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Review article

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

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ABSTRACT

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.

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

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[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 riskassessment 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

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