duration of diabetes, insulin requirement and complications increases, the fracture risk worsens by up to twofold [9].

Pathophysiology of Osteoporosis and Bone Fragility in Diabetes

T1D is a known cause of low BMD; however, BMD may be low, normal or even high in patients with T2D. The pathophysiology of bone fragility is thus complex.

(1) Advanced glycation end-products (AGEs) and bone strength

AGEs such as pentosidine (PEN) and carboxymethyl lysine are produced through non-enzymatic condensation reactions between amino groups and carbonyl groups. Enzymatic crosslinking is essential for maintaining bone strength by increasing collagen stiffness, whereas non-enzymatic crosslinking is deleterious to bone quality [10]. In patients with diabetes, there is an increase in non-enzymatic crosslinking of collagen by AGEs. Studies have shown that increased urinary and serum concentrations of PEN correlated with an increased risk of fractures, independent of BMD, in patients with both T1D and T2D [11–13]. This could explain the reason for an increased bone fragility in patients with diabetes with an apparently normal BMD.

Apart from an effect on the mechanical properties of the bone, AGEs significantly inhibit osteoblast proliferation, increase apoptosis of osteoblast, increase expression of sclerostin and decrease RANKL [14–16]. In addition, AGEs inhibit parathyroid hormone (PTH) secretion [17]. All these alterations ultimately lead to a state of suppressed bone turnover, characteristic of diabetes.

(2) Interactions at level of mesenchymal stem cells

The bone marrow consists of 2 population of cells, i.e. osteoblasts and adipocytes, derived from a common precursor, the mesenchymal stem cells (MSC). Two systems, the Wingless-related integration site (Wnt) signalling and the peroxisome proliferator-activated receptors-γ (PPAR-γ) pathways, modulate the balance between adipogenesis and osteogenesis. Activation of Wnt signalling pathway favours osteogenesis whilst inhibiting adipogenesis, whereas PPAR-γ promotes adipogenesis and inhibits osteogenesis [18]. Marrow adipogenesis is found to be associated with decreased bone formation, lower BMD and increased risk of fracture in several studies. Other factors in diabetes which can promote adipogenesis includes glucocorticoids use, advancing age, obesity and immobility [19].

(3) RANK/RANKL/OPG system

Diabetes and obesity are a state of chronic inflammation where the inflammatory cytokines increase bone loss. The association is bi-directional. osteoprotegerin (OPG) is found to be associated with increased atherosclerotic parameters and fat mass [20]. Receptor activator of nuclear factor-κB ligand (RANKL) has been found to worsen insulin resistance and predict the risk of development of T2D [21].

(4) Alterations in Wnt signalling pathway

Sclerostin and Dickkopf-1, inhibitors of Wnt signalling pathway has been shown to be higher in T2D compared to control population as a result of hyperglycemia. Thus, bone formation is impaired in T2D.

(5) Insulin deficiency

Insulin has anabolic action on osteoblasts. This widely explains the BMD differences in T1D and T2D. T1D has insulin deficiency and thus low bone mass, which improves with insulin therapy [22]. T2D with insulin resistance and hyperinsulinemia has a higher BMD [23]. Insulin promotes the proliferation and differentiation of osteoblast by increasing Runt-related transcription factor 2 (RUNX2) activity and increases collagen synthesis [24]. T1D has low IGF-1 levels, which further impairs bone formation as insulin-like growth factor-1 (IGF-1) is known to be anabolic to bone [25].

(6) BMI and bone

Studies have shown a positive correlation between body mass index (BMI) and bone mass. A study in conducted in North India showed that a normal body mass index (18.5–22.9 kg/m^2) had higher prevalence of osteoporosis and osteopenia compared to BMI ≥25 kg/m^2 [26]. Beneficial effect of weight specially fat mass is due to the increased mechanical loading on weight-bearing skeleton mediated by alterations in mechanostat function of osteocytes and changes in locally produced bone growth factors [27]. Weight loss has been found to increase bone resorption and lower BMD. However, when weight loss is accompanied by exercise training, it attenuates this bone loss [28].

(7) Role of incretins (Gut-bone axis)

Glucagon-like peptide-1 (GLP-1) receptors are present on the immature osteoblasts and stromal cells of bone marrow. It promotes osteogenesis and decreases differentiation of MSC to adipocytes [29]. GLP-1 may inhibit postprandial bone resorption via increasing calcitonin. Gastric inhibitory polypeptide (GIP) and Glucagon-like peptide-2 (GLP-2) also inhibits postprandial bone resorption. In diabetes, this incretin response is decreased or lost. Thus, incretin-based therapies may have a positive effect on bone health.

(8) Role of other hormones

Adipokines (leptin and adiponectin) have shown to have positive effects on bone by promoting osteogenesis and inhibiting osteoclastogenesis. Resistin levels are elevated in diabetics and a study has shown an inverse

relationship between resistin and lumbar spine BMD in males, though the effect was small [30].

(9) Inflammatory cytokines

Interleukin I-6, IL-1, tumour necrosis factor (TNF) as well as reactive oxidation species are increased in T2D and obesity due to marrow adiposity and insulin resistance. In addition, as a part of generalised immune activation in T1D, these cytokines are raised. This leads to an increased survival and function of osteoclasts and inhibits bone formation.

Thus, diabetes is a state of low bone turnover. The main cause of bone fragility is low bone formation.

Risk Factors for Osteoporosis and Bone Fragility in Diabetes

(1) Age and gender: old age and female gender have higher risk of bone fragility.

(2) Hyperglycemia.

There are various mechanisms how impaired blood glucose leads to poor bone health.

(a) Increased oxidative stress: raised levels of advanced glycation end-products have negative impact on structural proteins like type 1 collagen by forming crosslinks between the fibres and posttranslational modification. These ultimately results in reduced mechanical properties and strength of bone [31, 32]. In addition, increased levels of urinary pentosidine in diabetics were found to be associated with a 42% increase risk of new clinical fractures compared to non-diabetics [11].

(b) Hyperglycemia per se leads to impaired function of osteoblasts.

(c) Hyperglycemia-induced acidosis increases bone resorption [33].

In general, poor glycemic control is associated with higher bone fragility compared to those with adequate glycemic control [34]. A glycated haemoglobin (HbA1c) of > 7.9% in T1D and > 9% in T2D has shown to significantly increase the risk of fractures [35, 36].

(3) Presence of chronic complications of diabetes and comorbidities:

Risk of fractures is higher is patients with complications of diabetes. Retinopathy decreases vision, and balance and gait are impaired by neuropathy leading to increased risk of falls and fractures. In addition, impaired mechanical stress can occur due to neuropathy, sarcopenia and myopathy. Diabetic nephropathy is perhaps the most common complication that is associated with bone fragility, right from the early stages. It is mainly due to increased bone turnover as result of alterations in calcium, phosphate, vitamin D and parathyroid hormone levels [37]. Comorbidities associated with T2D such as ischaemic heart disease and hypertension, per se has detrimental effects on bone [38, 39].

(4) Duration of diabetes: low BMD is particularly seen in diabetics with disease duration > 5 years.

(5) Poor accrual of peak bone mass: as T1D affects relatively younger people when the skeletal growth is still incomplete, it may lead to poor gain in the peak bone mass. In addition, due to rising trend of obesity, T2D prevalence is increasing amongst relatively younger population, which impairs achieving adequate bone mass.

(6) Hypogonadism: around 1/3rd of T2D men are deficient in testosterone [40]. Testosterone inhibits osteoclastogenesis and decreases marrow adiposity. Increased oestrogen levels in T2D contribute to raised BMD. Early menopause and lesser use of hormone replacement therapy is also an important cause of osteoporosis in India.

(7) Nutritional status and physical activity: protein and calcium deficiency and decreased physical activity also adds to poor bone health. A study showed that patients with vitamin D deficiency (levels < 20 ng/ml) have a higher risk of osteopenia and osteoporosis, OR 7.8, 95% CI 3.1,19.5 and OR 7.3, 95% CI 2.8, 18.8, respectively, compared to those with vitamin D ≥ 30 ng/ml [41]. Prevalence of vitamin D deficiency is particularly high in India, more so in people with diabetes [42]. However, results of other studies are conflicting. The presence of malabsorptive conditions like celiac disease further worsens bone health. Sarcopenia in persons with diabetes also increases risk of falls and fractures [43].

Other risk factors such as family and personal history of fractures are similar to general population.

Effect of Glucose-Lowering Therapies on Bone (Table 1)

(1) Insulin: fracture risk is higher in T2D patients on insulin therapy compared to those not on insulin [44]. As such, insulin therapy does not per se has negative effects on bone. These studies may have been confounded by the fact that T2D who are requiring insulin usually have a longer disease duration, higher prevalence of complications. In addition, risk of hypoglycemia is higher in patients on insulin, which could lead to increased risk of falls [45]. A study conducted by

Table 1 Summary of effect of glucose-lowering therapies on bone

Drug	Effect on bone	Comments
(1) Insulin	Anabolic to bone	Increased risk of falls due to hypoglycemia. Increased fracture risk could be a confounding effect of long disease duration, poor glycemic control and chronic complications
(2) Insulin secretagogues	Neutral	May increase risk of falls by causing hypoglycemia
(3) Metformin	Neutral or slightly positive	–
(4) Thiazolidinediones	Decrease BMD	Increase bone marrow adipogenesis and decrease osteoblastic differentiation
(5) GLP-1 agonists	Neutral or favourable	–
(6) Dipeptidyl peptidase 4 (DPP4) inhibitors	Neutral or favourable	–
(7) SGLT2 inhibitors	Increased fracture risk	Data are mainly with canagliflozin

Raj et al. in 74 patients of T2D showed that treatment with insulin and sulfonylureas were associated with a lower risk of osteoporosis, possibly due to bone anabolic actions of insulin [46].

(2) Thiazolidinediones: TZDs acts as PPAR-gamma ligands, which promotes adipogenesis and inhibits osteogenesis in vitro [47]. They also increase the RANKL expression and recruitment of hematopoietic stem cells to form osteoclasts. Most of the studies suggesting increased bone fragility and fracture with TZDs are with rosiglitazone. ADOPT (A Diabetes Outcome Progression Trial) was the first study suggesting a negative impact of TZD on bone. In this study, the hazard ratio for fracture with rosiglitazone was 2.13 compared to glyburide and 1.81 compared to metformin [48]. Data are scare and conflicting regarding the now commonly used TZD, pioglitazone [49–51].

(3) Metformin: Data from the ADOPT trial did not show an increased risk of fracture with metformin or glyburide [48]. Some studies have shown a positive effect of metformin on bone health [4, 52].

(4) Sulfonylureas: as they carry a potential risk of hypoglycemia, sulfonylureas should be used with caution in elderly osteoporotic population. In a study on fracture risk in elderly male population, there was a 66% higher risk of non-vertebral fractures in sulfonylurea users compared to control [9].

(5) SGLT2 inhibitors: affects bone indirectly via altering the calcium and phosphate metabolism, causing increased excretion of calcium and leading to secondary hyperparathyroidism. In the CANVAS study, there was a significant higher risk of fracture in the canagliflozin group as compared to control arm (4 vs 2.6%). One of the factor responsible for higher fracture incidence in this could be presence of cardiovascular comorbidity. Furthermore, data from pooled analysis of non-CANVAS studies did not show an elevated fracture risk with canagliflozin [53].

(6) GLP-1 agonists: studies have suggested a neutral effect of GLP-1 agonists on bone [54, 55].

(7) Dipeptidyl peptidase 4 (DPP4) inhibitors: considering almost negligible risk of hypoglycemia and favourable effect of incretins on bone, these agent are one of the recommended drug for T2D adults with osteoporosis. However, further studies are needed.

Diagnosis of Osteoporosis and Bone Fragility in Diabetes

(1) Dual-energy X-ray absorptiometry (DEXA): it is the most commonly used technique for diagnosing osteoporosis. BMD is low in T1D, whereas it is normal or even high in T2D. In general, T2D has a mean 5–10% higher BMD compared to non-diabetics [56]. Fracture Risk Assessment Tool (FRAX) is a commonly used parameter to assess fracture risk in population. T1D is one of the secondary cause of osteoporosis in FRAX tool and the risk calculated has interpretation similar to non-diabetic population. However, FRAX underestimate the risk of fracture in T2D by 30–50% [57]. Thus, for diagnosing osteoporosis in T2D, a T-score of − 2.0 is advocated as compared to a score of − 2.5 for general population [58]. In addition, it is recommended to treat patients of T2D at a lower FRAX cutoffs. Various adjustment in calculating FRAX for T2D have been suggested: (1) trabecular bone score adjustment (TBS), (2) adding rheumatoid arthritis input, (3) decreasing the femoral neck T-score by 0.5 in the BMD input, and (4) increasing age by 10 years [59].

(2) Trabecular bone score (TBS): it is used to assess the microarchitecture of bone and thus bone quality. A TBS of ≤ 1.2 suggest degraded microarchitecture. TBS can be used as a parameter to adjust FRAX in T2D.

(3) High-resolution peripheral quantitative computed tomography (HR-pQCT): it is a 3-dimensional imag-

ine technique which provides volumetric BMD in a compartment-specific manner. Trabecular and cortical bone volume has been shown to be low in TID and this correlates with poor glycemic control and microvascular complications [60]. People with T2D have an increased cortical porosity compared to control. A study in post-menopausal women with T2D of long duration (> 10 years) by in-vivo microindentation testing of tibia showed a reduced bone mineral strength [61].

(4) Bone biopsy: analysis of bone histomorphometry in T1D with good glycemic control showed normal levels of bone-formation indices in T1D compared to control. However, there was increase in levels of AGEs deposition with non-enzymatic collagen crosslinks suggesting poor bone quality [62, 63]. This increased non-enzymatic crosslinking of collagen that is also found in T2D. The collagen-crosslink results in increased brittleness of bones.

(5) Bone turnover markers (BTM): BTM are not useful for diagnosis of osteoporosis. Studies have shown a reduced levels of osteocalcin and raised levels of bone alkaline phosphatase in T2D [64, 65]. Increased levels of sclerostin, an inhibitor of bone formation, has been found both in-vivo and in-vitro studies in T2D [14, 25]. BTM have not found to be useful to predict fracture risk in diabetes [66]. BTM have a role in the follow-up of patient who are receiving anti-osteoporotic therapy.

Other screening tools such as SCORE (Simple Calculated Osteoporosis Risk Evaluation), OSTA (osteoporosis self-assessment tool for Asians), and MORES (male osteoporosis risk estimation score) have been validated for Indian population [67, 68].

Falls risk assessment is a useful tool to identify patients who are at a high-risk for fracture and initiate early intervention to prevent the same. One such scoring system is FRAS (Falls risk assessment score), a self-reported tool to screen older patients for risk of falls. The scores ranges from 0 to 6.5 and more the score, higher is the risk of falls [69].

Treatment of Osteoporosis in Diabetics: How It is Different from Persons Without Diabetes

The treatment options for osteoporosis are same for diabetics as for those without diabetes. However, as diabetes is a low bone turnover state, further suppression of bone turnover by anti-resorptive therapies like bisphosphonates or denosumab might not be efficacious in this setting. Available data in this regard are limited to post hoc analysis or observational studies, with a limited number of patients with diabetes. Currently, there no randomised controlled trial published, focussing exclusively on diabetic population.

Post hoc analysis of Raloxifene Use for the Heart (RUTH) and Multiple outcomes of Raloxifene Evaluation (MORE) trial found a similar efficacy of raloxifene in improving BMD in diabetics compared to non-diabetics [70, 71]. In the Fracture Intervention Trail (FIT) trial of alendronate, the BMD gains were similar in diabetes versus non-diabetes patients. However, details regarding fracture risk reduction are not available [72]. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) trial, denosumab reduced the risk of vertebral fractures in patients with diabetes by 80% compared to placebo. However, there was an apparent increase in non-vertebral fractures which was found only during the initial 3 years of study and was not observed in the 10-year extension of the trial [73]. A study by Vestergaard et al. on a large cohort treated with anti-resorptives showed no significant differences in fracture risk reduction in patients with diabetes compared to control [74].

As diabetes is a state of low bone turnover, anabolic therapies seem to be an attractive option. A post hoc analysis of Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) study, for efficacy of teriparatide in patients with and without diabetes, the gain in spine BMD did not differ between the 2 groups, + 0.040 (95% CI 0.017–0.063) g/cm^2 vs. + 0.047(0.042–0.053) g/cm^2, respectively, $P = 0.542$, whereas there was a significantly higher gain in BMD at the femoral neck in T2D patients, + 0.034 (0.011–0.057)g/cm^2 vs. + 0.004 (− 0.001–0.009) g/cm^2, respectively, $P = 0.014$ [75]. In the post hoc analysis of Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) trial, abaloparatide lead to a significant improvement in lumbar spine BMD (8.9% versus 1.3%), femoral neck BMD (2.6 vs − 0.2%), and TBS (3.72 vs − 0.56%) compared to placebo [76]. As the sclerostin levels are high in diabetes, romosozumab is a potential therapy for osteoporosis in diabetes. However, data are scare and also there are cardiovascular concerns with this agent.

Recommendations for Osteoporosis in Diabetes

International Osteoporosis Foundation (IOF) provides recommendation for osteoporosis in diabetes [77]. BMD assessment by DEXA in T2D is recommended starting at 5 years of diabetes duration in the absence of other risk factors like steroids use or old age [77]. If fracture risk is low, repeat DEXA at interval of 3–5 years. As osteoporotic fractures occurs at a relatively younger age in India compared to the western population, India Society for Bone and Mineral Research (ISBMR) guidelines recommend screening starting at an earlier age [78].

For T1D, International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends performing DEXA in late adolescents, especially in the presence of celiac disease, poor glycemic control or any complications of diabetes.

Regarding prevention and management, lifestyle modifications to maintain a normal BMI are advisable. If a patient is overweight or obese, weight loss should be attained through a combined calorie restriction and an increased physical activity. Exercise particularly resistance and endurance training helps to prevent sarcopenia and falls [79]. Education regarding fall prevention should be an integral part of osteoporosis management. IOF suggests six steps for fall prevention. This includes techniques to keep home safe by ensuring adequate lightings and grab bars, use of non-slippery footwear, correction of any visual defects, exercise and healthy eating habits and reviewing medications which may predispose to falls [80].

Vitamin D should be maintained $\geq$ 20 ng/ml. Patients as per requirement should receive 1000–2000 IU of vitamin D per day to maintain target levels. Calcium supplements should be prescribed if the dietary calcium intake is less than 1.2 g per day [78].

In general, the indications for initiating anti-osteoporotic therapy in diabetes are same as in people without diabetes. Only difference is the threshold should be decreased to T-score $\leq$ -2 at either lumbar spine or femoral neck [78].

Once a patient develops fracture, after the necessary intervention for the fracture is performed, anti-osteoporotic therapy should be started before discharging the patient from the hospital [81]. The fracture healing is often delayed and post-intervention complications are also higher in patients with diabetes. In general, fracture associated mortality particularly from hip fracture is higher in T2D versus patients without diabetes [82].

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed Consent For this type of study, informed consent is not required.

References

1. 7th edition | IDF Diabetes Atlas [Internet]. [cited 2023 Jun 23]. Available from: https://diabetesatlas.org/atlas/seventh-edition/
2. Anjana, R. M., Deepa, M., Pradeepa, R., Mahanta, J., Narain, K., Das, H. K., et al. (2017). Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR–INDIAB population-based cross-sectional study. *The Lancet Diabetes & Endocrinology., 5*(8), 585–596.
3. Zhou, Y., Li, Y., Zhang, D., Wang, J., & Yang, H. (2010). Prevalence and predictors of osteopenia and osteoporosis in postmenopausal Chinese women with type 2 diabetes. *Diabetes Research and Clinical Practice, 90*(3), 261–269.
4. Vestergaard, P., Rejnmark, L., & Mosekilde, L. (2005). Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia, 48*(7), 1292–1299.
5. Fan, Y., Wei, F., Lang, Y., & Liu, Y. (2016). Diabetes mellitus and risk of hip fractures: A meta-analysis. *Osteoporosis International, 27*(1), 219–228.
6. Kaur, P., Anjana, R. M., Tandon, N., Singh, M. K., Mohan, V., & Mithal, A. (2020). Increased prevalence of self-reported fractures in Asian Indians with diabetes: Results from the ICMR-INDIAB population based cross-sectional study. *Bone, 135*, 115323.
7. Nicodemus, K. K., Folsom, A. R., Iowa Women's Health Study. (2001). Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care, 24*(7), 1192–1197.
8. Weber, D. R., Haynes, K., Leonard, M. B., Willi, S. M., & Denburg, M. R. (2015). Type 1 Diabetes Is Associated With an Increased Risk of Fracture Across the Life Span: A Population-Based Cohort Study Using The Health Improvement Network (THIN). *Diabetes Care, 38*(10), 1913–1920.
9. Napoli, N., Strotmeyer, E. S., Ensrud, K. E., Sellmeyer, D. E., Bauer, D. C., Hoffman, A. R., et al. (2014). Fracture Risk in Diabetic Elderly Men: The MrOS Study. *Diabetologia, 57*(10), 2057–2065.
10. Depalle, B., Qin, Z., Shefelbine, S. J., & Buehler, M. J. (2015). Influence of cross-link structure, density and mechanical properties in the mesoscale deformation mechanisms of collagen fibrils. *Journal of the Mechanical Behavior of Biomedical Materials., 52*, 1–13.
11. Schwartz, A. V., Garnero, P., Hillier, T. A., Sellmeyer, D. E., Strotmeyer, E. S., Feingold, K. R., et al. (2009). Pentosidine and increased fracture risk in older adults with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism, 94*(7), 2380–2386.
12. Neumann, T., Lodes, S., Kästner, B., Franke, S., Kiehntopf, M., Lehmann, T., et al. (2014). High serum pentosidine but not esRAGE is associated with prevalent fractures in type 1 diabetes independent of bone mineral density and glycaemic control. *Osteoporosis International, 25*(5), 1527–1533.
13. Yamamoto, M., Yamaguchi, T., Yamauchi, M., Yano, S., & Sugimoto, T. (2008). Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism, 93*(3), 1013–1019.
14. Ichiro, T. K., Yamaguchi, T., Kanazawa, I., & Sugimoto, T. (2015). Effects of high glucose and advanced glycation end products on the expressions of sclerostin and RANKL as well as apoptosis in osteocyte-like MLO-Y4-A2 cells. *Biochemical and Biophysical Research Communications., 461*(2), 193–199.
15. Kume, S., Kato, S., Ichi, Y. S., Inagaki, Y., Ueda, S., Arima, N., et al. (2005). Advanced Glycation End-Products Attenuate Human Mesenchymal Stem Cells and Prevent Cognate Differentiation Into Adipose Tissue, Cartilage, and Bone. *Journal of Bone and Mineral Research., 20*(9), 1647–1658.
16. Franke, S., Rüster, C., Pester, J., Hofmann, G., Oelzner, P., & Wolf, G. (2011). Advanced glycation end products affect growth and function of osteoblasts. *Clinical and Experimental Rheumatology, 29*(4), 650–660.
17. Yamamoto, T., Ozono, K., Miyauchi, A., Kasayama, S., Kojima, Y., Shima, M., et al. (2001). Role of advanced glycation end products in adynamic bone disease in patients with diabetic

nephropathy. *American Journal of Kidney Diseases, 38*(4 Suppl 1), S161-164.
18. Napoli, N., Strollo, R., Paladini, A., Briganti, S. I., Pozzilli, P., & Epstein, S. (2014). The alliance of mesenchymal stem cells, bone, and diabetes. *International Journal of Endocrinology., 2014*, 690783.
19. Rosen, C. J., & Bouxsein, M. L. (2006). Mechanisms of disease: Is osteoporosis the obesity of bone? *Nature Clinical Practice Rheumatology, 2*(1), 35–43.
20. Waluś-Miarka, M., Katra, B., Fedak, D., Czarnecka, D., Miarka, P., Woźniakiewicz, E., et al. (2011). Osteoprotegerin is associated with markers of atherosclerosis and body fat mass in type 2 diabetes patients. *International Journal of Cardiology., 147*(2), 335–336.
21. Kiechl, S., Wittmann, J., Giaccari, A., Knoflach, M., Willeit, P., Bozec, A., et al. (2013). Blockade of receptor activator of nuclear factor-κB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. *Nature Medicine, 19*(3), 358–363.
22. Campos Pastor, M. M., López-Ibarra, P. J., Escobar-Jiménez, F., Serrano Pardo, M. D., & García-Cervigón, A. G. (2000). Intensive insulin therapy and bone mineral density in type 1 diabetes mellitus: A prospective study. *Osteoporosis International, 11*(5), 455–459.
23. Stolk, R. P., Van Daele, P. L., Pols, H. A., Burger, H., Hofman, A., Birkenhäger, J. C., et al. (1996). Hyperinsulinemia and bone mineral density in an elderly population: The Rotterdam Study. *Bone, 18*(6), 545–549.
24. Eghbali-Fatourechi, G. Z., Lamsam, J., Fraser, D., Nagel, D., Riggs, B. L., & Khosla, S. (2005). Circulating osteoblast-lineage cells in humans. *New England Journal of Medicine, 352*(19), 1959–1966.
25. Ardawi, M. S. M., Akhbar, D. H., Alshaikh, A., Ahmed, M. M., Qari, M. H., Rouzi, A. A., et al. (2013). Increased serum sclerostin and decreased serum IGF-1 are associated with vertebral fractures among postmenopausal women with type-2 diabetes. *Bone, 56*(2), 355–362.
26. Aleti, S., Pal, R., Dutta, P., Dhibar, D. P., Prakash, M., Khandelwal, N., et al. (2020). Prevalence and predictors of osteopenia and osteoporosis in patients with type 2 diabetes mellitus: A cross-sectional study from a tertiary care institute in North India. *Int J Diabetes Dev Ctries., 40*(2), 262–268.
27. Frost, H. M., Ferretti, J. L., & Jee, W. S. (1998). Perspectives: Some roles of mechanical usage, muscle strength, and the mechanostat in skeletal physiology, disease, and research. *Calcified Tissue International, 62*(1), 1–7.
28. Shah, K., Armamento-Villareal, R., Parimi, N., Chode, S., Sinacore, D. R., Hilton, T. N., et al. (2011). Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. *Journal of Bone and Mineral Research, 26*(12), 2851–2859.
29. Sanz, C., Vázquez, P., Blázquez, C., Barrio, P. A., Alvarez, M. D. M., & Blázquez, E. (2010). Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow. *American Journal of Physiology. Endocrinology and Metabolism, 298*(3), E634-643.
30. Oh, K. W., Lee, W. Y., Rhee, E. J., Baek, K. H., Yoon, K. H., Kang, M. I., et al. (2005). The relationship between serum resistin, leptin, adiponectin, ghrelin levels and bone mineral density in middle-aged men. *Clinical Endocrinology-Oxford, 63*(2), 131–138.
31. Viguet-Carrin, S., Roux, J. P., Arlot, M. E., Merabet, Z., Leeming, D. J., Byrjalsen, I., et al. (2006). Contribution of the advanced glycation end product pentosidine and of maturation of type I collagen to compressive biomechanical properties of human lumbar vertebrae. *Bone, 39*(5), 1073–1079.
32. Strollo, R., Rizzo, P., Spoletini, M., Landy, R., Hughes, C., Ponchel, F., et al. (2013). HLA-dependent autoantibodies against post-translationally modified collagen type II in type 1 diabetes mellitus. *Diabetologia, 56*(3), 563–572.
33. Frassetto, L. A., & Sebastian, A. (2012). How metabolic acidosis and oxidative stress alone and interacting may increase the risk of fracture in diabetic subjects. *Medical Hypotheses, 79*(2), 189–192.
34. Gregorio, F., Cristallini, S., Santeusanio, F., Filipponi, P., & Fumelli, P. (1994). Osteopenia associated with non-insulin-dependent diabetes mellitus: What are the causes? *Diabetes Research and Clinical Practice, 23*(1), 43–54.
35. Li, C. I., Liu, C. S., Lin, W. Y., Meng, N. H., Chen, C. C., Yang, S. Y., et al. (2015). Glycated Hemoglobin Level and Risk of Hip Fracture in Older People with Type 2 Diabetes: A Competing Risk Analysis of Taiwan Diabetes Cohort Study. *Journal of Bone and Mineral Research, 30*(7), 1338–1346.
36. Leanza, G., Maddaloni, E., Pitocco, D., Conte, C., Palermo, A., Maurizi, A. R., et al. (2019). Risk factors for fragility fractures in type 1 diabetes. *Bone, 125*, 194–199.
37. Goliat, E., Marusza, W., Ostrowski, K., & Lipińska, A. (1998). Microalbuminuria as a risk factor for diabetic osteopathy in patients with IDDM and renal sufficiency. *Polskie Archiwum Medycyny Wewnetrznej, 100*(2), 111–118.
38. Laroche, M., Pécourneau, V., Blain, H., Breuil, V., Chapurlat, R., Cortet, B., et al. (2017). Osteoporosis and ischemic cardiovascular disease. *Joint, Bone, Spine, 84*(4), 427–432.
39. Hu, Z., Yang, K., Hu, Z., Li, M., Wei, H., Tang, Z., et al. (2021). Determining the association between hypertension and bone metabolism markers in osteoporotic patients. *Medicine, 100*(24), e26276.
40. Wang, C., Jackson, G., Jones, T. H., Matsumoto, A. M., Nehra, A., Perelman, M. A., et al. (2011). Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care, 34*(7), 1669–1675.
41. Prevalence and predictors of osteopenia and osteoporosis in patients with type 2 diabetes mellitus: a cross-sectional study from a tertiary care institute in North India | SpringerLink [Internet]. [cited 2023 Jun 23]. Available from: https://link.springer.com/article/https://doi.org/10.1007/s13410-019-00786-3
42. Aggarwal, A., Ram, S., Garg, A., Pal, R., Bhansali, A., Singh, P., et al. (2021). Metabolic Bone Profile of Healthy Adult North Indian Population from Chandigarh Urban Bone Epidemiological Study (CUBES). *Indian Journal of Clinical Biochemistry, 36*(1), 67–73.
43. Pal, R., Aggarwal, A., Singh, T., Sharma, S., Khandelwal, N., Garg, A., et al. (2020). Diagnostic cut-offs, prevalence, and biochemical predictors of sarcopenia in healthy Indian adults: The Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES). *European Geriatric Medicine., 11*(5), 725–736.
44. Monami, M., Cresci, B., Colombini, A., Pala, L., Balzi, D., Gori, F., et al. (2008). Bone fractures and hypoglycemic treatment in type 2 diabetic patients: A case-control study. *Diabetes Care, 31*(2), 199–203.
45. Schwartz, A. V., Vittinghoff, E., Sellmeyer, D. E., Feingold, K. R., Rekeneire, N. D., Strotmeyer, E. S., et al. (2008). Diabetes-Related Complications, Glycemic Control, and Falls in Older Adults. *Diabetes Care, 31*(3), 391–396.
46. Raj, J. P., Venkatachalam, S., Shekoba, M., Norris, J. J., & Amaravati, R. S. (2019). Conventional antidiabetic agents and bone health: A pilot case-control study. *Perspectives in Clinical Research, 10*(4), 177–182.
47. Botolin, S., Faugere, M. C., Malluche, H., Orth, M., Meyer, R., & McCabe, L. R. (2005). Increased Bone Adiposity and Peroxisomal

Proliferator-Activated Receptor-γ2 Expression in Type I Diabetic Mice. *Endocrinology, 146*(8), 3622–3631.
48. Kahn, S. E., Haffner, S. M., Heise, M. A., Herman, W. H., Holman, R. R., Jones, N. P., et al. (2006). Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *New England Journal of Medicine, 355*(23), 2427–2443.
49. Loke, Y. K., Singh, S., & Furberg, C. D. (2009). Long-term use of thiazolidinediones and fractures in type 2 diabetes: A meta-analysis. *Canadian Medical Association Journal., 180*(1), 32–39.
50. Grey, A., Bolland, M., Fenwick, S., Horne, A., Gamble, G., Drury, P. L., et al. (2014). The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: A randomized controlled trial. *European Journal of Endocrinology., 170*(2), 255–262.
51. Bone, H. G., Lindsay, R., McClung, M. R., Perez, A. T., Raanan, M. G., & Spanheimer, R. G. (2013). Effects of pioglitazone on bone in postmenopausal women with impaired fasting glucose or impaired glucose tolerance: A randomized, double-blind, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism, 98*(12), 4691–4701.
52. Melton, L. J., III., Leibson, C. L., Achenbach, S. J., Therneau, T. M., & Khosla, S. (2008). Fracture Risk in Type 2 Diabetes: Update of a Population-Based Study. *Journal of Bone and Mineral Research., 23*(8), 1334–1342.
53. Watts, N. B., Bilezikian, J. P., Usiskin, K., Edwards, R., Desai, M., Law, G., et al. (2016). Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. *Journal of Clinical Endocrinology and Metabolism, 101*(1), 157–166.
54. Gilbert, M. P., Michel, M., JJuul, H., Alan, G., Baeres, F. M. M., Henrik, T., et al. (2016). Comparison Of The Long-Term Effects Of Liraglutide And Glimepiride Monotherapy On Bone Mineral Density In Patients With Type 2 Diabetes. *Endocrine Practice, 22*(4), 406–411.
55. Driessen, J. H. M., Van Onzenoort, H. A. W., Starup-Linde, J., Henry, R., Burden, A. M., Neef, C., et al. (2015). Use of Glucagon-Like-Peptide 1 Receptor Agonists and Risk of Fracture as Compared to Use of Other Anti-hyperglycemic Drugs. *Calcified Tissue International, 97*(5), 506–515.
56. de Liefde, I. I., van der Klift, M., de Laet, C. E. D. H., van Daele, P. L. A., Hofman, A., & Pols, H. A. P. (2005). Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporosis International., 16*(12), 1713–1720.
57. Giangregorio, L. M., Leslie, W. D., Lix, L. M., Johansson, H., Oden, A., McCloskey, E., et al. (2012). FRAX underestimates fracture risk in patients with diabetes. *Journal of Bone and Mineral Research, 27*(2), 301–308.
58. Schwartz, A. V., Vittinghoff, E., Bauer, D. C., Hillier, T. A., Strotmeyer, E. S., Ensrud, K. E., et al. (2011). Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA, 305*(21), 2184–2192.
59. Leslie, W. D., Johansson, H., McCloskey, E. V., Harvey, N. C., Kanis, J. A., & Hans, D. (2018). Comparison of Methods for Improving Fracture Risk Assessment in Diabetes: The Manitoba BMD Registry. *Journal of Bone and Mineral Research, 33*(11), 1923–1930.
60. Shanbhogue, V. V., Hansen, S., Frost, M., Jørgensen, N. R., Hermann, A. P., Henriksen, J. E., et al. (2015). Bone Geometry, Volumetric Density, Microarchitecture, and Estimated Bone Strength Assessed by HR-pQCT in Adult Patients With Type 1 Diabetes Mellitus. *Journal of Bone and Mineral Research., 30*(12), 2188–2199.
61. Farr, J. N., Drake, M. T., Amin, S., Melton, L. J., McCready, L. K., & Khosla, S. (2014). In Vivo Assessment of Bone Quality in Postmenopausal Women With Type 2 Diabetes: Bone Quality In Women With T2D. *Journal of Bone and Mineral Research, 29*(4), 787–795.
62. Armas, L. A. G., Akhter, M. P., Drincic, A., & Recker, R. R. (2012). Trabecular bone histomorphometry in humans with Type 1 Diabetes Mellitus. *Bone, 50*(1), 91–96.
63. Farlay, D., Armas, L. A. G., Gineyts, E., Akhter, M. P., Recker, R. R., & Boivin, G. (2016). Nonenzymatic Glycation and Degree of Mineralization Are Higher in Bone From Fractured Patients With Type 1 Diabetes Mellitus. *Journal of Bone and Mineral Research, 31*(1), 190–195.
64. Sarkar, P. D., & Choudhury, A. B. (2013). Relationships between serum osteocalcin levels versus blood glucose, insulin resistance and markers of systemic inflammation in central Indian type 2 diabetic patients. *European Review for Medical and Pharmacological Sciences, 17*(12), 1631–1635.
65. Kulkarni, S. V., Meenatchi, S., Reeta, R., Ramesh, R., Srinivasan, A. R., & Lenin, C. (2017). Association of Glycemic Status with Bone Turnover Markers in Type 2 Diabetes Mellitus. *International Journal of Applied & Basic Medical Research, 7*(4), 247–251.
66. Napoli, N., Conte, C., Eastell, R., Ewing, S. K., Bauer, D. C., Strotmeyer, E. S., et al. (2020). Bone Turnover Markers Do Not Predict Fracture Risk in Type 2 Diabetes. *Journal of Bone and Mineral Research, 35*(12), 2363–2371.
67. Cherian, K. E., Kapoor, N., Shetty, S., Naik, D., Thomas, N., & Paul, T. V. (2018). Evaluation of Different Screening Tools for Predicting Femoral Neck Osteoporosis in Rural South Indian Postmenopausal Women. *Journal of Clinical Densitometry, 21*(1), 119–124.
68. Satyaraddi, A., Shetty, S., Kapoor, N., Cherian, K. E., Naik, D., Thomas, N., et al. (2017). Performance of risk assessment tools for predicting osteoporosis in south Indian rural elderly men. *Archives of Osteoporosis, 12*(1), 35.
69. El Miedany, Y., El Gaafary, M., Toth, M., Palmer, D., & Ahmed, I. (2011). Falls risk assessment score (FRAS): Time to rethink. *Journal of Clinical Gerontology and Geriatrics., 2*(1), 21–26.
70. Johnell, O., Kanis, J. A., Black, D. M., Balogh, A., Poor, G., Sarkar, S., et al. (2004). Associations between baseline risk factors and vertebral fracture risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. *Journal of Bone and Mineral Research, 19*(5), 764–772.
71. Ensrud, K. E., Stock, J. L., Barrett-Connor, E., Grady, D., Mosca, L., Khaw, K. T., et al. (2007). Effects of Raloxifene on Fracture Risk in Postmenopausal Women: The Raloxifene Use for The Heart Trial. *Journal of Bone and Mineral Research, 23*(1), 112–120.
72. Keegan, T. H. M., Schwartz, A. V., Bauer, D. C., Sellmeyer, D. E., & Kelsey, J. L. (2004). Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the fracture intervention trial. *Diabetes Care, 27*(7), 1547–1553.
73. Ferrari, S., Eastell, R., Napoli, N., Schwartz, A., Hofbauer, L. C., Chines, A., et al. (2020). Denosumab in postmenopausal women with osteoporosis and diabetes: Subgroup analysis of FREEDOM and FREEDOM extension. *Bone, 134*, 115268.
74. Vestergaard, P., Rejnmark, L., & Mosekilde, L. (2011). Are Antiresorptive Drugs Effective Against Fractures in Patients with Diabetes? *Calcified Tissue International, 88*(3), 209–214.
75. Schwartz, A. V., Pavo, I., Alam, J., Disch, D. P., Schuster, D., Harris, J. M., et al. (2016). Teriparatide in patients with osteoporosis and type 2 diabetes. *Bone, 1*(91), 152–158.
76. Dhaliwal, R., Hans, D., Hattersley, G., Mitlak, B., Fitzpatrick, L. A., Wang, Y., et al. (2020). Abaloparatide in Postmenopausal Women With Osteoporosis and Type 2 Diabetes: A Post Hoc Analysis of the ACTIVE Study. *JBMR Plus., 4*(4), e10346.
77. Ferrari, S. L., Abrahamsen, B., Napoli, N., Akesson, K., Chandran, M., Eastell, R., et al. (2018). Diagnosis and management of

bone fragility in diabetes: An emerging challenge. *Osteoporosis International, 29*(12), 2585–2596.
78. Bhadada, S. K., Chadha, M., Sriram, U., Pal, R., Paul, T. V., Khadgawat, R., et al. (2021). The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults. *Archives of Osteoporosis, 16*(1), 102.
79. Hovanec, N., Sawant, A., Overend, T. J., Petrella, R. J., & Vandervoort, A. A. (2012). Resistance training and older adults with type 2 diabetes mellitus: Strength of the evidence. *Journal of Aging Research, 2012*, 284635.
80. Falls prevention | International Osteoporosis Foundation [Internet]. [cited 2023 Jul 5]. Available from: https://www.osteoporosis.foundation/health-professionals/fragility-fractures/falls-prevention
81. Conley, R. B., Adib, G., Adler, R. A., Åkesson, K. E., Alexander, I. M., Amenta, K. C., et al. (2020). Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition. *Journal of Bone and Mineral Research, 35*(1), 36–52.
82. Tebé, C., Martínez-Laguna, D., Carbonell-Abella, C., Reyes, C., Moreno, V., Diez-Perez, A., et al. (2019). The association between type 2 diabetes mellitus, hip fracture, and post-hip fracture mortality: A multi-state cohort analysis. *Osteoporosis International, 30*(12), 2407–2415.