Osteoporosis: An Under-appreciated Complication of Diabetes

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The extension of the average life expectancy of people with diabetes that has accompanied improvements in medical care has increased the significance of osteoporosis. In addition to the usual causes of osteoporosis associated with aging, bone health is also compromised by diabetes. There is strong evidence that patients with type 1 diabetes and increasing evidence that those with type 2 diabetes have an increased risk of certain types of osteoporotic fractures. Several mechanisms have been proposed for diabetes-related osteoporosis. These include both the comorbidities of diabetes and more direct pathophysiological effects of the disease itself.

Osteoporosis and its resultant fractures are increasing as the population ages, making assessment of skeletal health an important component of routine care. Osteoporosis is a disorder of increased bone fragility and low bone mass with a consequent increase in fracture risk.[1] Data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that 13–18% of women in the United States over age 50 have osteoporosis and an additional 37–50% have low bone mass at the hip.[2] The disease results in more than 350,000 hip fractures alone each year in the United States, and the annual number of fractures is expected to double by 2025.[3,4]

Fortunately, recent advances have been made with therapies that significantly decrease fracture risk. But despite these extraordinary advances, it is alarming that more than 80% of patients with a recent hip or wrist fracture are not getting anti-osteoporosis therapy.[5,6] In this article, we review the presentation of osteoporosis in diabetes, potential mechanisms, prevention, and treatment.

Fractures

Hip fractures in particular are now recognized not only as a major cause of morbidity and mortality, but also for their significant economic and social impact. At age 50, a white woman in the United States has a 17% chance of sustaining a hip fracture[3] and a 32% chance of sustaining a vertebral fracture in her lifetime.[7] Hip fractures cause the most morbidity, with reported mortality rates up to 20–24% in the first year after a hip fracture.[8,9] Although some excess mortality may be attributable to comorbid factors rather than the hip fracture itself, up to 50% of patients are unable to walk without assistance, and 33% are totally dependent or in a nursing home in the year following a hip fracture.[8,10,11]

IN BRIEF

Care of patients with diabetes should include an assessment of bone health. It is now clear that patients with type 1 diabetes have lower bone mineral density (BMD) and higher risk of fractures. Evidence is accumulating that patients with type 2 diabetes who have complications are also at increased risk of certain types of osteoporotic fractures despite having a higher BMD when compared to patients with type 1 diabetes. Therapeutic interventions are key to preventing fractures, both by improving bone density and decreasing the risk for falls.

Vertebral fractures are also associated with significant comorbidity from pain, chronic disability, and reduced quality of life.[12]

Hip fractures are increased in patients with diabetes. Case-control studies of patients with hip fractures have found an excess of patients with diabetes, suggesting at least a twofold relative risk in all patients with diabetes.[13] Women with type 1 diabetes had a 6.9- to 12-fold relative risk of hip fractures compared to women without diabetes.[14,15]

Data are less clear about the risk of hip and vertebral fractures in patients with type 2 diabetes. Most studies in women with type 2 diabetes have also found an increased risk of hip fractures,[13–16] with estimates of relative risk almost double the risk in other postmenopausal women. The Study of Osteoporotic Fractures in women older than 65 years with type 2 diabetes found an increased risk of hip and proximal humerus fractures despite a higher bone mineral density (BMD) in those patients.[17] There was also a trend toward increased risk of vertebral, forearm, ankle, and foot fractures. In contrast, other investigators have found increased BMD at the spine in men and women with type 2 diabetes, with fewer fractures.[18,19]

The one site with an undisputed increased fracture risk is the foot, which may be related in part to obesity or neuropathy.[17,20,21] Focal osteopenia and fractures associated with severe peripheral neuropathy (Charcot foot) are long recognized as a complication of any type of diabetes. Mortality is high in the general

population with hip fractures, but the presence of diabetes in a patient with a hip fracture is a risk factor for increased mortality.[22]

Bone Density

Although many factors, including number and type of falls, influence the probability of fractures, the most significant factor is the strength of the bone itself. In the absence of clinically available methods to assess bone quality directly, we rely on the measurement of BMD. A strong relationship exists between bone density measurements and fracture risk: a 10% decrease in BMD at any site confers a 1.6–2.6 increased relative risk of hip fracture and a 1.7–2.3 increased relative risk of vertebral fracture.[23]

Recent advances in bone densitometry techniques have allowed more precise and accurate measurement of BMD at multiple sites. Early studies used single-photon and dual-photon absorptiometry. BMD is now typically performed using dual-energy x-ray absorptiometry (DXA) at the spine, hip, and wrist. More recent data are therefore more sensitive to differences between groups, facilitating the recognition of differences in patients with diabetes.

Even newer ultrasound techniques are appealing because of their lower cost and lack of radiation exposure as well as the theoretical benefits of evaluating an aspect of bone quality. Ultrasound has been correlated with fracture risk but is not standardized, and results vary across machines.[24] Portable DXA machines are able to assess peripheral sites (calcaneus and radius), but generalized fracture risk prediction is not well studied. However, both ultrasound and peripheral DXA still need to be validated in patients with diabetes because local changes in the bones of the foot resulting from peripheral neuropathy may affect results.[25] Quantitative CT and MRI are primarily research tools used to assess different types of bone: trabecular (vertebral bodies) versus cortical (radial shaft).

Using DXA, BMD is categorized by a T score in reference to young normal BMD. The World Health Organization (WHO) has established T score criteria to estimate fracture risk, with a T score of 1–2.5 standard deviations below normal representing osteopenia and > 2.5 standard deviations below normal representing osteoporosis.[26]

Osteopenia was initially described in adolescents with diabetes, 50% of whom were found to have decreased cortical and trabecular forearm BMD.[27] Several subsequent studies found that the forearm BMD in children with only 4–6 years of type 1 diabetes was 20–50% lower than that in control subjects.[28] One study examining vertebral BMD found a decreased cortical but not trabecular BMD in children with diabetes.[29] Most studies in children and adults confirm that BMD is lower in patients with type 1 diabetes than in subjects without diabetes.[30–33]

In contrast, studies in women with type 2 diabetes, controlling for age and obesity, show BMD that is either the same or greater than that in normal subjects,[18,19] even in patients treated with insulin[31] (Figure 1). The Rancho Bernardo studies, a large population-based longitudinal cohort, also looked at men with type 2 diabetes and found that their BMD was similar to that of men with

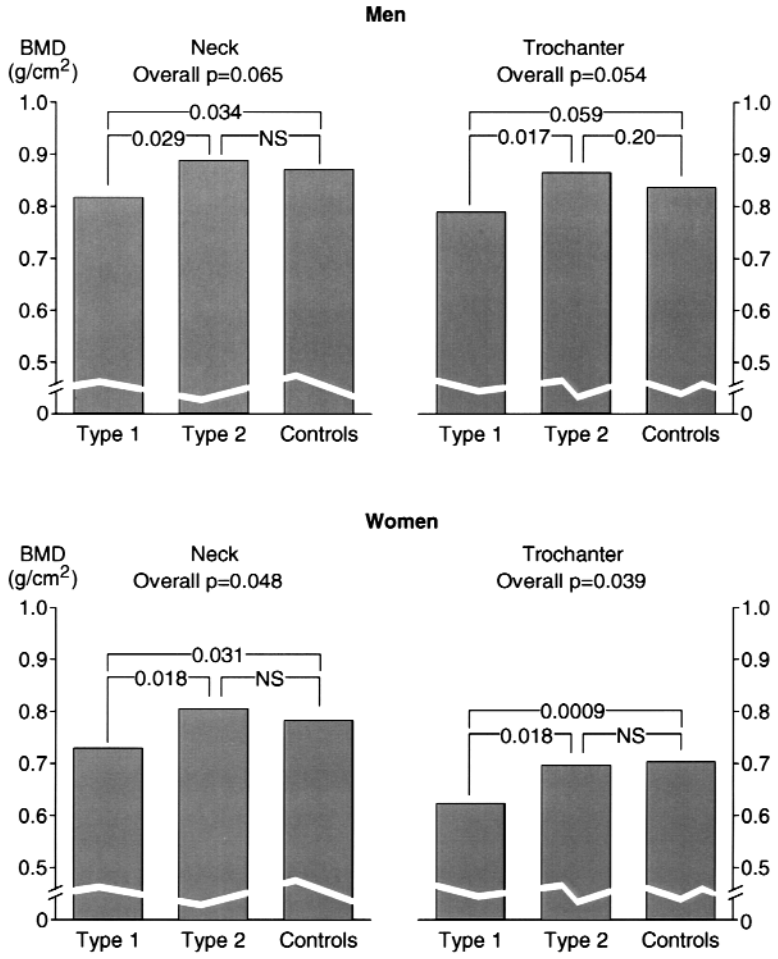

Figure 1. Mean age and BMI adjusted BMD at the proximal femur in subjects with type 1 diabetes (29 men, 27 women), type 2 diabetes (34 men, 34 women), and withouth diabetes (240 men, 258 women). Reprinted with permisison from ref. 31.

normal glucose tolerance, despite the increased BMD they found in women with diabetes.[34]

Mechanisms

Is osteoporosis another complication of poor glycemic control? No correlation between BMD and diabetes duration or current glycemic control (by hemoglobin A1c [A1C]) was seen in postmenopausal women (8.9 years duration, 14 years postmenopausal),[35] or children (5.2 years duration, excluded if complications).[29] Short-term measures of control, such as glucose levels or A1C results, would not be expected to reflect cumulative bone damage measured by BMD. This was demonstrated by Valerio et al.[32] in children with 6.9 years of diabetes in whom the latest A1C did not correlate with lumbar BMD, but the A1C averaged over the entire duration of diabetes did correlate with BMD.

Diabetes complications also represent cumulative results of long-term poor control. Several investigators have demonstrated an association between BMD and microvascular complications, with the BMD inversely correlated with the presence and extent of microvascular complications in women with normal menstrual cycles.[30,36] Mathiassen et al.[37] followed the BMD of 19 patients with type 1 diabetes (8 women), initially free of complications, and found that after 11 years, only those who developed retinopathy or proteinuria had worsening of their BMD. The presence of severe peripheral neuropathy in patients with type 1 diabetes has also been found to correlate with decreased BMD at all sites, in comparison to patients with type 1 diabetes without neuropathy and in comparison to healthy subjects.[25] Although these were small groups, they were matched for other complications and for activity levels.

Using the same paradigm, Forst et al.[38] found a decreased BMD in the cortical bone at the hip and a greater decrease at the distal limb in association with peripheral neuropathy. The lumbar spine had a nonsignificant decrease in BMD in these patients with type 1 diabetes. In the Blue Mountain Eye Study in Australia,[39] an association between retinopathy and all fractures was seen in both men and women with all types of diabetes.

Some studies have shown stabilized and improved BMD in patients with type 1 diabetes with improved glucose control over time.[40,41] Hypercalciuria, a potential risk factor for osteoporosis, has long been noted in patients with poorly controlled type 1 diabetes[42,43] or type 2 diabetes,[44,45] and was shown to improve with lower A1C results.[46] Thus, metabolic control appears to be a major factor in the increased incidence of osteoporosis in patients with diabetes. However, poor control cannot be the only factor unless there is a compensatory factor increasing BMD in type 2 diabetes.

If the relationship between osteoporosis and diabetes were only related to hyperglycemia, one would expect a similar incidence of osteoporosis in patients with type 1 and those with type 2 diabetes, but most studies show more osteoporosis in patients with type 1 diabetes.[31,47] There may be differences between types of diabetes other than glucose control that affect BMD. Several factors have been investigated, including treatment with insulin, endogenous insulin levels, age of onset, and A1C, but the actual mechanism for lower BMD in type 1diabetes is not known.

Krakauer et al.[40] and Tuominen et al.[31] have separately compared patients with type 1 and type 2 diabetes treated with insulin, showing that exogenous insulin is not the cause of the bone loss. Krakauer et al. also found decreased BMD in men and women with type 1 diabetes as compared with those with type 2 diabetes or with control subjects.

Epidemiological studies at Rancho Bernardo, Calif.,[48] and in Rotterdam, The Netherlands,[49] suggested correlations between fasting and post-challenge insulin levels and BMD in women without diabetes, but in the Rotterdam group only, these lost significance after adjusting for BMI. In patients with type 2 diabetes, no consistent association of BMD with endogenous insulin levels, using fasting or post-challenge levels, has been found.[34,50,51] However, insulin levels are quite variable within type 2 diabetes because of the decline of β-cell function over the course of the disease.

An autoimmune- or inflammation-mediated process has also been considered because a decrease in BMD has been noted during the first several months to years after diagnosis, with an attenuation thereafter.[27,37,52] This suggests an initial insult not specifically related to control, but perhaps to the autoimmune process, similar to that seen in rheumatoid arthritis, in which bone loss is seen in the involved joints.

Increasing evidence suggests that type 1 diabetes in particular may impede new bone formation possibly because of defective function of osteoblasts, the primary cells responsible for bone formation.[53,54] Preliminary data suggest that poorly controlled diabetes with hyperglycemia and consequently increased osmolarity contribute to decreased osteoblast function.[53] In addition, patients with type 1 diabetes are known to have lower levels of insulin-like growth factor I, an anabolic hormone that maintains healthy bone formation.[55]

Markers of Bone Turnover

Serum and urine markers of bone turnover have been developed to assess short-term changes leading to osteoporosis. Serum levels of alkaline phosphatase and osteocalcin reflect bone formation, whereas serum levels of collagen cross-links reflect bone resorption. Osteoblast secretion of osteocalcin is decreased by high glucose levels, so bone formation as assessed by osteocalcin is decreased in proportion to diabetes control.[56] Thus, the markers are applicable only in limited situations and often require very good glycemic control and stability to be useful.

Bone resorption measured by deoxypyridinoline after a 12-hour glucose clamp was greater in age- and height-for-age-matched adolescents with diabetes than in control subjects, sug-

gesting that bone loss in early-onset type 1 diabetes is related to increased turnover.[57] This is important because instead of the presumed high turnover rate, as can occur with excess cortisol or with hyperparathyroidism, a low turnover resulting in adynamic bone, also seen in renal failure, is an alternate mechanism for osteoporosis. This possibility is also supported by the observation that fractures take a longer time to heal in diabetes.[58] Krakauer et al.[59] have proposed the possibility of a low turnover state due to functional hypoparathyroidism and hyperglycemia to account for the differences between type 1 and type 2 diabetes, but this has yet to be investigated. The heterogeneity of types of diabetes, as well as variable contributions from associated conditions affecting BMD, make it difficult to designate one underlying mechanism for diabetic osteopenia.

Risk Factors for Low Bone Mass or Fractures

Multiple risk factors have been identified that may contribute to low bone mass. Risk factors consistently associated with osteoporosis include female sex, Caucasian, low body weight (< 127 lb), and maternal or personal history of fractures.[60,61] Risks factors particular to patients with diabetes are included in Table 1.

Fractures are the most specific risk factor. A history of any previous fracture increases the risk of further fracture by at least twofold.[62] Patients with a vertebral fracture will be three to five times more likely to suffer another vertebral fracture within the next year[62,63] and are also at increased risk of sustaining a hip fracture when compared with women without a vertebral fracture.[64]

A hip fracture occurs most typically after sustaining a fall.[65] In the Study of Osteoporotic Fractures, older women with diabetes were found to have an increased risk of falls, which was increased even further in insulin users.[66]

Bone density decreases with age, as fracture risk rises rapidly.[10] Fracture risk varies by race, with hip fracture rates in African-American women reported to be one-third that of white women.[7,67] African-American and possibly Hispanic women tend to have higher BMD values when compared with white women, although these effects are less apparent when BMD is corrected for bone size.[68,69]

Diabetes-Associated Risk Factors

As discussed above, poor metabolic control is a risk for osteoporosis and fractures in diabetes. Additionally, factors extrinsic to the metabolic changes of diabetes, such as age of onset of type 1 diabetes in relation to stage of bone growth, or lifestyle factors such as obesity and inactivity in type 2 diabetes, have secondary consequences relative to BMD.

One such age-related risk for osteoporosis is low peak BMD. In American women, peak BMD is achieved by the end of the third decade.[68] Thus, to the extent that diabetes may cause osteopenia, women who are young at diabetes onset may never achieve a normal peak bone density and thus reach osteoporotic thresholds earlier in life (Figure 2).

Delayed puberty is associated with a lower peak BMD;[70] therefore girls with diabetes and delayed menarche may also reach a lower peak BMD. One carefully controlled Finnish study by Tuominen et al.[31] defined type 1 diabetes by C-peptide values and therefore was able to use only subjects who had been diagnosed after age 30. Even in these patients, BMD was lower in patients with type 1 diabetes compared with those with type 2 diabetes or with control subjects, suggesting a secondary loss of bone.

Another age-related factor is estrogen status, the major cause of osteoporosis in the general population. Because of their increased risk for menstrual dysfunction,[71] women with type 1 diabetes may also have osteopenia due to estrogen deficiency. Most studies have not assessed the menstrual histories in these women, but one study did find a positive correlation between oral contraceptive use and BMD in women with type 1 diabetes, supporting a component of estrogen deficiency.[72]

Eating disorders, which are more common in patients with diabetes, are associated with decreased bone density.[73] One of the strongest predictors of osteoporosis is low body weight,[74] which is more typical of patients with type 1 diabetes than of those with type 2 diabetes. The obesity commonly present in people with type 2 diabetes (and often for years before it develops) may have a cumulative protective effect on bone density.

Among women with osteoporosis, almost all hip fractures result from falls.[75] The risk of falling is increased by diabetic complications including impaired vision from retinopathy or cataracts and poor balance and orthostatic hypotension from peripheral and autonomic neuropathy. Acute hypo- and hyperglycemia may also cause impaired vision, poor coordination, and muscle

Table 1. Risk Factors for Osteoporotic Fractures in Diabetes

Risks for Osteoporosis

Directly due to diabetes
- Type 1 diabetes
- Poor glycemic control
- Nephropathy

Due to complications of diabetes
- Neuropathy
- Diabetic diarrhea

Due to diseases associated with diabetes
- Grave's disease
- Celiac sprue
- Amenorrhea
- Delayed puberty
- Eating disorders

Risks for Falls
- Episodes of hypoglycemia
- Episodes of nocturia
- Poor vision due to retinopathy or cataracts
- Poor balance due to neuropathy, foot ulcers, or amputations
- Orthostatic hypotension
- Impaired joint motility due to cheiropathy

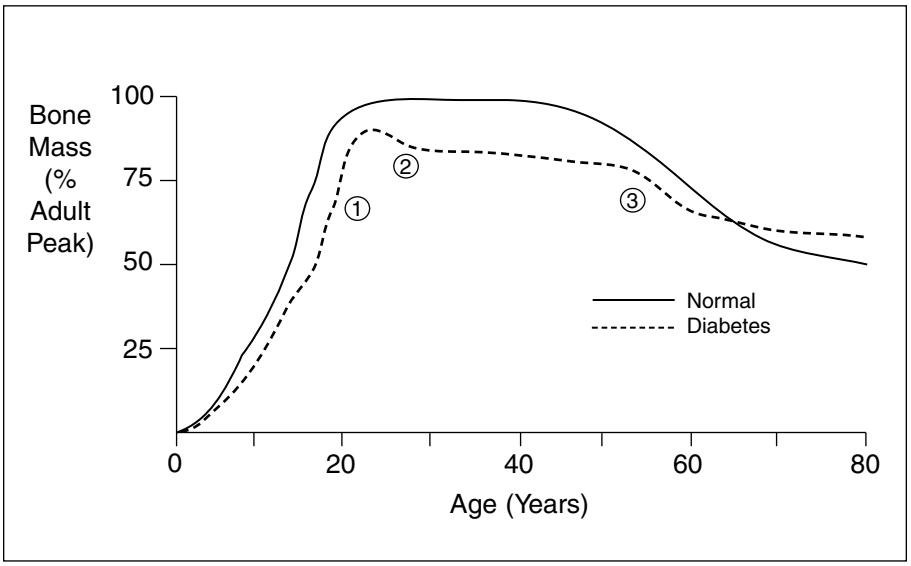

Figure 2. Model for the effects of diabetes on BMD at different times of life. Initial adolescent accumulation of bone is diminished (1), thus reaching a lower plateau with continued loss associated with hypercalciuria in early adult life (2), followed by later onset and retardation of age-related bone loss (3). Depending on the age of onset, stages could overlap. Reprinted with permission from ref. 40.

weakness. Patients with extensive neuropathy, foot ulcers, or amputations are at increased risk for falls and immobility-induced osteoporosis because of their limited mobility[76] (Table 1).

Several other diseases that increase the risk of osteoporosis are particularly relevant in diabetes. Diseases associated with autoimmune diabetes, including Graves' disease and celiac sprue, also carry an independent risk for osteoporosis. Treatments for hypertension and hyperlipidemia, which are associated with both types of diabetes, may also affect BMD. Use of loop diuretics to treat hypertension can increase urinary loss of calcium, whereas thiazides may decrease it. Interestingly, the large Canadian Multicentre Osteoporosis Study found an increase in BMD measurements in men and women with hypertension, even after adjusting for expected confounding factors such as type 2 diabetes, BMI, and thiazide use.[77] Although case-control studies have suggested that treatment of hyperlipidemia with HMG CoA reductase inhibitors may increase BMD,[78] these results have not been supported by other studies.[79]

There are preliminary data in animal studies that suggest thiazolidinediones, via actions on PPAR γ, may interfere with bone regulation.[80,81] The PPAR γ2 isoform may be important for differentiation of osteoblasts and adipocytes from a common progenitor cell. One group has reported that activation of PPAR γ may inhibit differentiation of osteoblasts or bone-forming cells. These results remain to be proved in human studies, and differences among thiazolidinediones may need to be investigated.

Screening Recommendations

There are no osteoporosis screening recommendations specifically for patients with diabetes. The U.S. Preventative Task Force recommends that screening should be routinely provided in all women over age 65 and in those women ages 60–64 who are at increased risk.[82] Risk factors were noted to be difficult to identify, but low body weight (< 70 kg) was found to be the best single predictor of low bone density. The National Osteoporosis Foundation also recommends screening for younger postmenopausal women (younger than age 65) who have had a fracture or who have one or more risk factors for osteoporosis. In patients with diabetes who do not yet meet these criteria, there are not yet evidence-based recommendations, but common sense would suggest BMD screening for type 1 patients, female or male with any complications, and thin women with other extensive complications of diabetes.

The age of the patient must be a factor since fracture risk is a function of age. Identification of osteopenia in a younger individual may help adherence with lifestyle interventions (adequate calcium, vitamin D, exercise, maintenance of regular menstrual cycles). It should be emphasized, however, that maintenance of healthy bone remodeling rather than near-term fracture prevention is the focus at younger ages since the 10-year fracture risk is low (< 10% at age 45 with osteoporosis by BMD).[83] Therefore, other therapeutic interventions (e.g., bisphosphonates) are rarely indicated.

Measures to Prevent Osteoporosis

In all individuals at risk for osteoporosis, appropriate nutrition and lifestyle interventions should be considered. Calcium is an accepted adjunct to anti-osteoporosis therapy. The National Academy of Science and National Institutes of Health recommend calcium intakes of 1,000–1,500 mg/day and vitamin D of at least 400–800 IU for postmenopausal women, particularly in individuals with little sun exposure.[84,85] A meta-analysis of all forms of vitamin D therapy suggest that overall there may be a reduced incidence of vertebral fractures.[86]

Regular exercise is important for healthy bone remodeling and to maintain muscle coordination and balance to decrease falls and therefore should be emphasized as an additional consideration beyond its benefits on glycemic control, atherosclerotic risk, and weight control.[87] Likewise, osteoporosis is one more reason smoking cessation is important for all patients with diabetes, although the effect of smoking on

osteoporosis outcomes is not rigorously studied.

Preventing falls in patients with diabetes is paramount, and beneficial interventions include muscle strengthening and balance retraining (use of walkers), home hazard assessment (use of nightlights), withdrawal of psychotropic medications, and use of multidisciplinary risk factor assessment programs.[88] Hip protectors have been demonstrated to reduce the risk of fractures in frail elderly adults.[89] These issues should be addressed in all diabetes patients with severe retinopathy or neuropathy or other risk factors discussed above.

Treatment Options

Any individual with a fracture should receive additional therapy, preferably with a bisphosphonate that has proven efficacy for hip and vertebral fracture reduction. It should be noted that the current treatment regimens have not been specifically tested in patients with diabetes and osteoporosis. Pamidronate (a bisphosphonate), however, has been efficacious in small studies of Charcot neuroarthropathy.[90]

The use of estrogen or estrogen-progesterone therapy continues to be a complex decision often based on factors other than osteoporosis benefits. In postmenopausal women who have not yet had a fracture but who have low BMD and risk factors, raloxifene or a bisphosphonate may be indicated, but this estrogen-antagonist should not be used in premenopausal women. Calcitonin should be relegated to second-line therapy but may be used in individuals who are unable to tolerate other regimens.

Parathyroid hormone (PTH) should be reserved for those at greatest risk (continuing fractures) initially due to its cost. The role of PTH in osteoporosis management, particularly in combination with bisphosphonates or for first-line management of fracture, is expected to be further clarified.

When considering therapeutic effects of osteoporosis agents, it should be recognized that most agents are primarily studied in Caucasian women who have adequate calcium and vitamin D intakes. For additional details, readers are referred to recent reviews of osteoporosis therapies[91,92] and to the summary of selected therapies in Table 2.

Clinical Considerations for Therapeutic Interventions

Treatment of osteoporosis for patients with diabetes is similar to that for patients without diabetes, except for those with nephropathy or gastrointestinal complications. Renal impairment necessitates evaluation of the parathyroid-vitamin D axis as well as dose adjustment of medications. Defects in bone metabolism in advanced renal disease are complex and require adequate therapies directed at bone turnover, phosphate control, and vitamin D suppression of PTH and have been recently reviewed in detail.[93] The current therapies for osteoporosis have not been clinically studied in renal failure. Gastroparesis, malabsorption or sprue, and diabetic diarrhea can all contribute to osteoporosis by interfering with calcium and vitamin D absorption and require separate evaluation and treatment.

Hormone therapy

Estrogen therapy has a consistent positive effect across trials in respect to increasing BMD (by 4–7% after 2 years) both in younger perimenopausal women and older postmenopausal women.[94,95] The Women's Health Initiative (WHI) is a large, randomized placebo-controlled trial of estrogen/progesterone therapy designed to demonstrate fracture efficacy.[96] Fractures of any type, including hip and vertebral fractures, were reduced with estrogen/progesterone therapy, resulting in five fewer hip fractures per 10,000 person-years of use.

These results are particularly important since hip fractures cause the most morbidity, and only one other class of agents, the bisphosphonates, has convincingly resulted in hip fracture reduction. Given the complexity of decision-making regarding estrogen therapy and the WHI conclusion that overall fracture benefit did not outweigh an increased global index of risk, the individual decision remains as always between patients and their providers.

Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption that increase BMD and reduce vertebral and non-vertebral fractures. Their oral bioavailability is low, and absorption is easily impaired (e.g., by calcium); thus they should be taken on an empty stomach. Additional recommendations include remaining upright and drinking water to ensure that tablets do not remain or reflux into the esophagus due to reports of esophagitis.[97]

Bisphosphonates have a long half-life in bone, with a continued decrease in bone loss for several years after cessation. Alendronate and risedronate have proven efficacy in the prevention and treatment of osteoporosis.[98,99] Both alendronate and risedronate are available in once-weekly doses that have been less well studied for fracture outcomes but increase BMD by a similar degree to daily dosing and may have better acceptability to patients.[100] No differences in gastrointestinal tract tolerability have been found for the different dosing regimens of alendronate.[101]

Selective estrogen receptor modulators

The WHI report has resulted in increased interest in alternatives to hormone therapy, particularly in selective estrogen receptor modulators such as raloxifene. Raloxifene acts as an agonist on bone and cholesterol metabolism and an antagonist at breast tissue and appears to have a neutral effect on uterine tissues.[102] Raloxifene does have the same clotting risks as estrogen and has not yet been studied with regard to the cardiovascular endpoints that terminated the WHI.

Table 2. Selected Therapeutic Agents for the Treatment of Osteoporosis

Class	Drug	Typical dose	Potential adverse effects	Increase in spine BMD (duration of therapy)[106,110,124]	Vertebral fracture reduction?	Hip fracture reduction?
Hormone therapy	Estrogen + progesterone	0.625 mg/ 2.5 mg by mouth daily	Venous thromboembolism; breast cancer	5–7% (2 years)	+++	++
Bisphosphonates	Alendronate	10 mg by mouth daily or 70 mg by mouth once a week	Administer while fasting, with 8 oz. water in upright position for 30 min. to prevent pill-induced esophagitis; contraindicated if CrCl < 30–35 cc/min; abdominal pain, dyspepsia	5–6% (2–3 years)	+++	++
	Risedronate	5 mg by mouth daily or 35 mg by mouth once a week		4–5% (1.5–3 years)	+++	++
Selective estrogen receptor modulator	Raloxifene	6 mg daily	Venous thromboembolism; hot flashes	2–3% (2–3 years)	+++	No*
Calcium regulating hormone	Calcitonin	200 IU nasal spray daily	Rhinitis	1–3% (5 years)	+	No
Anabolic hormone	Parathyroid hormone (teriparatide or rhPTH 1–34)	20 μg subcutaneously	Arthralgias; transient orthostatic hypoytension; contraindicated with nephrolithiasis or bone metastases	9% (18 months)	+++	Non-vertebral combined (++)**

+++ = strong consistent effects; ++ = consistent effects; + = some effects; rhPTH = recombinant humant parathyroid hormone; CrCl = creatinine clearance
*Not yet demonstrated for hip fracture reduction. The MORE trial[103] enrolled slightly younger women than the biphosphonate trials demonstrating hip fracture reduction.[125,126]
**Has demonstrated efficacy in reducing nonvertebral fractures combined but not hip fractures alone.

The largest placebo-controlled randomized controlled trial to evaluate the effects of raloxifene on fracture outcomes was the Multiple Outcome of Raloxifene Evaluation (MORE) trial of 7,705 postmenopausal women.[103] Despite only modest increases in BMD (2–3% in 3 years), a significant decrease in vertebral fractures was found in both patients with osteoporosis by BMD and those with vertebral fractures. The MORE data showed that despite relatively modest BMD increases compared to the bisphosphonates, similar absolute reductions in vertebral fractures can be found. However, no reduction in nonvertebral fractures (particularly hip) has been shown.

With respect to patients with diabetes in the MORE trial, raloxifene was not found to impair glycemic control and had similar favorable effects on lipid profiles as in women without diabetes.[104] In addition, abstracts from the MORE trial have reported no difference in BMD improvement or bone turnover markers in patients with or without diabetes.[105]

Calcitonin

Calcitonin, an endogenous peptide that inhibits bone resorption, is available in nasal and subcutaneous forms that make it an appealing alternative for women who do not tolerate bisphosphonates or raloxifene. However, it should be relegated to second-line therapy due to the lack of convincing fracture efficacy. Although a meta-analysis found calcitonin decreased vertebral fractures, most subjects were in the PROOF trial, which has come under scrutiny because of its lack of dose-response effect and significant loss to follow-up, which limits conclusions regarding its effect on vertebral fracture.[106]

PTH

PTH (1–34 fragment) is a new anabolic agent directed at stimulating bone formation. Increases in BMD at the spine are greater than those achieved with the antiresorptive regimens discussed previously

with rates up to 7–13% at the spine with no change or increases of 3% reported at the femoral neck.[107–109] The largest randomized controlled trial found reduced vertebral and nonvertebral fragility fractures after a median of 21 months of therapy in 1,637 postmenopausal women with vertebral fractures.[110] Adverse events may include mild asymptomatic hypercalcemia occurring early in treatment.[110] Preclinical studies in rats given long-term PTH at high doses found an increased risk of osteosarcoma.[111] This has not been observed in any human studies but had led the Food and Drug Administration to limit therapy duration to 2 years.

Combination therapies

Estrogen has been studied in combination therapy with alendronate,[112–114] risedronate,[115] and calcitonin,[116] and the combinations generally resulted in greater BMD, although site-specificity may differ by agent. Alendronate combined with raloxifene was more effective at increasing BMD at the spine and hip than raloxifene alone and was more effective at the femoral neck than alendronate alone.[117] Calcitonin given sequentially following PTH was not different than PTH alone[118] and was not as effective at increasing BMD when compared to alendronate alone.[119] BMD gains with PTH can be preserved when followed by alendronate[120] or estrogen therapy.[121] However, recent data suggest that PTH given in combination with alendronate may not have synergistic effects.[122,123]

Conclusions

Care of patients with diabetes should include an assessment of bone health. It has become increasingly clear that patients with type 1 diabetes have lower BMD and higher risk of fractures. Evidence is accumulating that patients with type 2 diabetes and complications, who were once thought to be protected from osteoporosis due to higher BMD and obesity, may in fact be at higher risk of fracture. Further work toward understanding the particular bone response to diabetes is important for disease-specific tailored prevention and therapeutic strategies.

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