MANAGEMENT PERSPECTIVE

How may osteoporosis be prevented in individuals with diabetes?



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Practice Points

- Physical activity should be encouraged, especially in patients undergoing weight loss for Type 2 diabetes.
- Smoking should be discouraged.
- Traditional dual-emission x-ray absorptiometry scans may not truly reflect bone strength in diabetic patients as well as they do in subjects without diabetes.
- Thiazolidinediones are associated with an increased risk of osteoporosis and should not be used in subjects already at risk of osteoporosis.
- Alendronate has been demonstrated to be associated with increased bone mineral density.
- More studies are needed in the field.

SUMMARY Diabetes may be linked to osteoporosis in a number of ways. General prevention may include physical activity, which may improve both metabolic control and help prevent bone loss, and good metabolic control may prevent osteoporosis by counteracting the negative effects of hyperglycemia on bone. Of the drugs available for use against diabetes, the thiazolidinediones may lead to osteoporosis by altering the balance between osteoblastogenesis and adipocytogenesis, whereas other drugs such as insulin, sulfonylureas and metformin seem to prevent osteoporosis by improving metabolic control. The thiazolidinediones thus should not be used in patients at risk of osteoporosis. Among the antiresorptive treatments, bisphosphonates have been demonstrated to increase bone mineral density but no studies with fractures as end points are available. No studies of strontium or parathyroid hormone are available. More studies on the pathogenesis and treatment of osteoporosis in patients with diabetes are needed.

Diabetes may be associated with osteoporosis through a number of mechanisms [1] including increased calcium loss in urine [2], increased formation of advanced glycation end products [3–8], functional hypoparathyroidism [9,10] and inflammation [1,11]. Furthermore, complications such as diabetic kidney disease [12], microangiopathy [13], endothelial function [14], macroangiopathy [15] and neuropathy contribute to osteoporosis [16]. These mechanisms are related to metabolic regulation and, thus, blood glucose levels, and should therefore be the same in Type 1 (T1D) and 2 (T2D) diabetes. However, available studies have indicated that differences may exist between

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T1D and T2D [17]. Patients with T1D have a decreased bone mineral density (BMD) and thus an increased risk of fractures, whereas patients with T2D have an increased BMD. However, in contrast to what might be expected, an increase in the risk of fractures has been observed in T2D [17]. This finding may be interpreted as being due to a decreased bone biomechanical competence [18], perhaps related to the accumulation of advanced glycation end products [17]. In addition, patients with T2D have a higher bodyweight than patients with T1D, and this may contribute to the smaller excess of fractures in T2D patients compared with the general population than in those with T1D [17]. Further factors differentiating the osteoporosis risk in T1D and T2D may include differences in IGF levels [1] and the presence of endogenous insulin secretion in T2D [19].

Bone disease in diabetes is related to low bone turnover [20,21]. This is particularly interesting as recent pivotal animal studies have shown a relationship between osteocalcin, which is formed by osteoblasts as a marker of bone turnover, and β -cell function [22–24]. Owing to the low turnover, a bone biopsy [25] may be indicated in some patients, especially if kidney disease is present (see later).

It has thus been speculated that traditional antiresorptive treatment for osteoporosis may be less suited to patients with diabetes, as these will already have an impaired bone turnover. Furthermore, it has been hypothesized that conventional dual-emission x-ray absorptiometry (DXA) scanning may not reflect bone biomechanical competence adequately in patients with diabetes and that changes in BMD should be interpreted with caution as they may not truly reflect improvements in bone strength. Also, DXA scans from patients with diabetes may not reflect bone strength and thus not reflect the degree of osteoporosis, as in patients without diabetes.

This article will focus on general ways of preventing osteoporosis in patients with diabetes and special features relating to the causes of osteoporosis in diabetic patients.

General prevention

In general, the major risk factors for osteoporosis are increasing age and female gender [101] with additional risk factors being smoking [26], immobilization (disuse osteoporosis) [27,28], low bodyweight [29] and weight loss [30]. Whereas age and gender are nonmodifiable risk factors, prevention of smoking and smoking cessation [29], mobilization and prevention of excessive weight loss may also prevent osteoporosis in patients with diabetes.

Alcohol intake in excessive amounts represents a specific concern, as this is related to both increased risk of diabetes from pancreatitis and increased risk of osteoporosis and fractures [31,32]. In addition, the use of systemic corticosteroids is associated with both an increased risk of diabetes and an increased risk of fractures [33–37]; the use of systemic corticosteroids should thus be limited.

A special feature is that weight loss is encouraged in obese patients with T2D. A randomized controlled trial in overweight patients with T2D showed that weight loss was associated with a decrease in BMD (0.9% decrease was observed in total body BMD over 12 months with nonsignificant decreases in spine and femur BMD) [38] and that exercise training seemed to prevent the loss of BMD [38]. In patients treated by a gastric bypass, which is used for weight reduction in morbidly obese patients with T2D, a decrease in BMD was observed [39].

Importantly, immobilization following Charcot foot may lead to loss of bone from the skeleton [40]. Physical activity may thus be encouraged in patients with diabetes, especially when weight loss is recommended in obese subjects. Furthermore, physical activity may help improve the metabolic control of diabetes.

Special prevention & treatment

Prevention and treatment includes interventions that specifically target the pathogenetic factors involved in osteoporosis associated with diabetes – that is, improvement of metabolic control, interventions in patients with kidney disease and the special features of antiosteoporosis treatment in patients with diabetes.

Improvement of metabolic control

In animal models, improvement of diabetes control has resulted in the reversal of the histomorphometric changes induced by diabetes [20]. Observational studies have pointed at a reversal of, for example, the loss of calcium in the urine and an improvement of BMD when blood glucose levels are better controlled [2]. Observational studies have also suggested that the excess risk of fractures may decline with time following the diagnosis of diabetes and, thus, improved metabolic control may be observed [41]. However, one observational study failed to show an association between HbA_{1C} and BMD [17]. This should be interpreted with caution: HbA_{1C} reflects blood glucose levels within the last 6–8 weeks, and bone turnover is a process that takes much longer than 6–8 weeks. In addition, BMD may not adequately reflect bone biomechanical competence in patients with osteoporosis.

Strict metabolic control should thus be encouraged in patients with diabetes to prevent osteoporosis, although this is based on observational studies. Further studies are therefore needed. Osteoporosis may actually be seen as a complication of diabetes in the same way as eye disease, kidney disease, macro- and micro-angiopathy and neuropathy.

Drugs against diabetes

Drugs against diabetes improve metabolic control and should thus be expected to also prevent osteoporosis. However, a particular feature should be observed: one group of drugs against osteoporosis stands out – the thiazolidinediones (glitazones), which interact with bone cells.

Thiazolidinediones

The thiazolidinedione class of drugs, also called glitazones or TZDs, act by stimulating the peroxisome proliferator-activating receptor- γ (PPAR- γ). PPAR- γ is expressed in most tissues, and stimulation of this receptor improves insulin resistance, decreases leptin levels and inflammatory cytokine levels, increases adiponectin levels and modifies adipocyte differentiation [42]. In this context, it should also be observed that diabetes and hyperglycemia *per se* may activate the PPAR- γ system [43].

The effect of TZDs on adipocyte differentiation is particularly important as it leads to a shift from osteoblastogenesis to adipocytogenesis, which results in adipocyte accumulation in the bone marrow and, thus, reduced formation of bone [42,44,45]. Another mechanism by which the TZDs may interfere with bone formation is inhibition of the aromatase enzyme, which leads to reduced estrogen formation [46], lowering of IGF levels [47], interaction with c-fos [48], and interaction with wnt signaling and G-protein coupled activity [49]. This leads to a decrease in osteocalcin levels [50] and other bone turnover markers [51], an accelerated bone loss [52-54] and an increased risk of fractures [55,56].

In general, use of TZDs should be discouraged in patients at risk of osteoporosis (i.e., underweight patients and postmenopausal women).

Other drugs against diabetes

In contrast to the TZDs, other drugs against diabetes such as insulin, the sulfonylureas and metformin seem to be associated with a decrease in the risk of fractures or a trend towards a decrease [57], probably related to encouraging better metabolic control of diabetes. Metformin has also been demonstrated to have positive effects on bone turnover by improving metabolic control [58]. Recently published results from rodent models suggest a positive effect of exenatide on bone, but no clinical studies have been conducted [59].

Other drugs against diabetes may thus be preferred over TZDs in patients with diabetes who are at risk of osteoporosis. However, no studies are available for the newer glucagon-like peptide 1 agonists and dipeptidyl peptidase 4 inhibitors.

Drugs against osteoporosis

Treatment and prevention of osteoporosis in patients with diabetes may pose a special challenge, since diabetic bone disease is a disease of low bone turnover. Calcium and vitamin D should be the basic treatment, as an increased loss of calcium in the urine can be expected. Calcium alone does not seem effective against osteoporosis [60], and may be associated with an increased risk of myocardial infarction [61]. By contrast, calcium plus vitamin D does seem effective in preventing osteoporosis [62,63], and an increased risk of cardiovascular events has not been reported with this combined treatment [63].

Antiresorptive drugs

Antiresorptive drugs include the bisphosphonates and the selective estrogen receptor modulators [60]. In theory, these may present a special problem as bone turnover is low in diabetic patients. Two studies have shown improvements in BMD with the bisphosphonate alendronate over placebo [64,65]: the paper by Keegan *et al.* was a *post hoc* analysis of a randomized trial [65] and the paper by Dagdelen *et al.* was an observational study without a placebo group [64]. In this study, the authors found that diabetic patients on alendronate lost bone compared with nondiabetic patients on alendronate. The study is difficult to interpret since we do not know how much bone the diabetic patients would have lost on placebo [64]. However, no fracture data are available. It may thus be concluded that the decrease in bone turnover does not lead to decreases in BMD; however, it is not possible to deduce whether the quality of the newly formed bone is adequate. Further studies are therefore needed. A *post hoc* analysis of a raloxifene trial identified reduced vertebral fracture with raloxifene compared with placebo in participants with diabetes [66]. However, this study only included patients with T2D and the number of patients was very limited [66]. Strontium ranelate is also effective against osteoporosis [67]; however, for this compound, no specific studies on the effects in patients with diabetes are available.

Anabolic drugs

Anabolic drugs include parathyroid hormone (PTH) and analogs [68,69]. In patients with diabetes, bone turnover is decreased, which may lead to an accumulation of old bone and no renewal of bone. Antiresorptive drugs, such as bisphosphonates, reduce bone turnover, which in theory may be a disadvantage as bone turnover is already low in patients with diabetes. Anabolic agents such as PTH and analogs increase bone turnover, and may thus, in theory, hold an advantage over antiresorptive drugs in patients with diabetes, as they increase bone turnover in contrast to antiresorptive drugs. However, no clinical studies are available, although one study has indicated that teriparatide may perhaps have a limited acute adverse effect on insulin resistance [70]. Further studies are needed.

Patients with kidney disease

Patients with kidney disease pose a special problem for treating osteoporosis. The conversion of cholecalciferol and ergocalciferol to activated vitamin D is impaired at glomerular filtration levels below 65 ml/min [71]. Below this limit, activated vitamin D (α -calcidol or calcitriol) should be used. Patients with impaired kidney function thus often have secondary hyperparathyroidism [71]. In impaired kidney function, the calcium–phosphorus turnover is also impaired with hyperphosphatemia and hypocalcemia.

The main treatment for these patients is correction of the calcium, phosphorus, vitamin D and PTH levels [71]. A particular feature is that patients with uremia are often PTH resistant – that is, lowering of PTH into the normal range may lead to adynamic bone disease with an increased risk of fractures [71].

Some studies have indicated that the newer phosphorus binders, such as sevelamer, may perhaps be more effective in terms of increasing bone density than the traditional use of calcium and activated vitamin D [72,73]. However, more research is needed. In some patients with low bone turnover, the use of calcium-containing phosphate binders may lead to adynamic bone disease by suppressing PTH, and ectopic calcifications may be seen in some patients. Cinacalcet is a specific calcium-sensing receptor agonist, which decreases PTH secretion [74]. Therefore, it may be used to treat severe secondary hyperparathyroidism in patients with uremia. A meta-analysis of randomized controlled trials has shown that, in uremia, cinacalcet may decrease the risk of fractures [75].

Regarding specific antiosteoporosis therapy, many patients have secondary hyperparathyroidism, and PTH and analogs should not be used in such patients. However, if PTH is within the target range, PTH and analogs may be used in patients with decreased kidney function [76].

Orally administered bisphosphonates may be used in patients with decreased kidney function [77,78] and even in patients on dialysis in reduced doses [79]. However, if osteomalacia is present, bisphosphonates should not be used owing to the risk of aggravation of osteomalacia. It should be noted that intravenous bisphosphonates may lead to the development of kidney failure from tubular necrosis [80,81]. The use of intravenous bisphosphonates should thus be discouraged in patients with impaired kidney function.

Raloxifene may be used in patients with impaired kidney function [82] while no data are available for strontium ranelate, although the majority of users in available studies were elderly, and many had decreased kidney function [67].

Future perspective

The association of osteoporosis and fractures with diabetes as a new complication in line with diabetic eye disease, kidney disease, nephropathy, neuropathy, and micro- and macroangiopathy has wide-ranging consequences, especially as bone density does not seem to be truly reflected by traditional DXA scanning.

Further research is needed, especially with respect to the detection and treatment of osteoporosis in patients with diabetes. Focus should be on hard end points such as fractures in users of antiresorptive drugs and on the effects of anabolic agents such as teriparatide and recombinant human PTH.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment,

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consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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MANAGEMENT PERSPECTIVE Vestergaard

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How may osteoporosis be prevented in individuals with diabetes? MANAGEMENT PERSPECTIVE

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