

# Osteoporosis and Diabetes

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**O**steoporosis is a bone condition defined by low bone mass, increased fragility, decreased bone quality, and an increased fracture risk.<sup>1</sup> It is the most prevalent metabolic bone disease in the United States. Using World Health Organization (WHO) criteria, the third National Health and Nutrition Examination Survey (NHANES III, 1988–1991) reported that 34–50% of postmenopausal white women have osteopenia (T score  $-1$ – $-2.49$ ) and ~17–20% have osteoporosis (T score  $\leq -2.5$ ).<sup>2</sup> Both low bone mass conditions increase fracture risks, with osteoporosis having the greater impact.

In 1995, the National Osteoporosis Foundation (NOF) reported the annual cost of treating osteoporotic fractures to be \$13.8 billion, an amount that is expected to double over the next 25 years because of the increasing elderly population.<sup>3</sup>

Although the disease historically has been reported mostly in white women, it can affect individuals of either sex and all ethnic groups.

Osteoporosis is not symptomatic until there is a fracture. One in five women are not diagnosed with osteoporosis despite presenting with a fracture. Any fracture (unrelated to motor vehicle accidents) sustained between the ages of 20 and 50 years is associated with a 74% increase in the future risk of fractures after the age of 50 years.<sup>4</sup> Thus, the true occurrence of osteoporosis may be significantly underestimated because many women who suffer minimal trauma fractures still are not being evaluated for osteoporosis.<sup>5</sup>

The incidence of fractures increases with age, and this is associated with an increased mortality rate and an overall functional decline. During the first year following a hip fracture, the mortality rate is 36% for men and 21% for women.<sup>6</sup> In certain patient groups, such as those with psychiatric disorders, the mortality rate has been reported to be  $>50\%$ .<sup>7</sup>

If patients survive their fractures, they face greater risks of having a permanent disability and often require long-term nursing home care. The degree of recovery after a fracture is age- and disease-dependent. Those who are younger or healthier have better outcomes.

Osteoporosis is a major public health problem because of its associated fractures. Thus, identifying and evaluating populations at increased risk of developing osteoporosis is critical to disease prevention and management. Although osteoporosis traditionally has not been listed as a complication of diabetes, patients with either type 1 or type 2 diabetes are among those at increased risk for this disease. In this article, we review this important relationship.

## Risk Factors

There are many known risk factors for osteoporosis and fractures. In addition to the risk factors noted in Table 1, there are also physical characteristics of bone that contribute to the occurrence of osteoporotic fractures. Historically, bone strength has been determined by bone mass, geometry, and quality. The WHO defines osteoporosis in terms of bone density measurements compared to the young adult mean. Bone mineral density

(BMD) obtained via dual x-ray absorptiometry (DXA) is the most common standard tool for bone mass assessment.

Although DXA is the best current predictor and evaluator of osteoporosis, it is not a perfect diagnostic tool because there are many micro-architectural bone qualities and bone geometries that are not detectable via DXA. Therefore, a comprehensive risk assessment for osteoporosis should reach beyond BMD measurements. This is particularly true when assessing patients with diabetes. Old debates regarding whether diabetes

**Table 1. Osteoporosis Risk Factors**

### Modifiable

- Cigarette smoking
- Low body weight ( $<127$  lb)
- Estrogen or androgen deficiency
- Low calcium intake
- Excessive alcohol intake
- Inadequate physical activity or falls risks
- Medications (e.g., steroids, anti-seizure medications, hormone suppressants, vitamin A)
- Chronic conditions (e.g., thyroid, liver, or renal disease; cystic fibrosis; diabetes)

### Non-modifiable

- White race
- Advanced age
- Female sex
- Dementia
- Poor health/frailty
- History of fracture in first-degree relative
- Personal history of fracture as adult

Adapted from ref. 8.

is associated with an increased risk of osteoporosis are largely resolved if all risk factors are considered.

### Type 1 diabetes

Type 1 diabetes has long been associated with low bone density. However, it was unclear until recently whether this translated into increased fracture rates. Results from the Nord-Trondelag Health Survey from Norway showed a significant increase in hip fracture rates among female type 1 diabetic patients (relative risk 6.9, confidence interval 2.2–21.6) compared to nondiabetic female patients.<sup>9</sup>

Duration of diabetes seems to play a key role given the lower BMD found among patients who have had diabetes for >5 years. In the Iowa Women's Health Study, women with type 1 diabetes were 12.25 times more likely to report having had a fracture compared to women without diabetes.<sup>10</sup>

The mechanism of bone loss in type 1 diabetes is still unknown, although several theories exist based on animal and cellular models. Insulin-like growth factors and other cytokines may influence diabetic bone metabolism.<sup>11</sup> Diabetic retinopathy, advanced cortical cataracts, and diabetic neuropathy have all been associated with increased fractures.<sup>12,13</sup> These are also risk factors for increased falls because of visual impairment and alterations in balance or gait.

For patients with type 1 diabetes, the initial onset of the disease often occurs at a young age, when bone mass is still being accrued. Thus, low bone mass would seem a likely complication of type 1 diabetes.

### Type 2 diabetes

Type 2 diabetes was previously believed to provide bone protection because of its associated normal to increased BMD. These reports were primarily based on the concept of BMD alone and were generally not from prospective controlled large trials.

When considering all of the risk factors (Table 2), patients with diabetes

generally have an increased risk of falling because of peripheral neuropathy, possible hypoglycemia, nocturia, and visual impairment. Because many type 2 diabetic patients are obese and sedentary, coordination and balance factors that are protective in falls may be absent. Thus, patients with generally larger body size and relatively high bone mass may have higher fracture rates. Conversely, patient groups with low BMD, such as Asians, may have lower fracture rates when one considers all factors in a risk assessment.

Bone quality changes may also be affected by microvascular events common in diabetes.<sup>14</sup> Schwartz et al.,<sup>15</sup> in a large prospective study of older women obtained from the Study of Osteoporotic Fractures, confirmed that women with type 2 diabetes experience higher fracture rates in regions of the hip, humerus, and foot than do nondiabetic women. Bone loss has been observed to be greater in patients with poorly controlled diabetes than in those whose diabetes is in good control.<sup>16</sup>

### Gestational diabetes

Diabetes that occurs during pregnancy has not been reported to be associated with bone loss in prospective trials. However, a small study involving Hispanic women with gestational dia-

betes noted that 40% of the 20 enrolled subjects had DXA-detected bone loss within 3 months postpartum.<sup>17</sup>

Advanced age and higher oral glucose tolerance test values during pregnancy may be associated with increased bone loss. Larger prospective studies are needed to confirm these findings.

### Prevention

Prevention of osteoporosis requires not only recognition of populations who are at risk, but also screening programs targeting those populations.

Available BMD screening options include DXA (central and peripheral), peripheral quantitative ultrasound (QUS), and quantitative computed tomography (QCT). These tests have differing strengths, but none alone addresses all of the issues involved in disease assessment. Decisions regarding which method to use depend on the indications for the evaluation.

The NOF recommends baseline BMD screening of all postmenopausal women over the age of 65 and of those under age 65 who are in high-risk groups. In addition to screening, attempts should be made to address all potentially modifiable risk factors. If patients are at an increased risk of falling, a comprehensive falls evaluation and gait-training program (e.g., physical therapy, tai-chi) may be beneficial.<sup>18</sup> Additionally, patients should be advised to wear hip protectors. These devices have been reported to reduce the risk of hip fractures by 60%.<sup>19</sup>

### Evaluation

All patients who present with low trauma fractures should be evaluated for primary or secondary osteoporosis. Primary osteoporosis is the most common form of bone loss and refers to that seen in postmenopausal women or elderly individuals of either sex. Secondary osteoporosis is that caused by an associated medical illness. All patients should have a comprehensive history and physical exam with a focus on potential secondary causative factors for osteoporosis.

**Table 2. Risk Factors for Falls Among Patients With Diabetes**

#### Vision-Related

- Diabetic retinopathy
- Advanced cataracts (visual field deficits)
- Laser therapy for retinopathy (peripheral and night vision decreases)
- Hypoglycemia

#### Gait/Balance-Related

- Peripheral neuropathy
- Foot ulcers
- Polyuria and nocturia, urgent and frequent trips to the restroom, especially at night
- Decreased reflexes

Osteoporosis usually is not associated with symptoms. If a review of symptoms reveals weight loss, diarrhea, weakness, persistent bone pain, kidney stones, or other complaints, then thorough evaluations should be pursued to try to identify an underlying illness. Diseases known to cause low bone mass include intestinal malabsorption, anorexia nervosa, cystic fibrosis, Marfan's syndrome, chronic renal disease, amenorrhea, hypogonadism, thyroid and parathyroid disease, multiple myeloma, acquired immunodeficiency syndrome, liver diseases, and vitamin D deficiency, among others. If history and physical exam do not point clearly toward any other pathology as a cause for the bone loss and if there are risk factors present, an extensive evaluation often is not needed.

Although no consensus exists regarding a standard evaluation, common screening studies are appropriate before starting therapy. These include thyroid function test (subclinical disease); a comprehensive chemistry panel (kidney, liver function, calcium, phosphorus, and albumin); complete blood count (bone marrow process); and 24-hour urine calcium (low levels suggest vitamin D deficiency, and high levels are seen with hypercalciuria).<sup>20</sup> If a 24-hour urine collection is not feasible, a 25-hydroxy (OH) vitamin D level should be considered. A bone density test should be performed to assess the severity of disease.

Interpretations of these tests are fraught with technical errors, but when done correctly, they can aid in the overall assessment of disease. Any further testing should be tailored to the individual patient's needs.

**Treatment**

Treatment should be offered to all patients with osteoporosis-related fractures (Table 3).

**Nonpharmacological therapy**

The NOF recommends that all adults receive at least 1,200 mg/day of elemental calcium and 400–800 IU/day of vita-

**Table 3. Treatment Options for Osteoporosis**

<p><b>Nonpharmacological</b></p> <ul style="list-style-type: none"> <li>• Calcium</li> <li>• Vitamin D</li> <li>• Exercise</li> <li>• Surgical interventions</li> </ul> <p><b>Pharmacological</b></p> <ul style="list-style-type: none"> <li>• Hormone replacement therapy</li> <li>• Selective estrogen receptor modulators</li> <li>• Calcitonin</li> <li>• Biphosphonates</li> <li>• Anabolic agents</li> </ul>
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min D. Supplements, food, and juices can all be good sources of calcium. Urinary calcium increases are higher with calcium citrate. Thus, many experts believe that calcium citrate is more readily absorbed than calcium carbonate in standard available doses. Calcium should be given with meals to enhance absorption. Ninety percent of our vitamin D supply comes from the skin's production of this nutrient through sunlight activation. Vitamin D deficiencies can easily occur in people who spend most of their time indoors, especially elderly patients, whose skin activity has diminished with age.

Exercise can have many clinical benefits. In addition to improvements in bone mass, it also results in improved overall muscle strength, which is important in preventing falls. It should be noted that while exercise is advocated, patients should not undertake exercise programs that could be harmful. Patients who have vertebral osteoporosis, for example, should avoid back flexion exercises, particularly those involving weights, because such activities can increase fractures.<sup>21</sup>

Appropriate exercise programs may also reduce pain from vertebral compression fractures. If pain persists longer than 3 months after compression fractures, minimally invasive surgical options, such as vertebroplasty and kyphoplasty, are available. Kyphoplasty has the advantage of potentially restoring

vertebral body height loss from the compression. Both procedures can improve pain and restore function. However, these procedures do not address the underlying osteoporosis.

**Pharmacological therapy**

Hormone replacement therapy (HRT) was long thought to be the treatment of choice for osteoporosis because it improved in BMD at the hip and spine by 5% and 2.5%, respectively.<sup>22</sup> However, views on this issue have changed recently because of the lack of hip fracture reduction data from large randomized controlled trials. The Food and Drug Administration (FDA) removed the approval of estrogen for the *treatment* of osteoporosis, but did permit estrogen to maintain its indication for the *prevention* of osteoporosis. Although combination HRT has not been shown to have definitive adverse effects on glucose metabolism, its use in women with type 2 diabetes should be limited to low dose formulations as recommended by the recent consensus statement from the North American Menopause Society (NAMS).<sup>23</sup>

For men, androgen replacement in those who qualify for it has resulted in improvements in BMD.<sup>24</sup> Androgen replacement is contraindicated in men with a history of prostate cancer. Little is known about the metabolic effects of testosterone on diabetes.

Raloxifene (RLX, Evista) is a selective estrogen receptor modulator (SERM) that has indications for both prevention and treatment of osteoporosis.<sup>25</sup> Trials involving SERMs have shown a 55% reduction in vertebral fractures.<sup>26</sup> Both estrogens and SERMs have a small increased risk of thromboembolic disease. Recent published trials measuring fasting blood glucose, hemoglobin A1c, and insulin levels in type 2 diabetic patients revealed that RLX does not significantly affect glycemic control.<sup>27</sup>

Salmon calcitonin is a synthetic polypeptide that duplicates the molecular structure of calcitonin found in the salmon fish. Salmon calcitonin is more

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potent than human calcitonin in its effects on bone osteoclasts. Its use has been approved by the FDA for treatment of postmenopausal osteoporosis. Calcitonin inhibits osteoclast-induced bone resorption. Calcitonin (salmon) nasal spray (Miacalcin) is the most convenient form of the drug currently available and has minimal side effects compared to other treatments. However, data from large trials have shown no major increase in BMD.<sup>28</sup> Calcitonin may reduce vertebral fractures via effects on bone quality that are not detectable when measuring BMD. No large trials have established calcitonin's effectiveness in the prevention of osteoporosis in early menopause.

Hyperglycemic effects of salmon calcitonin have been reported. Inhibition of insulin secretion may be related to this effect.<sup>29</sup> There are no large randomized trials to support any significant effect on diabetes control from the use of nasal salmon calcitonin. A small trial involving insulin-dependent diabetic patients suggested that calcitonin depresses elevated levels of circulating glucagon and glucose.<sup>30</sup>

The current treatment recommendations have shifted toward the use of bisphosphonates (BPNs) as a result of numerous clinical trials showing marked reductions of 40 to 50% in both spine and hip fractures.<sup>31,32</sup> BPNs also inhibit osteoclast function and decrease bone turnover. The oral BPNs alendronate (Fosamax) and risedronate (Actonel) have poor absorption rates and must be taken on an empty stomach with 6–8 oz of water. They are indicated for both prevention and treatment of osteoporosis.

A combination of HRT/BPN therapy has been shown to increase BMD.<sup>33</sup> Although not considered significant, there were more fractures reported among users of an HRT/BPN combination than among users of an HRT/placebo combination.

There have been no negative reports in large randomized controlled trials regarding the use of BPNs in those with diabetes. In fact, a recent small trial sug-

gests that alendronate may actually decrease daily insulin requirements (–21.6% at 12 months and –36.2% at 24 months) among type 1 diabetic patients with osteoporosis.<sup>34</sup> Larger confirmatory trials are needed.

Parathyroid hormone (PTH) is a potent anabolic agent for the treatment of osteoporosis that will soon enter the U.S. drug market under the trade name Forteo. PTH is the principal regulator of calcium homeostasis. Although both primary and secondary hyperparathyroidism can cause osteoporosis, intermittent exposure to PTH can enhance bone mass.

The paradoxical effects of PTH on bone have not been clarified. A large randomized clinical trial by Neer et al.,<sup>35</sup> reported that treatment of postmenopausal osteoporosis with PTH (1–34) decreased the risk of vertebral and nonvertebral fractures and increased vertebral, femoral, and total-body BMD. Thus PTH appears to hold promise for the treatment of osteoporosis.

### Summary

Osteoporosis is a highly prevalent disease that has devastating effects. Aggressive screening of high-risk populations is warranted.

Recognition of at-risk patients is critical in both prevention and treatment of osteoporosis. Having either type 1 or type 2 diabetes increases a patient's risk of developing an osteoporosis-related fracture. BMD measurements, although supportive of the diagnosis of osteoporosis in diabetic populations, are not foolproof assessment tools. All diabetes-related factors should be considered in assessing osteoporosis, and fracture risk reduction should be recommended to diabetic patients.

Patients with low-impact fractures or osteoporosis should be offered treatment including both nonpharmacological and pharmacological therapies. Many agents are available for the prevention and treatment of osteoporosis in the diabetic population. The decision to initiate therapy should be individualized.

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