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 antosteoporosis pharmacotherapy in the diabetic population.

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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 FRAX® score 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 diabetes 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 glycemic 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. Thiazolidinediones 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 Study of Diabetes/American Diabetes Association guidelines [35]. Thiazolinediones use has clearly been associated with an increased risk of fragility fractures [40] although whether this is due to the insulin per se 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 exenatide found divergent risk of fractures with liraglutide associated with a significant reduced risk and exenatide 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. Antiesteoporosis 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 diabetes [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

| Antidiabetic agent       | BMD | Fractures |
|-------------------------|-----|-----------|
| Thiazolidinediones      |     | ++        |
| Rosiglitazone           |     | ++        |
| Pioglitazone            |     | ++        |
| Metformin               |     | ++        |
| Sulfonylureas           |     | ++        |
| Incretin therapies      |     | ++        |
| GLP-1 analogues         |     | ++        |
| DPP-4 inhibitors        |     | ++        |
| Insulin                 |     | ++        |
| SGLT2 Inhibitors        |     | ++        |
| Canagliflozin           |     | ++        |
| Dapagliflozin           |     | ++        |

BMD, bone mineral density; GLP-1, glucagon like peptide-1; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium/glucose co-transporter 2; ++, increased; +, increased; –, decreased; |, 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?
Antiestrogen 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 antioestrogen therapies could be effective in preventing fractures in diabetic patients as they do in nondiabetics. The antifracture efficacy in diabetes of typical antioestrogen 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 a 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/cm², 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 antiscerostin 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 antiosteoporotic 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.

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