Review article

Clinical aspects and management of osteoporosis and fragility fractures in patients with diabetes

CrossMark

Manju Chandran*

Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, Singapore

A B S T R A C T

Both diabetes and osteoporosis are assuming epidemic proportions throughout the world. Accumulating data suggest that both types 1 and 2 diabetes are associated with an increased risk of fragility fractures. This increased risk appears to be largely independent of bone mineral density (BMD) which is most often noted to be low in type 1 diabetes and normal or increased in type 2 diabetes. This review explores the clinical characteristics of bone fragility in patients with diabetes and highlights studies that have evaluated BMD and fracture prediction tools in these patients. It also briefly reviews the current management principles of osteoporosis in diabetes, with special emphasis on the impact of diabetes medications on bone health as well as explores the efficacy of currently available antiosteoporosis pharmacotherapy in the diabetic population.

© 2017 The Korean Society of Osteoporosis. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Both diabetes and osteoporosis are increasing rapidly worldwide. This epidemic appears to be more markedly manifest in the Asian continent. By the year 2030 it is predicted that the prevalence of diabetes in Asian countries will be more than double the rates in 2000 [1]. Similarly, it has been forecasted that 50% of all hip fractures in the world will be occurring in Asia by the year 2050 [2,3].

Accumulating data suggest that both types 1 and 2 diabetes may be associated with an increased risk of osteoporotic fractures. Whether this reflects the coexistence of the 2 common diseases or whether involvement of the skeleton should be regarded as a unique complication of diabetes, is a subject of intense debate and study. A meta-analysis involving 11 cohort studies from Western populations documented a risk elevation of 1.8 (95% confidence interval [CI], 1.3–2.4) among people with diabetes relative to individuals without a history of diabetes [4]. This increased risk of osteoporotic fractures in diabetics has been noted in Asians also, with data from the Singapore Chinese Health Study showing that the risk of osteoporotic hip fracture, after adjustment for other risk factors, was almost double amongst people with diabetes

compared with people without diabetes (relative risk [RR], 1.98; 95% CI, 1.71–2.29) [5]. The risk appears to be higher in patients with type 1 diabetes when compared to those with type 2 diabetes. A pooled RR of any osteoporotic fracture of 3.16 (95% CI, 1.51–6.63; P = 0.002) was found in a meta-analysis that included 27,300 patients with type 1 diabetes and 4,364,125 subjects without it [6]. A RR for hip fracture of 1.4 (95% CI, 1.2–1.6) in type 2 diabetesand that of 1.7 (95% CI, 1.3–2.2) in type 1 diabetes has been reported in a large case-control study from Denmark [7]. In this study, interestingly, type 2 diabetes was associated with a significant increase in forearm fractures (odds ratio [OR], 1.2; 95% CI, 1.0–1.5) while type 1 diabetes was associated with an increased risk of spine fractures (OR, 2.5; 95% CI, 1.3–4.6) [7]. In a large meta-analysis, the association with hip fractures was stronger for type 1 (summary RR, 6.3; 95% CI, 2.6–15.1) than for type 2 diabetes (summary RR, 1.7; 95% CI, 1.3–2.2) [4].

Associations between duration of diabetes and diabetic control with fragility fractures are still being investigated and have shown conflicting results. A population based study interestingly has shown a biphasic pattern for risk of fractures in type 2 diabetic patients with the risk actually decreased at the time of diagnosis of type 2 diabetes and increasing significantly after 5 years [8]. The investigators postulated that the effects of overweight and obesity at time of diagnosis versus that of diabetes related complications subsequently could account for this observed biphasic fracture risk. Observational studies from a few countries including Taiwan have also reported increased fracture risk with poor diabetes control

* Corresponding author. Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, 20 College Road, Academia, 169856, Singapore.
E-mail address: manju.chandran@singhealth.com.sg (M. Chandran).
Peer review under responsibility of The Korean Society of Osteoporosis.

[9,10] and fracture risk has been reported to be higher in patients with diabetes related complications [11]. On the other hand, intensive glycemic control may also be associated with a higher risk for falls and fractures. An association between tight glycemic control (glycosylated hemoglobin <7%) and greater risk of hip fracture was found in individuals being treated for type 2 diabetes in a study from Singapore [12] though in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) randomized trial, intensive glycemic control was not found to be associated with a higher risk of fractures or falls [13].

2. Evaluation of fracture risk in diabetes

2.1. BMD and FRAX

Almost all studies conducted so far show that type 1 diabetic patients have lower bone mineral density (BMD) compared to healthy subjects [14,15]. In contrast, although there is significant heterogeneity between studies with regards to different protocol designs and definitions of diabetes, overall, type 2 diabetes is usually associated with normal or increased areal BMD compared to healthy subjects [11,16–18]. Interestingly, the higher BMD noted in type 2 diabetes may be independent of an increased body mass index as it has been also described in type 2 diabetes diabetic Asian subjects who are underweight [19].

Despite the higher BMD, patients with type 2 diabetes exhibit increased fracture risk as detailed above. Among older adults with type 2 diabetes, femoral neck BMD T-score and the score obtained from the World Health Organization fracture risk assessment tool (FRAX®) have been found to be associated with hip and nonspine fracture risk with lower femoral neck T-score and higher FRAXscore being associated with hip and nonspine fracture risk [20]. However, in the diabetic patients, compared with participants without diabetes, the fracture risk was higher for a given T-score and age and for a given FRAX-score. For a similar fracture risk, patients with type 2 diabetes have nearly 0.5 higher T-score compared to nondiabetic people [20]. Nevertheless, data have clearly confirmed that although BMD does underestimate fracture risk in patients with type 2 diabetes, it does still help to stratify fracture risk in them. In a large observational study conducted in Manitoba, Canada where more than 60,000 men and women aged 40 years and older with or without diabetes were studied, diabetes was found to be a significant independent risk factor for major osteoporotic fractures after adjustment for FRAX risk factors including BMD (adjusted hazard ratio [aHR], 1.32; 95% CI, 1.20–1.46) [21]. For predicting hip fractures however, age significantly modified the effect of diabetes (age < 60 years [aHR, 4.67; 95% CI, 2.76–7.89], age 60–69 years [2.68, 1.77–4.04], age 70–79 years [1.57, 1.20–2.04], age > 80 years [1.42, 1.10–1.99]; P < 0.001) indicating that diabetes exerts a much stronger effect on hip fracture risk in younger than older individuals [21].

2.2. Trabecular bone score

Abnormalities in trabecular micro architecture may partly explain the paradox of increased risk of fractures occurring at higher BMDs in type 2 diabetes. Trabecular bone score (TBS) is an indirect index of trabecular microarchitecture based upon evaluating pixel grey-level variations from dual-energy X-ray absorptiometry (DXA) images [22]. A low TBS value is associated with fewer, less well connected and more widely distributed trabeculae while high TBS values are correlated with better trabecular structure. TBS has been shown to predict osteoporotic fractures independent of BMD [23] and it may have the potential to discern differences between DXA scans that show similar BMD measurements. In a large

retrospective cohort study using BMD results from a clinical registry in the province of Manitoba, Canada when 29,407 women 50 years old and older among whom 2356 had diagnosed diabetes were studied, lumbar spine TBS was found to be a BMD-independent predictor of fracture and predicted fractures in those with diabetes (aHR, 1.27; 95% CI, 1.10–1.46) and without diabetes (aHR, 1.31; 95% CI, 1.24–1.38) [24].

2.3. What can be done clinically to improve fracture risk prediction using BMD and/or FRAX in patients with diabetes?

Although type 1 diabetes is indirectly considered as one of the secondary causes in the FRAX model, diabetes is not one of the primary entry variables in it and it must be noted that there is a significant potential of underestimating fracture risk in patients with type 2 diabetes when the current FRAX risk scoring is used. Since type 2 diabetes confers an increased risk of fracture that is independent of the conventional clinical risk factors (CRFs), it has been proposed that type 2 diabetes be considered for inclusion in future iterations of FRAX. At the present time, potential strategies to improve fracture risk prediction in patients with diabetes include using the rheumatoid arthritis in the FRAX calculation as a proxy for type 2 diabetes (since the effect on fracture risk with rheumatoid arthritis appears to be similar to that of diabetes), adjusting FRAX score for lumbar spine TBS or using an altered hip T-score (lowered by 0.5 standard deviation) [25]. These adjustments may help to avoid systematically underestimating the risk of osteoporosis-related fractures in those with diabetes. However, it should be noted that these adjustments do not completely capture the nuances of the effect of diabetes on fracture risk since it may also be influenced by multiple other factors such as duration of the disease, glycemic control, use of insulin as well as end organ complications and hypoglycemia induced falls.

2.4. Bone turnover markers

Most biochemical studies appear to confirm that diabetes both types 1 and 2 are low turnover states [26,27]. In addition, bone turnover markers have been reported to be involved in risk of fractures in diabetic subjects' independent of BMD. The serum insulin growth factor-1 level in female type 2 diabetic patients has been reported to be lower than in nondiabetic subjects and this is related to an increased risk of vertebral fractures independent of BMD [28]. Sclerostin is a protein secreted by osteocytes that binds to the osteoblast low-density lipoprotein receptor-related proteins 5 and 6 (LRP 5/6) and suppresses the canonical Wnt/Beta-catenin pathway. Elevated sclerostin levels have been shown to be significantly associated with an increased risk of vertebral fractures in patients with diabetes mellitus [28,29]. Despite these findings that appear to suggest a role for altered bone turnover in the development of fragility fractures in diabetes, their role in assessing fracture risk in patients with diabetes and their clinical utility for this purpose should be elucidated in more detail.

3. Management of osteoporosis in diabetes

Management considerations in diabetic patients with osteoporosis are predominantly based on good clinical practice rather than from evidence obtained from randomized controlled trials (RCTs).

3.1. General measures

3.1.1. Lifestyle intervention
Lifestyle intervention is always recommended in diabetics and should be the basis of any clinical guideline. It should be

remembered that children with early onset of type 1 diabetes may have difficulties in achieving peak bone mass. Regular physical activity is the best way to build up bone mass and strength. Regular weight bearing exercise has been shown to promote bone mineral accretion in children with type 1 diabetes just as it does in nondiabetic children [30]. Adequate energy and protein intake and weight bearing exercises (40 min/d, 3-5 times a week) are recommended. Other nonpharmacological measures such as avoidance of smoking, limitation of alcohol (to less than 3 units per day) is important to promote bone mass accrual as well as to prevent bone loss in both types 1 and 2 diabetes.

Studies from different geographic locations suggest that vitamin D insufficiency may be more prevalent in individuals with diabetes compared to the general population [31,32]. Although the results of studies exploring the effect of vitamin D on metabolic parameters in diabetes are not conclusive, it appears prudent to recommend an adequate daily intake of vitamin D of >800 IU/d along with a calcium intake of at least 1000 mg/d.

3.1.2. Optimizing metabolic control

Controversy exists as to the role of glycemic control on BMD and fracture risk in patients with diabetes. Given that invitro data suggests that hyperglycemia is toxic to osteoblasts [27] and some clinical evidence points to a relationship between glycemic control and fracture incidence [9,10,33], efforts should be made to optimize metabolic control in patients with diabetes. Though the established higher propensity for falls in individuals with diabetes [34] does not fully explain the increased fracture risk observed in this population, peripheral neuropathy, retinopathy, hypotension, and autonomic neuropathy should be noted and corrected as much as possible since they may increase falls and fracture risk in this vulnerable population.

Although conflicting data exists to whether stringent glycemic control is associated with an increased risk of fractures and falls [12,13], a less stringent glycaemic target in order to avoid risk of hypoglycemic events and thus in general reduce the risk of falls has been recently recommended in the European Association for the Study of Diabetes/American Diabetes Association guidelines [35].

3.2. Impact of diabetes medications on fracture risk

It is becoming increasingly evident that diabetes medications may modulate bone loss and fracture risk. Careful selection of medications that are not detrimental to bone health while at the same time will help with optimizing glycemic control should be made. Thiazolinedione use has clearly been associated with increased fracture risk. Evidence that rosiglitazone increases fracture risk in humans emerged with the results of the A Diabetes Outcome Progression Trial (ADOPT) that showed increased fracture risk in women enrolled in the trial. The trial enrolled 1840 women and 2511 men from 488 centres in 17 countries of which 645 women and 811 men were on rosiglitazone. A *post hoc* analysis of the trial showed an increased cumulative incidence of fractures in women treated with rosiglitazone (9.3%) compared with 5.1% with metformin and 3.4% with glyburide-a sulfonylurea [36]. A recent meta-analysis of 22 RCT's that included 24,554 participants found fracture risk in women to be similar with pioglitazone (OR, 1.73; 95% CI, 1.18—2.55) and rosiglitazone (OR, 2.01; 95% CI, 1.61—2.51) [37]. Sodium/glucose cotransporter 2 inhibitors, especially canagliflozin have been associated with increased fracture risk [38]. This is possibly mediated through increased phosphate reabsorption with resultant increased parathyroid hormone (PTH) and increased bone resorption [39]. The use of insulin has been associated with an increased risk of fragility fractures [40] although whether this is due to the insulin perse or whether it is due to tight control and

thus hypoglycaemia-induced falls [41] or whether it is in part a marker of disease severity is debatable. Metformin and sulfonylureas may have neutral or even slightly protective associations with fracture risk [42,43]. A meta-analysis of studies including RCTs involving approximately 11,000 participants exploring the risk of fractures associated with the Glucagon Like Peptide-1(GLP-1) analogues liraglutide and exanetide found divergent risk of fractures with liraglutide associated with a significant reduced risk and exanetide with an elevated risk [44]. The clinical significance of this divergent finding is not clear. The findings from published studies on the effect of antidiabetes agents on BMD and fracture risk are summarized in Table 1.

3.3. Antiosteoporosis treatments in diabetic patients

3.3.1. Who to treat and when to treat?
3.3.1.1. Patients with CRFs for osteoporosis. Conventional CRFs can be employed to identify patients with diabetes at increased fracture risk even though diabetes has been shown to be a significant predictor of subsequent major osteoporotic fracture even after correcting for those CRFs in risk assessment tools such as FRAX.

3.3.1.2. When DXA derived BMD is in the osteoporosis range. An osteoporosis range BMD in postmenopausal women and men over age 50 years confirms the diagnosis of osteoporosis and has traditionally been considered as a threshold to consider pharmacotherapy. However as noted earlier, T-score BMD measured by DXA may under-estimate fracture risk in type 2 diabetics [20]. For example, as mentioned earlier, it has been shown that a diabetic woman with a T-score of −1.9 would have an estimated 10-year hip fracture risk similar to a nondiabetic woman with a T-score of −2.5, the threshold generally used for a diagnosis of osteoporosis [20]. Thus, in contrast to nondiabetics, an areal BMD intervention threshold at T-score −2 at the spine or hip could possibly be considered appropriate to initiate intervention though it should be noted that this has not been vigorously tested in clinical trials.

3.3.1.3. When there is the presence of a fragility fracture. In general, the presence of a typical fragility fracture confirms the diagnosis of osteoporosis and suggests that intervention with pharmacologic treatment should be considered regardless of BMD. Typical osteoporotic fractures in diabetics as in nondiabetics, are those of the spine, hip, pelvis and humerus. Fractures occurring in the subtrochanteric and diaphyseal regions of the femur have been also strongly associated with diabetes [45,46] and type 2 diabetes has been associated with an increased risk of forearm fractures [7]. Ankle fractures pose a challenge. These fractures are thought to

Table 1
Effect of antidiabetic agents on BMD and fragility fractures in humans.

Antidiabetic agent	BMD	Fractures
Thiazolidinediones		
Rosiglitazone	↓	↑ ↔ (↔ in men in some studies)
Pioglitazone	↔	↑ ↔ (↔ in men in some studies)
Metformin	↑ ↔	↓ ↔
Sulfonylureas	−	↓ ↔
Incretin therapies		
GLP-1 analogues	↑ ↔	↔
DPP-4 inhibitors	−	↓ ↔
Insulin	↔	↑ ↔
SGLT2 Inhibitors		
Canagliflozin	↓ (total hip)	↑
Dapagliflozin	↔	↑ ↔

BMD, bone mineral density; GLP-1, glucagon like peptide-1; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium/glucose co-transporter 2; ↓, decreased; ↑, increased; ↔, no change noted.

occur more frequently in subjects with diabetes [17] and to be associated more often with non-, mal-, or delayed union in diabetics compared to nondiabetics. Whether an ankle fracture indicates osteoporosis in diabetic (or nondiabetic) subjects however remains unclear and whether treatment should be initiated in a patient with normal or osteopenic range BMDs and history of only an ankle fracture is a point of debate.

3.3.2. What to treat with?

Antiosteoporosis therapies have primarily been tested in the settings of high bone turnover and low BMD. The effectiveness of these agents in fracture prevention in the milieu of low bone turnover that appears to characterize diabetes; both types 1 and 2 is thus unclear. On the other hand, low BMD is a risk factor for fractures in diabetes suggesting that antiosteoporosis therapies could be effective in preventing fractures in diabetic patients as they do in nondiabetics. The antifracture efficacy in diabetes of typical antiosteoporosis pharmaceutical agents have not been directly evaluated in randomized clinical trials. Rather, the clinical evidence regarding their efficacy is provided by a few observational studies and *post hoc* analyses in subgroups from randomized clinical trials that primarily enrolled osteoporosis patients. The choice of therapy is therefore largely empirical and based on general good practice rather than hard evidence.

3.3.2.1. Bisphosphonates.
In a *post hoc* analysis of the Fracture Intervention Trial (FIT), in which postmenopausal women including diabetic participants with a femoral neck T-score < −1.6 were randomly treated with alendronate or placebo for 3 years, it was shown that the increase in BMD noted with treatment was similar for women with and without diabetes. Treatment with Alendronate was associated with BMD increases of 5.7% (95% CI, 4.4—7.0) at the lumbar spine and 4.3% (95% CI, 3.2—5.3) at the total hip respectively. This increase was similar for women with and without diabetes (6.2% [95% CI, 5.9—6.4] and 4.3% [95% CI, 4.1—4.5] at the LS and TH, respectively) [47]. However, it was not possible to consider fractures as an endpoint in this analysis, because of the small number of diabetic patients (n = 297) included in the trial. In an observational study conducted in postmenopausal osteoporotic Japanese women with (n = 16) and without (n = 135) diabetes, Alendronate was shown to significantly increase lumbar spine BMD and decrease markers of bone turnover [urinary N-Telopeptide (NTX) and serum Alkaline Phosphatase (ALP)] compared to baseline values in both the diabetic as well as the nondiabetic subjects [48]. The efficacy and safety of risedronate treatment has been tested in Japanese women with diabetes and osteoporosis in 3 phase III trials. *Post hoc* analysis of the combined data from the 3 trials showed that lumbar spine BMD and bone turnover marker responses to risedronate were not significantly different between diabetic and nondiabetic patients [49]. There is no data regarding the use of intravenous bisphosphonates such as ibandronate or zoledronic acid in diabetic patients. Caution should be exercised if these agents are used in diabetic patients with renal function impairment.

3.3.2.2. Selective estrogen receptor modulators.
In the MORE (Multiple Outcomes of Raloxifene Evaluation) study, a higher efficacy of raloxifene in reducing vertebral fracture risk in diabetic women compared to those without diabetes (P = 0.04) was noted [50]. The efficacy of raloxifene in reducing vertebral fractures was found to be similar in patients with and without diabetes in the RUTH (Raloxifene Use for The Heart) trial [51]. Similar results were reported in a Danish cohort study with fracture rates found to be similar in diabetic and nondiabetic patients treated with raloxifene and bisphosphonates [52]. The low-turnover state of diabetes did not thus seem to be a hindrance to the effect of these medications.

The authors of this study thus concluded that patients with diabetes should receive treatment for osteoporosis in the same way as nondiabetic patients.

3.3.2.3. Teriparatide.
The effect of up to 24 months of teriparatide (human recombinant PTH 1—34) 20 μg/d subcutaneously on skeletal outcomes in patients with and without diabetes has been explored in a *post hoc* analyses of the DANCE (Direct Analysis of Nonvertebral Fractures in the Community Experience) study [53]. The effect of teriparatide treatment on vertebral and total hip BMD was similar in diabetic and nondiabetic subjects. Interestingly, the effect on femoral neck was greater in the diabetic treated patients compared to those without diabetes (+0.34 and + 0.004 g/cm^2, respectively; P = 0.014). The incidence of nonvertebral fracture at 6 months was 3.5 per 100 patient-years in type 2 diabetes patients and 3.2 per 100 patient-years in nondiabetic patients [53].

No data currently exists on the use of medications such as denosumab and strontium in the clinical management of osteoporosis in diabetes. The results obtained from the observational studies and *post hoc* analyses briefly described above are promising but obviously the efficacy of osteoporotic treatments in diabetic patients need to be confirmed in prospective RCTs. Romosozumab, an antisclerostin antibody, is currently under investigation as a new anabolic treatment and has been shown to enhance bone mass and strength in diabetic animals [54]. Whether it will improve bone health in humans with diabetes remains to be elucidated. Currently, bisphosphonates remain among the first choices for osteoporosis treatment in diabetic as in nondiabetic subjects.

4. Conclusion

Patients with diabetes are undoubtedly at increased risk for fragility fractures. However, how to properly assess fracture risk and manage osteoporosis in patients with diabetes is still not clear and validated guidelines do not exist. Currently the evidence is still too premature to make definitive recommendations and those available are based on expert consensus. Conventional BMD and FRAX thresholds used to assess fracture risk and to decide on intervention thresholds can still be used albeit with modifications. When evaluating the risk-benefit ratio of antidiabetic medications, the effect on skeletal fragility should also be considered. The concept of "reversibility of risk" exists and osteoporosis in diabetes is likely to be amenable to treatment intervention with conventional anti-osteoporosis pharmacotherapy. Whether the antifracture efficacy of osteoporosis therapies would be as robust in those type 2 diabetic patients with BMD T-scores higher than −2.5 needs to be studied.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

References

[1] Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world: a growing challenge. N Engl J Med 2007;356:213—5.

[2] Odén A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: secular increases 2010-2040. Osteoporos Int 2015;26:2243—8.

[3] Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporos Int 2011;22:1277—88.

[4] Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495—505.

[5] Koh WP, Wang R, Ang LW, Heng D, Yuan JM, Yu MC. Diabetes and risk of hip fracture in the Singapore Chinese Health Study. Diabetes Care 2010;33:1766—70.

[6] Shah VN, Shah CS, Snell-Bergeon JK. Type 1 diabetes and risk of fracture: meta-analysis and review of the literature. Diabet Med 2015;32:1134—42.

[7] Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia 2005;48:1292—9.

[8] Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: a population-based study. Bone 2007;40:1595—601.

[9] Schneider AL, Williams EK, Brancati FL, Blecker S, Coresh J, Selvin E. Diabetes and risk of fracture-related hospitalization: the atherosclerosis risk in communities study. Diabetes Care 2013;36:1153—8.

[10] Li CI, Liu CS, Lin WY, Meng NH, Chen CC, Yang SY, et al. Glycated hemoglobin level and risk of hip fracture in older people with type 2 diabetes: a competing risk analysis of taiwan diabetes cohort study. J Bone Min Res 2015;30: 1338—46.

[11] Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes: a meta-analysis. Osteoporos Int 2007;18:427—44.

[12] Puar TH, Khoo JJ, Cho LW, Xu Y, Chen YT, Chuo AM, et al. Association between glycemic control and hip fracture. J Am Geriatr Soc 2012;60:1493—7.

[13] Schwartz AV, Margolis KL, Sellmeyer DE, Vittinghoff E, Ambrosius WT, Bonds DE, et al. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes Care 2012;35:1525—31.

[14] Shah VN, Harrall KK, Shah CS, Gallo TL, Joshee P, Snell-Bergeon JK, et al. Bone mineral density at femoral neck and lumbar spine in adults with type 1 diabetes: a meta-analysis and review of the literature. Osteoporos Int 2017 Jun 3. http://dx.doi.org/10.1007/s00198-017-4097-x [Epub].

[15] Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quattrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. Diabetes Care 2008;31:1729—35.

[16] de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. Osteoporos Int 2005;16:1713—20.

[17] Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, et al. Risk of fracture in women with type 2 diabetes: the Women's health initiative observational study. J Clin Endocrinol Metab 2006;91:3404—10.

[18] Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol 2012;27:319—32.

[19] Chandran M, Tay D, Tan M, Hao Y, Huang XF, Khoo J, et al. Axial BMD in diabetic and nondiabetic Southeast Asians with hip fractures: do race and body mass index matter? Endocr Pract 2016;22:716—25.

[20] Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA 2011;305:2184—92.

[21] Leslie WD, Morin SN, Lix LM, Majumdar SR. Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? Osteoporos Int 2014;25:2817—24.

[22] Martineau P, Leslie WD. Trabecular bone score (TBS): method and applications. Bone 2017 Feb 1. http://dx.doi.org/10.1016/j.bone.2017.01.035 [Epub]. pii: S8756—3282(17)30035-2.

[23] Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Min Res 2011;26:2762—9.

[24] Leslie WD, Aubry-Rozier B, Lamy O, Hans D. Manitoba Bone Density Program. TBS (trabecular bone score) and diabetes-related fracture risk. J Clin Endocrinol Metab 2013;98:602—9.

[25] Schacter GI, Leslie WD. DXA-based measurements in diabetes: can they predict fracture risk? Calcif Tissue Int 2017;100:150—64.

[26] Hygum K, Starup-Linde J, Harsløv T, Vestergaard P, Langdahl BL. Mechanisms in endocrinology: diabetes mellitus, a state of low bone turnover - a systematic review and meta-analysis. Eur J Endocrinol 2017;176:R137—57.

[27] Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL, et al. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol 2017;13:208—19.

[28] Ardawi MS, Akhbar DH, Alshaikh A, Ahmed MM, Qari MH, Rouzi AA, et al. Increased serum sclerostin and decreased serum IGF-1 are associated with vertebral fractures among postmenopausal women with type-2 diabetes. Bone 2013;56:355—62.

[29] Yamamoto M, Yamauchi M, Sugimoto T. Elevated sclerostin levels are associated with vertebral fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2013;98:4030—7.

[30] Maggio AB, Rizzoli RR, Marchand LM, Ferrari S, Beghetti M, Farpour-Lambert NJ. Physical activity increases bone mineral density in children with type 1 diabetes. Med Sci Sports Exerc 2012;44:1206—11.

[31] Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatr 2009;154:132—4.

[32] Tahrani AA, Ball A, Shepherd L, Rahim A, Jones AF, Bates A. The prevalence of vitamin D abnormalities in South Asians with type 2 diabetes mellitus in the UK. Int J Clin Pract 2010;64:351—5.

[33] Miao J, Brismar K, Nyrén O, Ugarph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. Diabetes Care 2005;28:2850—5.

[34] Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25:1749—54.

[35] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American diabetes association and the European association for the study of diabetes. Diabetologia 2015;58:429—42.

[36] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427—43.

[37] Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014;68:115—23.

[38] Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2016;101:157—66.

[39] Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol 2015;3:8—10.

[40] Napoli N, Strotmeyer ES, Ensrud KE, Sellmeyer DE, Bauer DC, Hoffman AR, et al. Fracture risk in diabetic elderly men: the MrOS study. Diabetologia 2014;57:2057—65.

[41] Kachroo S, Kawabata H, Colilla S, Shi L, Zhao Y, Mukherjee J, et al. Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: analysis of a U.S. commercial database. J Manag Care Spec Pharm 2015;21: 243—53.

[42] Chandran M. Diabetes drug effects on the skeleton. Calcif Tissue Int 2017;100: 133—49.

[43] Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. Diabetes Care 2008;31:199—203.

[44] Su B, Sheng H, Zhang M, Bu L, Yang P, Li L, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. Endocrine 2015;48:107—15.

[45] Abrahamsen B, Eiken P, Prieto-Alhambra D, Eastell R. Risk of hip, sub-trochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study. BMJ 2016;353. i3365.

[46] Napoli N, Schwartz AV, Palermo L, Jin JJ, Wustrack R, Cauley JA, et al. Risk factors for subtrochanteric and diaphyseal fractures: the study of osteoporotic fractures. J Clin Endocrinol Metab 2013;98:659—67.

[47] Keegan TH, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL. Fracture Intervention Trial. Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the fracture intervention trial. Diabetes Care 2004;27:1547—53.

[48] Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H. Three-year experience with alendronate treatment in postmenopausal osteoporotic Japanese women with or without type 2 diabetes. Diabetes Res Clin Pract 2011;93:166—73.

[49] Inoue D, Muraoka R, Okazaki R, Nishizawa Y, Sugimoto T. Efficacy and safety of risedronate in osteoporosis subjects with comorbid diabetes, hypertension, and/or dyslipidemia: a post hoc analysis of phase III trials conducted in Japan. Calcif Tissue Int 2016;98:114—22.

[50] Johnell O, Kanis JA, Black DM, Balogh A, Poor G, Sarkar S, et al. Associations between baseline risk factors and vertebral fracture risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. J Bone Min Res 2004;19: 764—72.

[51] Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, et al. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Min Res 2008;23:112—20.

[52] Vestergaard P, Rejnmark L, Mosekilde L. Are antiresorptive drugs effective against fractures in patients with diabetes? Calcif Tissue Int 2011;88:209—14.

[53] Schwartz AV, Pavo I, Alam J, Disch DP, Schuster D, Harris JM, et al. Teriparatide in patients with osteoporosis and type 2 diabetes. Bone 2016;91:152—8.

[54] Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375):1532—43.