

Diabetes, Bone Density, and Fractures

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Abstract

All types of diabetes increase risk for osteoporosis and fracture due to multiple factors. Hyperglycemia itself may play a role, but frequent hypoglycemia, falls, hypogonadism, vitamin D deficiency, body mass index (BMI), and advanced complications may play an even larger role. Very low BMI in type 1 diabetes and elevated BMI in youth with type 2 diabetes can increase fracture risk, as well as visceral obesity in postmenopausal women. Those with advanced complications, such as peripheral and autonomic neuropathy, visual impairment, renal failure, and vascular disease are also at greater risk, in part due to greater risk for falls. Many medications can contribute to bone loss, but the thiazolidinediones are the only diabetes medications known to have a direct impact on bone mass, particularly in women. After transplant, immunosuppressant medications also contribute to fracture risk.

Bone density screening in patients with diabetes should be initiated with any known risk factors, such as at onset of menopause or other types of hypogonadism, or if part of a known high-risk sub-group, such as cystic fibrosis related diabetes or organ transplant recipients. Vitamin D screening should be performed in those with borderline low calcium, lactose intolerance, celiac sprue, post-menopause, or history of fracture. Therapy of osteoporosis should be tailored to the patient, while optimizing vitamin D concentration, and with special attention to renal function.

In summary, decreased bone density and fractures are more common in diabetes due to multiple factors that should be systematically considered and addressed. Bone density screening should be considered part of health care maintenance in many sub-groups of diabetes patients even though it has not yet been incorporated into the usual care guidelines for all diabetes patients.

Keywords: Diabetes; Fractures; Obesity; Bone density; Osteoporosis; Vitamin D

Abbreviations: BMD: Bone Mineral Density; CFRD: Cystic Fibrosis Related Diabetes; DXA: Dual-Energy X-Ray Absorptiometry; NIST: National Institute of Standards and Technology; NOF: National Osteoporosis Foundation; PCOS: Polycystic Ovarian Syndrome; PPAR-gamma: Peroxisome Proliferator-Activated Receptor-gamma; RANK: Receptor Activator Of Nuclear Factor Kappa-B; TZDs: Thiazolidinediones; GFR: Glomerular Filtration Rate; NHW: Non-Hispanic White

Introduction

Diabetes increases risk for decreased bone density and fracture

Risk of fractures has been observed in those with type 1 and type 2 diabetes [1]. Both men and women with diabetes have a higher risk for hip fractures and fractures at other sites, such as the humerus and foot, compared to those without diabetes [1-9], and bone density is less likely to fully account for the higher fracture risk [8]. Most studies have focused on risk in Caucasians with diabetes, but Japanese studies also show increased vertebral fractures in women with diabetes (Odds Ratio =1.86), despite having normal to minimally low bone density [10].

Studies that have carefully differentiated type 1 from type 2 diabetes show higher fracture risks in both types compared to the general population [4,11-13]. In an observational study of 35,444 people 50 years of age and older, adjusted relative risk of hip fracture for women with type I diabetes compared with women without diabetes was 6.9 [4]. Men with type 1 DM had similar risk but did not reach significance. In the same study, among women 50-74 years of age with type 2 DM for more than 5 years, the relative risk of hip fracture was 1.8 compared to those without diabetes [4]. In another case-control study where subjects diagnosed with a fracture (n=124,655) were compared to control subjects without fracture (n=373,962), type 1 and type 2 DM

were associated with increased risk of any fracture (OR 1.3 and 1.2 for type 1 and type 2 DM respectively) and specifically hip fractures (OR 1.7 and 1.4, for type 1 and type 2 DM respectively), compared to general population [13]. However, according to a systematic review of risk of fracture in diabetics, increased risk is more consistent in those with type 1 diabetes, who are reported to have a relative risk for hip fracture from 1.7 to 12.3 [1]. In the Nurse's Health Study, a prospective study of diabetes and risk of fracture in 109,983 women aged 34-59 years, women with type 1 diabetes had a 6-fold increase in fracture compared to the general population [14]. Spine and proximal humerus fracture are also moderately increased in type 1 diabetes [1,11,13]. In a case-control study, type 1 diabetes was associated with an increased risk of spine fractures (OR=2.5) compared to general population [13]. In the few available studies, women and men with type 1 diabetes have a similar increase in fracture risk. Many factors may affect the prevalence of osteopenia and osteoporosis in type 1 diabetes: age of diagnosis, duration of disease, insulin dose, BMI, and associated complications [15-18]. Those diagnosed with diabetes in either childhood or young adulthood have been reported to be less likely to attain peak bone mass after diagnosis [15,16]. Impact on bone density may also be site-specific as suggested in a more recent study of 175 type 1 diabetics where lumbar (mean Z score of -0.11 ± 1.2) and femoral bone densities (mean Z score of -0.32 ± 1.4) of type 1 diabetics were lower than those

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of control subjects (0.59 ± 1 , and 0.63 ± 1 respectively). The lumbar and femoral bone densities positively correlated with BMI while spine was negatively associated with daily insulin dose, and femoral bone density was positively associated with creatinine clearance. In this study, neither site correlated with age at diabetes diagnosis or A1c [18].

Patients with type 2 diabetes also have a higher risk of hip fractures than the general population [19]. A systematic review by Janghorbani, et al showed that type 2 diabetes was associated with a relative risk of 2.8 for hip fracture in men and 2.1 for women [1,6]. In the Women's Health Initiative Observational Study a prospective study of postmenopausal women, those with type 2 diabetes ($n = 5,285$) were compared with those without diabetes ($n = 88,120$) [8]. After 7 years of follow up, women with diabetes had a 20% risk (relative risk 1.2) of fracture compared to those without diabetes. This study also showed that diabetes is a risk factor for fractures in black women, who tend to be at lower risk for fracture than non-Hispanic white women (NHW); in this study the relative risk for fracture was 1.33 for black women with diabetes compared to 1.18 for NHW women without diabetes. Fractures of the wrist and foot were only increased in those being treated with either oral antidiabetic agents or insulin [8,9,20]. Vertebral fracture risk was not increased in type 2 diabetes [8,13,21]. In the Nurse's Health Study, hip fracture incidence was roughly 2.5 greater in women with type 2 diabetes compared to the general population, and more than 3 times in women with type 2 diabetes treated with insulin than the general population [5].

Potential Mechanisms for Risk

Chronic hyperglycemia results in the non-enzymatic glycosylation of bone proteins, including type I collagen which may impair the biomechanical properties of bone [22]. However, there is little data correlating risk of fracture with A1C in clinical studies, although duration of disease is consistently a factor [23].

Many other mechanisms have been suggested as outlined in Table 1, such as frequent hypoglycemia associated with intensive therapy, likely because it can contribute to falls. Falls, in turn, contribute to fractures, regardless of bone density. Diabetes is associated with a higher risk of falls [24,25], and insulin, in particular, increases risk of falls in the elderly [25]. Neuropathy and neuromuscular impairment are additional contributors to falls in diabetes [25-27], as well as impaired vision due to diabetic retinopathy or cataracts, stroke, chronic renal failure, and longer duration of diabetes [6,25,28,29]. Medications are recognized as factors for falls, particularly sedatives, opiates, antiepileptics, and anti-Parkinson agents [6]. In one study, functional disability, visual impairment, peripheral neuropathy, and use of long-acting benzodiazepines were the strongest overall factors [23].

Commonly prescribed medications in diabetic patients can contribute or may ameliorate risk. Thiazolidinediones (TZDs), pioglitazone and rosiglitazone, are now well established to affect bone

metabolism. Even after short-term treatment, rosiglitazone decreased bone formation markers and femoral neck bone mineral density (BMD) in healthy postmenopausal women [30]. Long-term use (4 yrs) reduced whole body and lumbar BMD in older women with type 2 diabetes [31]. Fracture risk was increased in randomized controlled trials of both thiazolidinediones [32-35]. The target of TZDs, PPAR-gamma, is also expressed in bone marrow cells, and acts as a molecular switch that regulates the fate of pluripotent mesenchymal stem cells, reducing their differentiation into adipocytes or osteoblasts [36]. Animal studies support the hypothesis that TZDs induce bone loss characterized by deficient osteoblast function [32,37]. Hydrochlorothiazide, commonly used for the treatment of hypertension [38], and fluvastatin [39], a statin used for prevention of vascular disease, and both prescribed in diabetes patients, have been shown to modestly improve BMD ($< 1\%$ for both hydrochlorothiazide and fluvastatin), although there have been no studies to confirm whether this benefit is realized in diabetic patients in light of all their other risk factors.

Body mass index (BMI) is another recognized variable in risk for osteoporosis and fracture. Women with low BMI are at greatest risk, as often observed in type 1 diabetes [40-43]. However, higher BMI can also be a factor in some groups, such as youth with type 2 diabetes [44], as well as postmenopausal women with visceral obesity as commonly observed in type 2 diabetes. BMI is now well recognized to be negatively associated with vitamin D concentration, although the mechanism for the association is not well established [45]. Nonetheless, vitamin D deficiency does contribute to low BMD, as well as muscle weakness, which can increase risk for falls. Since vitamin D concentration is negatively correlated with risk for diabetes, many individuals with type 2 diabetes have low vitamin D concentration [46].

Obesity may contribute to decreased bone density and fractures through other mechanisms, as well. Obesity is a cause of hypogonadotropic hypogonadism, and hypogonadism of any kind, in turn, contributes to osteoporosis and fractures in men and women. Thus, it is not surprising to find that hypogonadism is more common in men and women with type 2 diabetes, unrelated to duration of diabetes, glycosylated hemoglobin, or presence of microvascular complications of diabetes [47]. Dhindsa et al. showed that hypogonadism occurred in as many as one-third of men with type 2 diabetes, irrespective of the glycemic control, duration of disease, and the presence of complications of diabetes or obesity [48]. A meta-analysis and systematic review of 43 studies of 6427 men and 6974 women suggested an inverse association between plasma testosterone and risk of type 2 diabetes in men, but a linear relation between testosterone and risk of type 2 diabetes in women [49]. Both obesity and low levels of testosterone in men contribute to a pro-inflammatory profile, another potential contributor to bone loss, although testosterone treatment did not reverse the inflammatory state [50].

Hypogonadism is a particular factor for risk for bone loss and fracture in all women with diabetes and is more common in women with diabetes. Women who have type 1 diabetes and poor glucose control as well as weight loss will commonly develop amenorrhea and hypogonadotropic hypogonadism that can reverse with weight gain and improved glucose control. Prolonged amenorrhea and hypogonadism results in delayed or reduced peak bone mass. Women with type 1 diabetes are also at risk for early or premature menopause due to autoimmune anti-ovarian antibodies. Hypogonadism in type 2 diabetes is more likely to be due to obesity itself or hyperandrogenemia as can occur with polycystic ovarian syndrome (PCOS). If accompanied by amenorrhea, women with PCOS have lower spine and femoral

Mechanism	Type 1 diabetes	Type 2 diabetes
Hyperglycemia	+	+
Hypoglycemia	+	+
Functional disability or falls	+	+
Hypogonadism	+	+
Medications	+	+
Vitamin D deficiency	+	+
Low BMI	+	
High BMI/visceral obesity	+	+

Table 1: Proposed mechanisms for bone loss and/or fracture in diabetes.

neck BMD than non-amenorrhoeic PCOS patients [51]. However, a more recent study showed that spine and femoral neck BMD was not different in women with PCOS than healthy controls matched for age and BMI [52]. Thus, hypogonadism, as suggested by amenorrhea, may be a more significant factor than elevated BMI alone.

There are many other conditions that can occur as a consequence of diabetes or more common in individuals with diabetes that impacts fracture risk. Chronic kidney disease is one of the most significant as chronic kidney disease itself affects bone turnover [53]. However, diabetes further increases risk of fracture in those with chronic kidney disease or after transplantation. The risk associated with chronic kidney disease is greater for type 1 than type 2 diabetes, as shown in one trial where the relative risk for hip fracture was 6.4 vs. 1.4 for those with type 1 vs type 2 diabetes, respectively [54]. While kidney transplantation markedly improves mortality as well as kidney function, many of the immune suppression medications required to prevent rejection also increase fracture risk. Diabetes is a risk factor for fracture after solid organ transplant, along with recent use of narcotics, antidepressants, and loop diuretics [55]. While anyone who receives immune suppression agents is at increased risk for fractures, there is less data on whether individuals who develop diabetes after transplantation, called post-transplant diabetes or new onset diabetes after transplant, are at even greater risk, as observed in those with diabetes before transplant.

Type 1 diabetes predisposes the individual to other autoimmune diseases. Many of these conditions, or their treatment, further increases their risk of bone loss. Examples include celiac sprue, premature autoimmune-mediated menopause, multiple sclerosis, rheumatoid arthritis, lupus erythematosus, and hyperthyroidism or excessive thyroid replacement for hypothyroidism.

Specific types of diabetes are of particular risk for osteoporosis and fracture: diabetic patients following transplantation as discussed above, diabetes following pancreatectomy with exocrine insufficiency, and cystic fibrosis related diabetes (CFRD). Pancreatic exocrine insufficiency requires treatment to optimize fat absorption. Since vitamin D absorption is also affected, these patients should be routinely coached to take their pancreatic enzymes and their vitamin D should be monitored frequently and supplemented as indicated.

Cystic fibrosis related diabetes (CFRD) develops in 10% of individuals with cystic fibrosis [56]. Patients with cystic fibrosis have multiple risk factors for reduced bone mineral accrual and enhanced bone loss: vitamin D deficiency due to fat malabsorption, malnutrition, inflammation, hypogonadism, inactivity, and frequent treatment with exogenous glucocorticoids. While CFRD is distinct from type 1 and type 2 diabetes, many of the same mechanisms contribute to their risk: hyperglycemia, chronic infection with increased inflammatory cytokines, fat malabsorption with risk of vitamin D deficiency, reduced physical activity during times of exacerbation, and hypogonadism, all of which may be additive to increase their overall fracture risk. No studies have established the relative impact of the multiple risks for bone loss in this population. However, amenorrhea appears to be a particular risk for low bone mass and fracture in women with CFRD [56]. Periodic bone density screening and regular monitoring of vitamin D with initiation of vitamin D supplementation as indicated to achieve optimal concentrations should be considered in both men and women, as per the Guide to Bone Health and Disease in Cystic Fibrosis [56].

Screening for Decreased Bone Density: When and How

- The National Osteoporosis Foundation (NOF) and American

Association of Clinical Endocrinologists (AACE) have made general recommendations for who should be considered for bone density screening with dual energy x-ray absorptiometry (DXA) [57]. Where data supports it, we have added modifiers specific to diabetes patients to the NOF guidelines as shown in italics below: Women age 65 and older and men age 70 and older, regardless of clinical risk factors.

- Younger postmenopausal women and men age 50 to 69 about whom you have concern based on their clinical risk factor profile, such as frequent amenorrhea during premenopausal years, hypogonadism in men, visceral obesity in women, decreased renal function, history of celiac sprue, or medications known to affect risk such as treatment with TZDs or corticosteroids.
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture or high-risk medication as described above.
- Adults who have a fracture after age 50.
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., ≥ 5 mg prednisone/day or equivalent for ≥ 3 months) associated with low bone mass or bone loss, such as post-transplant, post-pancreatectomy, or with cystic fibrosis related diabetes.
- Anyone being considered for pharmacologic therapy for osteoporosis.
- Anyone being treated for osteoporosis, to monitor treatment effect.
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Postmenopausal women discontinuing estrogen.

The NOF recommendations for calcium and vitamin D supplements are shown in Table 2. Where vitamin D deficiency is common or severe, such as those with celiac sprue, cystic fibrosis related diabetes, post-enteric diversion gastric bypass procedures, or other causes of exocrine insufficiency, including post-pancreatectomy, regular measurements should be performed. Ensuring adequate intake of calcium and vitamin D with achievement of the recommended daily allowances for each is important even before considering other treatments [57].

Recommendations for Anabolic and Anti-Resorptive Therapies

Prior to outlining a treatment plan, it is important to evaluate the

	Calcium (Daily)	Vitamin D (Daily)
Children & Adolescents		
1 through 3 years	500 mg	400 IU*
4 through 8 years	800 mg	400 IU*
9 through 18 years	1,300 mg	400 IU*
Adult Women & Men		
19 through 49 years	1,000 mg	400-800 IU
50 years and over	1,200 mg	800-1000 IU
Pregnant & Breastfeeding Women		
18 years and under	1,300 mg	400-800 IU
19 years and over	1,000 mg	400-800 IU

*NOF does not have specific vitamin D recommendations for these age groups. These are the recommendations of the American Academy of Pediatrics

Table 2: National Osteoporosis Foundation 2010 Calcium and Vitamin D Recommendations [57].

patient for secondary, treatable causes of osteoporosis with serum calcium, albumin, serum creatinine with estimated glomerular filtration rate (GFR), phosphate, 25-hydroxy-vitamin D, and PTH concentration for any individual with low or high calcium. Measurement of 25-hydroxy-vitamin D should be performed in a reference laboratory that is using the new National Institute of Standards and Technology (NIST) standard [58]. Testing for other secondary causes of osteoporosis (e.g., thyroid function tests, serum protein electrophoresis), should be tailored to the individual based on specific characteristics. Separately, the individual should be examined for factors that could contribute to falls, such as peripheral neuropathy, muscle weakness, orthostasis, or low vision. A discussion of prevention measures, such as removing throw rugs that can slip, avoiding travel outside after ice or snow, and wearing low-heeled shoes with non-slip soles should be undertaken. Regular weight-bearing exercise maintains muscle strength as well as BMD. Thiazolidinediones should be discontinued in any woman identified with osteoporosis when alternatives can be considered.

When a pharmacologic therapy is warranted, the benefits of therapy, whether with anti-resorptive or anabolic agents, need to be weighed against the risks. Patients with diabetes who otherwise meet the indications for treatment based on bone density and fracture risk profile can safely be treated with bisphosphonates such as alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), or zoledronic acid (Reclast®), as long as they have an estimated GFR above 35 ml/min. Patients who plan to undergo either a root canal or tooth extraction in the immediate future should stop the bisphosphonate medication for 12 weeks before and after the dental procedure to reduce risk of osteonecrosis of the jaw [59]. A drug holiday for one to two years should be planned after around 5 years of bisphosphonate therapy to reduce over suppression of bone turnover, now thought to be the main risk factor for sub-trochanteric fracture [60,61]. Teriparatide (Forteo®) is indicated for treatment of women with postmenopausal osteoporosis and in men with idiopathic or hypogonadal osteoporosis who are at high risk of fracture or who have failed or been intolerant of previous osteoporosis therapy, with the exception of those who are at increased risk of osteosarcoma (patients with Paget disease of bone, open epiphyses, history of skeletal irradiation or unexplained elevation of alkaline phosphatase of skeletal origin) [61]. The newest treatment available is the monoclonal antibody focused on the RANK ligand inhibitor, denosumab (Prolia®), which has been used safely in renal failure so may be of particular benefit in this setting.

Conclusions

Diabetes patients are at increased risk for fractures. While hyperglycemia may contribute, many other factors may also be involved, including BMI, diabetic complications, associated autoimmune diseases, hypogonadism, falls, hypoglycemia, and medications. Type 1 diabetes is associated with greater risk of fractures compared to type 2 diabetes or general population. However, youth with obesity, as well as postmenopausal women with visceral obesity, are also at increased risk for fracture of the humerus and ankle. Other specific types of diabetes at particular risk include those with cystic fibrosis related diabetes and those with diabetes who are receiving an organ transplant. Because of the greater overall risk for bone loss and fracture in diabetes, bone density screening and treatment should be considered for those with low BMI (<19 kg/m²), hypogonadism, significant neuromuscular dysfunction, frequent severe hypoglycemia or other autonomic neuropathies that increase their risk of falls, or have concomitant diseases that further increase their risk such as celiac sprue, strong family history of osteoporosis, corticosteroids or other

immunosuppressant medications, seizure disorder or treatment with many anti-seizure medications.

Measurement of 25-hydroxy-vitamin D, deficiency of which is common in those with obesity, celiac sprue, or fat malabsorption, should be considered in anyone considered at particular risk, with initiation of vitamin D supplementation alongside other osteoporosis treatments. While frequency of bone density surveillance has not been well established in diabetes, once osteoporosis has been identified, follow-up screening should continue at least every two years while on treatment to confirm stability of bone density, or more frequently in certain clinical situations.

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