Osteoporosis Among Patients With Diabetes: An Overlooked Disease

Diane L. Chau, MD; Jordi Goldstein-Fuchs, DSc, RD; and Steven V. Edelman, MD

Although osteoporosis is the most prevalent metabolic bone disease in the United States, its impact in a people with diabetes is not often considered. Routine screening or initiation of preventive medications for osteoporosis in all patients with type 1 or type 2 diabetes is not recommended at this time. However, all patients with diabetes, and particularly those with fractures, should be given general recommendations regarding adequate dietary calcium intake, regular exercise, and avoidance of other potential risk factors. Consideration of bone density evaluation should be part of the fracture evaluation, and respective preventive or therapeutic interventions should be applied.

Case Presentation

S.A. is a 48-year-old white woman who has had type 1 diabetes for 28 years and has been on numerous insulin regimens. She presents with acute ankle and wrist pain after tripping over her new small dog and falling onto her outstretched right hand.

Her past medical history reveals a fracture involving her first metacarpal 5 years ago while she was learning to snow board. She has no family history of osteoporosis. She does not smoke or drink alcohol. Her diet history is poor because she "eats on the run."

S.A. has maintained her hemoglobin A_{1c} [A1C] around 7.5–8% during the past 5 years. She states that she has had A1C concentrations close to 8% for most of her life with diabetes.

She recalls having a height of 5'6" in her 20s, but she is currently 5'4" tall. Her weight is 120 lb., giving her a body mass index (BMI) of 20.6 kg/m^2.

She has had normal menses all of her life until her current perimenopausal state. She has developed complications of diabetes including mild neuropathy and retinopathy without laser therapy.

Physical examination reveals a mild dowager's hump and right wrist and ankle edema, with pain to palpation. X-rays confirm fractures at both sites. She is placed in splints and referred to an orthopedic surgeon for further evaluation.

Six months later, S.A. returns for a visit with her primary care provider with healed fractures.

Laboratory values obtained at her 6-month follow-up, including serum calcium, alkaline phosphatase, complete blood count, complete chemistry profile, thyroid-stimulating hormone, and urinary calcium, are all normal. A bone density measurement shows a hip T score of ¯1.5 and spine L1-L4 T score of ¯2.8.

S.A. is started on a weekly bisphosphonate (BPN); calcium, 500 mg three times daily; and vitamin D, 600 IU/day. A nutrition consultation is requested for evaluation of her overall diet, with an emphasis on adequate calcium intake.

The physical therapy department evaluates her gait and works with her on gait maneuvers to decrease her falling risk. She is advised to wear hip pads in all of her activities to protect her in case of a fall.

In addition, she is referred to an eye specialist to optimize her visual acuity, and she is given home safety advice to reduce the risk of falls around her home.

Discussion

This case illustrates a common presentation of osteoporosis in a patient with type 1 diabetes. Osteoporosis is a bone condition defined by low bone mass, increased fragility, decreased bone quality, and an increased fracture risk.[1] 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 ≤ ¯2.5).[2] Both low bone mass conditions increase fracture risks, with osteoporosis having the greater impact.

Any fracture unrelated to motor vehicle accidents that is 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.[3] Thus, it is important not only to treat a patient's present fracture, but also to implement a plan for future fracture risk reduction.

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. However, because of the different

pathogenetic mechanisms of type 1 and type 2 diabetes, there is no uniform entity of diabetic osteopathy. In the remainder of this article, we review the important relationship between diabetes and osteoporosis and the current management recommendations.

Risk Factor Assessment

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 include a falls risk assessment, visual acuity testing, and nutrition evaluation. Risk factors for osteoporosis are listed in Table 1.

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[4] showed a significant increase in hip fracture rates among females with type 1 diabetes (relative risk 6.9, confidence interval 2.2–21.6) compared to nondiabetic age-matched female control subjects.

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,[5] women with type 1 diabetes were 12.25 times more likely to report having had a fracture than women without diabetes.

Diabetic retinopathy, advanced cortical cataracts, and diabetic neuropathy have all been associated with increased fractures.[6,7] These are also risk factors for increased falls because of visual impairment and alterations in balance or gait. Thus, any diabetic patient presenting with an osteoporosis-related fracture should also have vision and balance evaluations.

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 is not a surprising complication of type 1 diabetes. Levels of glucose control among this population has not been correlated with the severity of osteoporosis. However, bone resorption is decreased during periods of high blood glucose.[8]

Type 2 diabetes

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. Bone quality changes may also be affected by microvascular events common in diabetes.[9]

Schwartz et al.,[10] 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 than do nondiabetic women in regions of the hip, humerus, and foot.

Bone loss has been observed to be greater in patients with poorly controlled diabetes than in those whose diabetes is in good control.[11] Bone resorption has been reported to be higher in patients with poorly controlled type 2 diabetes, and this was shown to normalize with glycemic control.[8] Had the present case involved a patient with type 2 diabetes, a similar evaluation and treatment recommendation would have been performed.

Evaluation

Although no consensus exists regarding a standard evaluation, common screening studies were obtained for S.A. to rule out any potential secondary causes of osteoporosis before starting therapy. Theses 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).

A bone density test was performed to assess the severity of her disease. Interpretations of these tests are fraught with errors. Had her DXA test report shown normal bone density, the formal report would have been requested for review to rule out technical errors that may cause the test to be falsely normal.

Table 1. Osteoporosis Risk Factors

Modifiable	Nonmodifiable
Cigarette smoking	White race
Low body weight (< 127 lb.)	Advanced age
Estrogen or androgen deficiency	Female sex
Low calcium intake	Dementia
Excessive alcohol intake	Poor health/frailty
Inadequate physical activity or falls risks	History of fracture in first-degree relative
Medications (e.g., steroids, anti-seizure medications, depot medroxyprogesterone acetate, hormone suppressants, vitamin A)	Personal history of fracture as an adult
Chronic conditions (e.g., thyroid, liver, or renal disease; cystic fibrosis; diabetes)	

Table 2. Risk Factors for Falls Among Patients With Diabetes

Vision-Related	Gait/Balance-Related
Diabetic retinopathy	Peripheral neuropathy
Advanced cataracts (visual field deficits)	Foot ulcers
Laser therapy for retinopathy (peripheral and night vision decreases)	Polyuria and nocturia, urgent and frequent trips to the restroom, especially at night
Hypoglycemia	Decreased reflexes

If a normal test was confirmed, an argument regarding the micro-architectural abnormalities not seen on DXA could be made to clinically treat this patient given her history of low impact fractures. Although there is lack of data regarding the use of drug treatments in the case of a normal DXA, other treatment interventions discussed are still applicable regardless of DXA results.

Treatment

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

Nonpharmacological therapy

Nutritional considerations. Several nutrients and metabolic factors have an impact on the development and maintenance of adequate bone mass and density. Protein; phosphorus; calcium; vitamins C, D, and K; fluoride; manganese; and zinc all play a role in bone development and maintenance.[12] The calcium-to-phosphorus ratio, caffeine and sodium intake, and body weight are other factors that have all been considered when evaluating the optimal nutritional intervention for osteoporosis prevention and management.

However, it has been well documented that of all these nutrients, dietary calcium intake by most Americans, particularly females, is below the recommended levels for optimizing bone mass during growth and minimizing bone loss during aging.[12] Therefore, the focus of nutrition recommendations for osteoporosis has been on this important mineral.

The National Osteoporosis Foundation (NOF) recommends that all adults receive at least 1,200 mg/day of elemental calcium and 400–800 IU/day of vitamin D. Dietary supplements are helpful in meeting the NOF recommendations for calcium. Increases in urinary calcium are higher with calcium citrate than with other forms of calcium supplementation. 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.

The bioavailability of calcium from foods needs to be considered when determining total dietary calcium intake and planning calcium-adequate diets.[12] In animal-derived foods, calcium is attached to readily digested protein, which is then absorbed. In contrast, the calcium in some vegetables is in complex forms that are indigestible or in the form of poorly absorbed phytates and oxalates (organic anions).[13] A 1-cup (8-oz.) serving of milk, which provides 300 mg of calcium, will actually provide ~99 mg of delivered calcium. In contrast, a 300-mg serving of spinach, will provide ~9 mg of delivered calcium.[12]

Dairy products, particularly fluid milk, are a concentrated source of soluble dietary calcium. For patients who are lactose-intolerant, the calcium from soybeans is well absorbed. Current fortification of foods with calcium will assist in planning diets providing a higher level of calcium. Beverages such as orange juice and bread products enriched with calcium are now readily available. Table 4 provides a listing of the average calcium content of selected foods.

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. A main role of vitamin D in bone health is to promote intestinal calcium absorption. Therefore, vitamin D and calcium impact osteoporosis in an interdependent manner.

Excessive intake of vitamin D, a fat-soluble vitamin, can lead to toxicity, promote soft tissue calcification (particularly in the kidney), and induce hypercalcemia. Vitamin D deficiency can result in secondary hyperparathyroidism and increased bone turnover.

The 400–800 IU/day recommendation for vitamin D is more easily met than the recommendation for calcium. Milk is fortified to provide 400 IU of vitamin D, and many grain products are enriched in vitamin D.

The key to nutrition management of diabetes and osteoporosis is to provide an individualized diet that meets the goals of optimal blood glucose control and maximizes calcium intake by eating a wide variety of foods.

Weight control. It is recognized that lean women are at a higher risk of developing osteoporosis than are heavy women. However, obesity and overweight are associated with comorbidities including type 2 diabetes, hypertension, cardiovascular disease, and hypertension. It is therefore recommended that nutrition intervention include weight management such that body weight falls within the acceptable BMI range of 18.5–24.9 kg/m^2.

Table 3. Treatment Options for Osteoporosis

Nonpharmacological	Pharmacological
Calcium	Hormone replacement therapy
Vitamin D	Selective estrogen receptor modulators
Exercise	Calcitonin
	Bisphosphonates
	Anabolic agents

Table 4. Average Calcium Content of Selected Foods[24]

Food (portion size)	Calcium (mg)
Dairy products	
Milk, 2% (1 cup)	295
American cheese (1 oz.)	146
Cottage cheese, low-fat (1/2 cup)	76
Ice cream, vanilla (1/2 cup)	84
Yogurt, flavored, nonfat (1 cup)	326
Fruits/Juices	
Figs, dried (5)	135
Orange (1 average)	50
Orange juice, calcium-fortified (1 cup)	285
Vegetables	
Broccoli, cooked (1/2 cup)	45
Bok Choy cabbage (1/2 cup)	80
Okra, cooked (1/2 cup)	75
Protein	
Almonds, raw (2 oz.)	150
Beans, black, cooked (1 cup)	120
Egg, 1 average	28
Soybeans (1 cup)	175
Soymilk, fortified (1 cup)	350
Soymilk, unfortified (1 cup)	10
Salmon, canned with bones (3 oz.)	180
Sardines, canned with bones (3 oz.)	65
Sardines (100 g)	368

as recommended by the National Institutes of Health.[14]

Exercise, along with diet, is a critical component of successful weight management programs. Exercise can have many clinical benefits. In addition to yielding 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.[15]

Stretching, strengthening, impact, and balance exercises are effective ways to improve flexibility and prevent falls. Of the balance exercises, tai chi has proved to be the most successful in decreasing falls.[16]

Pharmacological therapy

Of the available prescription agents available for osteoporosis treatment, a BPN was chosen as the therapeutic agent for S.A. because there are data to support reduction of both vertebral and hip fractures with its use. Hip fractures are associated with morbidity that results in loss of independence and is our primary target for future fracture reduction for the patient discussed. BPNs are also available in an oral weekly formulation, making compliance easier for S.A., who is always on the go. Most current treatment recommendations have shifted toward the use BPNs as a result of numerous clinical trials showing marked reductions of 40–50% in both spine and hip fractures.[17]

There have been no negative reports in large randomized controlled trials regarding the use of BPNs in people with diabetes. In fact, a recent small trial suggests 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.[18] Larger confirmatory trials are needed.

Had this patient not been able to tolerate bisphosphonate therapy, our second choice might have been raloxifene (RLX), although there are no hip fracture reduction data for this product. Recent published trials measuring fasting blood glucose, A1C, and insulin levels in type 2 diabetic patients revealed that RLX does not significantly affect glycemic control.[19]

The other agents available, including salmon calcitonin, have been approved by the Food and Drug Administration for treatment of postmenopausal osteoporosis. Hyperglycemic effects of salmon calcitonin have been reported. Inhibition of insulin secretion may be related to this effect.[20] 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.[21]

Estrogen and parathyroid hormone (PTH) therapy were not chosen for this patient because they are not indicated based on current literature. Results from the recent Women's Health Initiative study[22] indicate that combination hormone replacement therapy should not be initiated or continued for the primary prevention of coronary heart disease because the overall health risks (e.g., development of breast cancer, heart disease, stroke, and blood clots) exceed the benefits (e.g., reduction in hip fractures and colon cancer rates). PTH is a potent anabolic agent that has been shown to increase bone density of both spine and hip when given as an intermittent injection.[23] However, it is currently not used as first-line treatment for osteoporosis and is quite costly compared to the other agents available.

Patient Education Points

Patients with diabetes should be educated about the following:

- BMD screening is necessary for all postmenopausal women > 65 years of age and of those < 65 who are in high-risk groups.
- Patients with low bone density or high falls risk should wear hip protectors. These devices have been reported to reduce the risk of hip fractures by a significant 60%.[24]
- Proper nutrition should include a variety of calcium-containing foods. Exercise, including a balance program, is also important.
- Home safety measures should be implemented to reduce hazards around the home that could increase the risk of falls.

Summary

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. The decision to initiate therapy should be individualized.

References

[1]World Health Organization: *Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis: Report of a WHO Study Group*. Geneva, World Health Org., 1994 (Tech. Rep. Ser., no. 843)

[2]Looker AC, Johnston CC Jr, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Lindsay RL: Prevalence of low femoral bone density in older U.S. women from NHANES III. *J Bone Miner Res* 10:796–802, 1995

[3]Wu F, Mason B, Horne A, Ames R, Clearwater J, Liu M, Evans MC, Gamble GD, Reid IR: Fractures between the ages of 20 and 50 years increase women's risk of subsequent fractures. *Arch Intern Med* 162:33–36, 2002

[4]Forsen L, Meyer HE, Midthjell K, Edna TH: Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. *Diabetologia* 42:920–925, 1999

[5]Nicodemus KK, Folsom AR: Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care* 24:1192–1197, 2001

[6]Ivers RQ, Cumming RG, Mitchell P, Peduto AJ: Diabetes and risk of fracture: the Blue Mountains Eye Study. *Diabetes Care* 24:1198–2003, 2001

[7]Piepkorn B, Kann P, Forst T, Andreas J, Pfuzner A, Beyer J: Bone mineral density and bone metabolism in diabetes mellitus. *Horm Metab Res* 29:584–591, 1997

[8]Okazaki R, Totsuka Y, Hamano K, Ajima M, Miura M, Hirota Y, Hata K, Fukomoto S, Matsumoto T: Metabolic improvement of poorly controlled non insulin dependent diabetes melli-

tus decreases bone turnover. *J Clin Endocrinol Metab* 82:2915–2920, 1997

[9]Vogt MT, Cauley JA, Kuller LH, Nevitt MC: Bone mineral density and blood flow to the lower extremities. *J Bone Miner Res* 12:283–289, 1997

[10]Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR: Older women with diabetes have an increased risk of fractures: a prospective study. *J Clin Endocrinol Metab* 86:32–38, 1997

[11]Gregorio F, Cristallini S, Santeusanio F, Filipponi P, Fumelli P: Osteopenia associated with non-insulin-dependent diabetes mellitus: what are the causes? *Diabetes Res Clin Pract* 23:43–54, 1994

[12]Heaney R: Osteoporosis. In *Nutrition in Women's Health*. Drummel D, Kris-Etherton PM, Eds. Gaithersburg, Md. Aspen, 1996, p. 418–439

[13]Minerals. In *Manual of Nutritional Therapeutics*. 3rd ed. Alpers D, Stenson W, Bier D, Eds. Philadelphia, Pa., Little Brown, 1995, p. 210–222

[14]National Institutes of Health: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: the Evidence Report. Bethesda, Md., National Institutes of Health (NIH Publ. No. 98-4083), 1998.

[15]Marcus R: Role of exercise in preventing and treating osteoporosis. *Rheum Dis Clin North Am* 27:131–141, 2001

[16]Lane JM, Nydick M: Osteoporosis: current modes of prevention and treatment. *J Am Orthop Surg* 7:19–31, 1999

[17]Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE: Randomized trial of alendronate on risk of fracture in women with existing vertebral fractures: Fracture Intervention Trial Research Group. *Lancet* 348:1535–1541, 1996

[18]Maugeri D, Panebianco P, Rosso D, Calanna A, Speciale S, Santangelo A, Rizza I, Motta M, Lentini A, Malaguarnera M: Alendronate reduces the daily consumption of insulin (DCI) in patients with senile type I diabetes and osteoporosis. *Arch Gerontol Geriatr* 34:117–122, 2002

[19]Andersson B, Johannsson G, Holm G, Bengtsson BA, Sashegyi A, Pavo I, Mason T, Anderson PW: Raloxifene does not affect insulin sensitivity or glycemic control in postmenopausal women with type 2 diabetes mellitus: a randomized clinical trial. *J Clin Endocrinol Metab* 87:122–128, 2002

[20]Young AA, Wang MW, Gedulin B, Rink TJ, Pittner R, Beaumont K: Diabetogenic effects of salmon calcitonin are attributable to amylin-like activity. *Metabolism* 44:1581–1589, 1995

[21]Starke A, Keck E, Berger M, Zimmermann H: Effects of calcium and calcitonin on circulating levels of glucagon and glucose in diabetes mellitus. *Diabetologia* 20:547–552, 1981

[22]Women's Health Initiative Writing Group: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 288:321–332, 2002

[23]Neer RM, Arnaud CD, Zanchetta JR: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344:1434–1441, 2001

[24]Kannus P, Parkkari J, Niemi S, Pasanen M, Palvanen M, Jarvinen M, Vuori I: Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 343:1506–1513, 2000

[25]Pennington JA: *Bowes & Church's Food Values of Portions Commonly Used*. 17th ed. Philadelphia, Pa., Lippincott-Raven, 1998

Diane L. Chau, MD, is an assistant professor of medicine in the Division of Geriatric Medicine at the University of Nevada School of Medicine and the Geriatric Education Director at the VA Sierra Health Care Systems in Reno, Nev. Jordi Goldstein-Fuchs, DSc, RD, is an associate research professor in the Division of Medical Nutrition at the University of Nevada School of Medicine. Steven V. Edelman, MD, is a professor of medicine in the Division of Endocrinology and Metabolism at the University of California, San Diego, and the Division of Endocrinology and Metabolism at San Diego VA Health Care Systems.