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Diabetes and Fractures — An overshadowed association

Natasha B. Khazai, M.D.¹, George R. Beck, Ph.D.^{1,2}, and Guillermo E. Umpierrez, M.D.¹

¹Division of Endocrinology, Diabetes & Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA,

²Emory Winship Cancer Institute, Atlanta, GA

Abstract

Purpose of review—To review recent literature on fracture risk in patients with type 1 and type 2 diabetes.

Recent findings—Observational and population studies have reported a higher risk of fractures in patients with type 1 and type 2 diabetes, especially at the hip. Type 2 diabetics have a higher BMD compared to the general population, and yet, remain unprotected from fractures. Type 1 diabetics have a greater risk of fractures and a lower BMD compared to the general population. Their lower BMD, however, does not fully account for the raised fracture risk. Therefore, impaired bone quality rather than lower bone density appears to mediate the increased fracture risk in patients with type 1 and 2 diabetes.

Recently, studies have shown an association between advanced glycation end products with increased fracture risk in diabetics. These studies support the hypothesis of poor glycemic control and chronic hyperglycemia having a direct detrimental effect on bone quality. In addition, increased fracture risk has been reported in patients with peripheral and autonomic neuropathy, recurrent hypoglycemic events, vitamin D deficiency, and those receiving thiazolidinedione therapy.

Summary—Diabetes is associated with an increased risk of fractures in patients with type 1 and type 2 diabetes. Appropriate measures aimed at fracture prevention should be considered in the complex care of the diabetic patient.

Keywords

Fractures; Type 1 diabetes; Type 2 diabetes; Advanced glycation end products (AGEs); bone mineral density (BMD)

Introduction

Diabetes affects one third of those aged 65 and older [1] and poses a considerable burden on health care resources. Observational and population studies in patients with type 1 and type 2 diabetes have shown an increased fracture risk in this population [2]. However, this association is not widely recognized or addressed by those caring for diabetic patients. In this review we aim to discuss the evidence supporting the association between diabetes and fractures and review potential underlying mechanisms leading to this association.

Fracture Risk

The frequency, fracture risks and type of fractures affecting patients with type 1 and type 2 diabetes are somewhat different. We therefore discuss each type separately and focus on studies that distinguish their analysis between type 1 and type 2 diabetes.

Type 2 Diabetes

The data on fracture risk in type 2 diabetes are not entirely consistent. Several cohort studies [3–10] and a case-control study [11] have found an increased fracture risk in type 2 diabetes compared to the general population (see Table 1). Whereas, a few studies report a decreased [12, 13] or similar fracture [14, 15] risk in type 2 diabetes compared to the general population.

Most studies that report a positive association have limited their analysis to and have found that patients with type 2 diabetes have a higher risk of hip fractures. However, studies that evaluated all types of fractures [5, 8, 11] still found hip fractures to contribute the most to the fracture risk seen in type 2 diabetes. Wrist [9] and foot [5, 10] fractures also appear to be increased in type 2 diabetes but only in patients who are on treatment with either oral anti-diabetic agents (OAD)[9] or insulin[5, 10]. The risk for vertebral fractures is similar to non-diabetics [6, 10, 11]. The risk of hip fractures appears to be slightly higher in men compared to women with type 2 diabetes [2, 16] and slightly higher in black compared to white women with type 2 diabetes [10]. In a large prospective study of nurses aged 34–59 years [3], the incidence of hip fractures in females with type 2 diabetes is reported at 153 per 100,000 patients compared to 63 per 100,000. The incidence increases to 209/100,000 for those type 2 diabetic females treated with insulin.

A few studies have reported a similar or lower fracture risk in type 2 diabetes compared to the general population (see Table 1) [14] [13] [17] [12]. Of these, two [14, 15] showed no difference in fracture risk and both only adjusted for age. One was a small cross-sectional study [14] and the other [15], when further adjusting for calcaneal stiffness, actually found a significantly increased risk of hip fractures in type 2 diabetics compared to non-diabetic controls.

Of those studies that reported a lower fracture risk in type 2 diabetes compared to the general population two of them were unable to show this decrease to reach statistical significance, either on initial report [17] or when reanalyzed in a meta-analysis [2, 12]. The third study [13] included a large percentage (42%) of diet controlled diabetics. Interestingly, of the positive studies, those that showed only a minimal increase in fracture risk involved diet controlled [4] or early onset type 2 diabetics[8]. Perhaps, early on in the course of diabetes a higher bone mineral density (BMD) [13, 18] [5, 19] protects from fractures. However, as the diabetes progresses, certain factors such as hyperglycemia [9, 19] may impair bone quality, and this, then, overcomes the protective effects of a higher BMD and results in a higher risk of fractures. This hypothesis is supported by a study done by de Liefde et al [9] that showed a higher BMD in subjects with impaired glucose tolerance, who also had a lower fracture risk HR 0.8 (0.63–1.00), whereas treated type 2 diabetics had a higher fracture risk HR 1.69 (1.16–2.46) despite an equally high BMD.

Finally, a recent meta-analysis [2] of 12 positive and negative studies [4–7, 11, 12, 17, 20–23] found that the overall relative risk of hip fractures in type 2 diabetics significantly increased with a relative risk (RR) of 1.7 (1.3–2.2). The association became stronger when examining the 4 cohorts with more than 10 years of follow-up, RR 2.7(1.7–4.4). Foot fractures were the only other type of fracture found to be increased in type 2 diabetics in this meta-analysis [2].

Type 1 Diabetes

The risk of fractures is significantly greater in type 1 diabetes when compared to the general population as well as to patients with type 2 diabetes[3]. The evidence supporting a higher fracture risk in type 1 diabetes comes mostly from the same studies comparing fracture risk in type 2 diabetes to the general population, but the results for type 1 are more consistent (see Table 2) [11] [7, 24, 25]. Studies of type 1 diabetes have focused mostly on hip fractures and have found a higher risk of hip fractures in type 1 diabetes with a range of RR from 1.7–12.3 [2]. However, fracture risk was also found to be moderately increased at the spine and proximal humerus [11, 24].

The risk appears to be similar between men and women with type 1 diabetes although due to a smaller number of studies examining this relationship no definite conclusions can be drawn. A recent meta-analysis of 5 cohort studies showed an overall RR of 8.9 (CI 7.1–11.2) for hip fractures in type 1 diabetics [2]. The incidence of hip fractures in the Nurses Health Study was reported as 383 per 100,000 over a follow up period of 2.2 million person-years [3]. This is a 6-fold increase from the overall incidence of hip fractures in this population, reported at 63 per 100,000, and a 2.5-fold increase from the incidence of hip fractures in type 2 diabetics in this population.

Pathogenesis underlying increased fracture risk in diabetes

Bone mineral density is increased in type 2 diabetes [5, 6, 13, 14, 19, 26] even after adjustment for obesity which is known to increase BMD [13]. A recent meta-analysis found BMD to be increased at both the spine and hip, and yet type 2 diabetics, especially those with longer duration of diabetes, are not protected from fractures[19]. Unlike type 2 diabetes, type 1 diabetes is associated with decreased bone mineral density [19]. However, lower BMD alone is unable to explain the magnitude of fracture risk seen in type 1 diabetics [19]. Therefore, impaired bone quality rather than impaired bone density appears to be the main contributor to the higher fracture risk seen in either type of diabetes [27]. Additional factors mediating the increased fracture risks in diabetic patients are peripheral and autonomic neuropathy, recurrent hypoglycemic events, vitamin D deficiency, and thiazolidinedione therapy.

Impaired Bone Quality

Longstanding or poorly controlled diabetes may offset the beneficial effects of higher BMD via glycation of bone proteins and cells. Advanced glycation end products (AGEs) may adversely affect collagen, osteocytes, and multipotent bone marrow stem cells [28, 29] [30, 31]. The ability of multipotent bone marrow stem cells to proliferate or differentiate into bone or adipose tissue is decreased in the presence of AGEs in in-vitro studies [31]. Osteoclast induced bone resorption is enhanced by AGEs in mouse models [32] and the addition of AGE to osteoblast-like cells significantly impairs their ability to produce collagen [30]. Glycated collagen in turn may be able to inhibit expression of osteoblasts [30] or become stiff and resistant to proteolytic degradation, necessary for bone turnover [33]. Rodent studies have shown impaired biomechanical properties and decreased bone formation in hyperglycemic rats. These findings were significantly attenuated when hyperglycemia was controlled [34]. Pentosidine, a cross-link structure between lysine and arginine residues, is a major AGE. A recent analysis of the Health ABC study participants[35] showed a significant association between urinary pentosidine levels and clinical fractures in elderly diabetics but not in those without diabetes. This finding supports the role of AGEs in impairing bone quality.

Few studies have looked at the association between HbA1c and fractures. Elevated HbA1c has been associated with decreased markers of bone turnover, serum osteocalcin and C-

terminal telopeptide (β -CTX), in elderly nursing home patients with type 2 diabetes [15]. Another study showed that having both a higher BMI (>24) and HbA1c ($>9\%$) was associated with a greater risk of multiple vertebral fractures on spine x-rays (OR 5.4 CI 1.2,26.1) [36]. Other studies have shown a lower incidence of fractures in diabetics with a higher HbA1c. In a study of type 2 diabetic women aged 50–74 years, 26% of those with a hip fracture had an HbA1c $>9\%$ as compared to 50% of those who did not have a hip fracture [7]. It needs to be noted, however, that the HbA1c in this population was determined at baseline, i.e. nine years prior to their hip fracture and thus may not be reflective of their glycemic control during the follow-up period. A longer duration of diabetes is associated with a greater fracture risk in most [3–5, 9, 16] but not all [8, 11] studies in type 2 diabetics. The greater risk of fractures reported in patients with advanced diabetes may be due to the prolonged exposure to hyperglycemia and to the detrimental effects of AGEs on bone. The duration after which studies find an escalation in fracture risk is approximately 12–14 years after the diagnosis of diabetes [2, 4].

In addition to the effect of hyperglycemia on bone quality, bone mineralization may be altered in diabetes due to impaired vitamin D and calcium metabolism [37, 38]. Diabetics are more likely to be vitamin D deficient compared to the general population [39, 40]. Vitamin D deficiency may be greater in type 2 diabetics compared to type 1 diabetics, even after adjusting for obesity which is known to contribute to a higher distribution volume of this fat-soluble vitamin [41]. Hyperglycemia has been shown to impair renal calcium absorption [42] and this finding is corrected when hyperglycemia is controlled [43]. Finally, the development of renal insufficiency with its associated secondary or tertiary hyperparathyroidism and impaired vitamin D metabolism may further contribute to impaired bone quality in diabetes.

Falls

Diabetes is associated with a higher risk of falls [44, 45]. Diabetic neuropathy and neuromuscular impairment have been shown to be a major risk factor for falls [45, 46]. Furthermore, diabetic neuropathy may lead to falls that are more severe and falls that are sideways, as opposed to forward or backward. Both of these fall characteristics have been associated with a greater risk of fractures [47, 48]. This is supported by findings linking diabetic neuropathy with calcaneal and metatarsal fractures [49] [50].

A higher risk of falls has also been seen in diabetes of longer duration, and as discussed above, longer duration of diabetes is also associated with a greater fracture risk [2]. Higher rates of diabetes-related complications such as neuropathy, impaired vision due to retinopathy or cataracts [22, 45], stroke [16, 51], and impaired renal function [45], more prevalent in advanced diabetes may underlie the higher risk of falls and fractures in this population.

Diabetics are also more likely to be on medications that increase fall risk. A large retrospective study of older diabetics (>66 years old) found that male and female subjects with diabetes not only had a higher risk of hip fractures, but also, when compared to age matched controls, they were more likely to be on medications that increased fall risk (59% vs. 47%, $p<0.001$). These medications include sedatives, opiates, anti-epileptics and anti-parkinsonian agents [16].

Severe hypoglycemia may be another contributor to fall risk. Intensive glycemic control (HbA1c $<6\%$) has been associated with an increased risk of falls but only in those diabetics treated with insulin (OR 4.36, CI 1.3,14.5) not in those treated with oral agents [45]. Some [4, 16, 20] [5, 8] but not all [6, 7] studies have shown an increased risk of fracture with insulin treatment. The higher fracture risk associated with insulin use remains unchanged

even when adjusted for duration of diabetes [5, 16]. A possible explanation for this finding may be an increased frequency of severe hypoglycemic events in insulin treated diabetics. This may be one reason for why type 1 diabetics have a greater risk of fractures compared to type 2 diabetics. Other potential contributors to the observed difference in fracture risk between type 1 and type 2 diabetes may be lower body mass index, longer duration of disease, higher rates of diabetic retinopathy resulting in impaired vision [52], and a higher incidence of associated autoimmune diseases such as celiac disease [53] potentially predisposing type 1 diabetics to calcium malabsorption.

Thiazolidinediones

Recent studies have suggested an association between thiazolidinedione treatment and an increased risk of bone fractures in patients with type 2 diabetes [54] [55, 56], as well as in subjects with pre-diabetes [57] and older women with diabetes [58]. Fractures associated with thiazolidinediones were first reported in 2006, as an adverse outcome in the ADOPT Trial, a large, double blind randomized controlled study comparing the glycemic durability in patients with type 2 diabetes receiving monotherapy with rosiglitazone, metformin or glyburide [59]. This study showed an increased number of fractures in women treated with rosiglitazone but not in men. There was an increased rate of fractures in the hand, humerus, and foot in these women but not in the hip [59]. The cumulative incidence of fractures was 15.1% after 5 years of rosiglitazone treatment as compared to 7.3% and 7.7% for metformin and glyburide treatment respectively. The average age of subjects was 56.3 ± 10.0 , which was no different from the other treatment groups. However, the increase in fractures was also seen in younger, pre-menopausal subjects of this study [60]. Similar findings regarding fractures have also been reported with pioglitazone use in postmenopausal diabetic women [61]. A recent case control analysis of the UK General Practice Research Database, confirmed the association of thiazolidinedione use with incident fractures (OR 2.43) [62]. Fractures were mainly reported in the hips and wrist and, unlike prior studies, the association of fractures with TZDs was found to be independent of age or gender. The association of fractures and TZD use in men has been further confirmed by a cross-sectional study of 43 males with type 2 diabetes. This study revealed a higher rate of radiographically confirmed vertebral fractures in those on metformin plus rosiglitazone compared to those on metformin alone (66.7% vs. 27.3% $p=0.01$) [56]. These findings remained true even after adjustment for BMD and age. Based on in-vitro studies and animal models, TZDs seem to act on pluripotent mesenchymal bone marrow stromal cells to cause an increase in adipocyte precursors at the expense of osteoblast precursors. These changes shift the balance of osteoblast and adipocyte precursors leading to increased fat accumulation, bone loss and ultimately increased fracture risk [63, 64]. However, studies in humans have not been done and other potential mechanisms, including an indirect negative effect on osteoblasts via enhanced secretion of adipocyte factors, remains to be elucidated.

Conclusion

Both type 1 and type 2 diabetes are associated with a higher risk of fractures, especially at the level of the hip [2]. Primary care practitioners, endocrinologists, and diabetologists need to be more vigilant in addressing fracture prevention in diabetic patients, especially type 1 diabetics and elderly patients with longstanding type 2 diabetes who are at greatest risk. Vitamin D status should be assessed on a yearly basis and vitamin D deficiency must be corrected and routine calcium supplementation instituted. Avoiding medications that increase fall risk or further increase fracture risk might reduce the high morbidity, mortality, and the economic burden associated with bone fractures in diabetics.

References

1. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care*. 2009; 32:287–94. •A report of the prevalence of diabetes and prediabetes both diagnosed and undiagnosed in the during 2005–2006, using both fasting blood sugar and 2hr-OGT results. [PubMed: 19017771]
2. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol*. 2007; 166:495–505. [PubMed: 17575306]
3. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care*. 2006; 29:1573–8. [PubMed: 16801581]
4. Nicodemus KK, Folsom AR. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care*. 2001; 24:1192–7. [PubMed: 11423501]
5. Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab*. 2001; 86:32–8. [PubMed: 11231974]
6. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. *Arch Intern Med*. 2005; 165:1612–7. [PubMed: 16043679]
7. Forsen L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag Health Survey. *Diabetologia*. 1999; 42:920–5. [PubMed: 10491750]
8. Ahmed LA, Joakimsen RM, Berntsen GK, et al. Diabetes mellitus and the risk of non-vertebral fractures: the Tromsø study. *Osteoporos Int*. 2006; 17:495–500. [PubMed: 16283065]
9. de L II, van der Klift M, de Laet CE, et al. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int*. 2005; 16:1713–20. [PubMed: 15940395]
10. Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. *J Clin Endocrinol Metab*. 2006; 91:3404–10. [PubMed: 16804043]
11. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia*. 2005; 48:1292–9. [PubMed: 15909154]
12. Heath H 3rd, Melton LJ 3rd, Chu CP. Diabetes mellitus and risk of skeletal fracture. *N Engl J Med*. 1980; 303:567–70. [PubMed: 7402221]
13. van Daele PL, Stolck RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. *Ann Intern Med*. 1995; 122:409–14. [PubMed: 7856988]
14. Sosa M, Saavedra P, Jodar E, et al. Bone mineral density and risk of fractures in aging, obese postmenopausal women with type 2 diabetes. The GIUMO Study. *Aging Clin Exp Res*. 2009; 21:27–32. •A recent, but cross-sectional study of the prevalence of non-vertebral and radiographically confirmed vertebral fractures, as well as evaluation of spine and proximal femur BMD, and calcaneal QUS in postmenopausal women from Spain. [PubMed: 19225266]
15. Dobnig H, Pischinger-Solkner JC, Roth M, et al. Type 2 diabetes mellitus in nursing home patients: effects on bone turnover, bone mass, and fracture risk. *J Clin Endocrinol Metab*. 2006; 91:3355–63. [PubMed: 16735485]
16. Lipscombe LL, Jamal SA, Booth GL, Hawker GA. The risk of hip fractures in older individuals with diabetes: a population-based study. *Diabetes Care*. 2007; 30:835–41. [PubMed: 17392544]
17. Gerdhem P, Isaksson A, Akesson K, Obrant KJ. Increased bone density and decreased bone turnover, but no evident alteration of fracture susceptibility in elderly women with diabetes mellitus. *Osteoporos Int*. 2005; 16:1506–12. [PubMed: 15824889]
18. Weinstock RS, Goland RS, Shane E, et al. Bone mineral density in women with type II diabetes mellitus. *J Bone Miner Res*. 1989; 4:97–101. [PubMed: 2718784]
19. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int*. 2007; 18:427–44. [PubMed: 17068657]
20. Ottenbacher KJ, Ostir GV, Peek MK, et al. Diabetes mellitus as a risk factor for hip fracture in mexican american older adults. *J Gerontol A Biol Sci Med Sci*. 2002; 57:M648–53. [PubMed: 12242318]

21. Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women. *Osteoporos Int.* 2006; 17:1065–77. [PubMed: 16758143]
22. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: The Blue Mountains Eye Study. *Diabetes Care.* 2001; 24:1198–203. [PubMed: 11423502]
23. Meyer HE, Tverdal A, Falch JA. Risk factors for hip fracture in middle-aged Norwegian women and men. *Am J Epidemiol.* 1993; 137:1203–11. [PubMed: 8322761]
24. Kelsey JL, Browner WS, Seeley DG, et al. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. *Am J Epidemiol.* 1992; 135:477–89. [PubMed: 1570814]
25. Miao J, Brismar K, Nyren O, et al. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. *Diabetes Care.* 2005; 28:2850–5. [PubMed: 16306544]
26. Dennison EM, Syddall HE, Aihie Sayer A, et al. Type 2 diabetes mellitus is associated with increased axial bone density in men and women from the Hertfordshire Cohort Study: evidence for an indirect effect of insulin resistance? *Diabetologia.* 2004; 47:1963–8. [PubMed: 15565368]
27. Vestergaard P. Bone metabolism in type 2 diabetes and role of thiazolidinediones. *Curr Opin Endocrinol Diabetes Obes.* 2009; 16:125–31. [PubMed: 19300092]
28. Paul RG, Bailey AJ. Glycation of collagen: the basis of its central role in the late complications of ageing and diabetes. *Int J Biochem Cell Biol.* 1996; 28:1297–310. [PubMed: 9022289]
29. Vashishth D, Gibson GJ, Khoury JI, et al. Influence of nonenzymatic glycation on biomechanical properties of cortical bone. *Bone.* 2001; 28:195–201. [PubMed: 11182378]
30. Hein G, Weiss C, Lehmann G, et al. Advanced glycation end product modification of bone proteins and bone remodelling: hypothesis and preliminary immunohistochemical findings. *Ann Rheum Dis.* 2006; 65:101–4. [PubMed: 16344492]
31. Kume S, Kato S, Yamagishi S, et al. Advanced glycation end-products attenuate human mesenchymal stem cells and prevent cognate differentiation into adipose tissue, cartilage, and bone. *J Bone Miner Res.* 2005; 20:1647–58. [PubMed: 16059636]
32. Miyata T, Notoya K, Yoshida K, et al. Advanced glycation end products enhance osteoclast-induced bone resorption in cultured mouse unfractionated bone cells and in rats implanted subcutaneously with devitalized bone particles. *J Am Soc Nephrol.* 1997; 8:260–70. [PubMed: 9048345]
33. Wang X, Li X, Shen X, Agrawal CM. Age-related changes of noncalcified collagen in human cortical bone. *Ann Biomed Eng.* 2003; 31:1365–71. [PubMed: 14758927]
34. Follak N, Kloting I, Wolf E, Merk H. Improving metabolic control reverses the histomorphometric and biomechanical abnormalities of an experimentally induced bone defect in spontaneously diabetic rats. *Calcif Tissue Int.* 2004; 74:551–60. [PubMed: 15354863]
35. Schwartz AV, Garner P, Hillier TA, et al. Pentosidine and Increased Fracture Risk in Older Adults with Type 2 Diabetes. *J Clin Endocrinol Metab.* 2009
36. Kanazawa I, Yamaguchi T, Yamamoto M, et al. Combination of obesity with hyperglycemia is a risk factor for the presence of vertebral fractures in type 2 diabetic men. *Calcif Tissue Int.* 2008; 83:324–31. [PubMed: 18946627]
37. Nyomba BL, Verhaeghe J, Thomasset M, et al. Bone mineral homeostasis in spontaneously diabetic BB rats. I. Abnormal vitamin D metabolism and impaired active intestinal calcium absorption. *Endocrinology.* 1989; 124:565–72. [PubMed: 2536313]
38. Christiansen C, Christensen MS, McNair P, et al. Vitamin D metabolites in diabetic patients: decreased serum concentration of 24,25-dihydroxyvitamin D. *Scand J Clin Lab Invest.* 1982; 42:487–91. [PubMed: 6760373]
39. Bener A, Alsaied A, Al-Ali M, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. *Acta Diabetol.* 2008
40. Littorin B, Blom P, Scholin A, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). *Diabetologia.* 2006; 49:2847–52. [PubMed: 17072585]

41. Di Cesar DJ, Ploutz-Snyder R, Weinstock RS, Moses AM. Vitamin D deficiency is more common in type 2 than in type 1 diabetes. *Diabetes Care*. 2006; 29:174. [PubMed: 16373927]
42. McNair P, Madsbad S, Christensen MS, et al. Bone mineral loss in insulin-treated diabetes mellitus: studies on pathogenesis. *Acta Endocrinol (Copenh)*. 1979; 90:463–72. [PubMed: 425786]
43. McNair P, Christiansen C, Christensen MS, et al. Development of bone mineral loss in insulin-treated diabetes: a 1 1/2 years follow-up study in sixty patients. *Eur J Clin Invest*. 1981; 11:55–9. [PubMed: 6783430]
44. Maurer MS, Burcham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. *J Gerontol A Biol Sci Med Sci*. 2005; 60:1157–62. [PubMed: 16183956]
45. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care*. 2008; 31:391–6. [PubMed: 18056893]
46. Richardson JK, Hurvitz EA. Peripheral neuropathy: a true risk factor for falls. *J Gerontol A Biol Sci Med Sci*. 1995; 50:M211–5. [PubMed: 7614243]
47. Greenspan SL, Myers ER, Maitland LA, et al. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. *JAMA*. 1994; 271:128–33. [PubMed: 8264067]
48. Greenspan SL, Myers ER, Kiel DP, et al. Fall direction, bone mineral density, and function: risk factors for hip fracture in frail nursing home elderly. *Am J Med*. 1998; 104:539–45. [PubMed: 9674716]
49. Cundy TF, Edmonds ME, Watkins PJ. Osteopenia and metatarsal fractures in diabetic neuropathy. *Diabet Med*. 1985; 2:461–4. [PubMed: 2951118]
50. Kathol MH, el-Khoury GY, Moore TE, Marsh JL. Calcaneal insufficiency avulsion fractures in patients with diabetes mellitus. *Radiology*. 1991; 180:725–9. [PubMed: 1871285]
51. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke*. 2001; 32:702–6. [PubMed: 11239190]
52. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care*. 2006; 29:1300–6. [PubMed: 16732012]
53. Lorini R, Scaramuzza A, Vitali L, et al. Clinical aspects of coeliac disease in children with insulin-dependent diabetes mellitus. *J Pediatr Endocrinol Metab*. 1996; 9(Suppl 1):101–11. [PubMed: 8887160]
54. Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care*. 2007; 30:1574–6. [PubMed: 17363747]
55. Solomon DH, Cadarette SM, Choudhry NK, et al. A Cohort Study of Thiazolidinediones and Fractures in Older Adults With Diabetes. *J Clin Endocrinol Metab*. 2009
56. Mancini T, Mazziotti G, Doga M, et al. Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. *Bone*. 2009
57. Grey A, Bolland M, Gamble G, et al. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2007; 92:1305–10. [PubMed: 17264176]
58. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab*. 2006; 91:3349–54. [PubMed: 16608888]
59. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006; 355:2427–43. [PubMed: 17145742]
60. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008; 31:845–51. [PubMed: 18223031]
61. Grey A. Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int*. 2008; 19:129–37. [PubMed: 17901911]
62. Meier C, Kraenzlin ME, Bodmer M, et al. Use of thiazolidinediones and fracture risk. *Arch Intern Med*. 2008; 168:820–5. [PubMed: 18443256]

63. Ali AA, Weinstein RS, Stewart SA, et al. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology*. 2005; 146:1226–35. [PubMed: 15591153]
64. Soroceanu MA, Miao D, Bai XY, et al. Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. *J Endocrinol*. 2004; 183:203–16. [PubMed: 15525588]

Table 1

Studies of fracture risk in type 2 diabetic adults compared to non-diabetic adults.

	n	Case/controls	Distinguishing criteria between DM T2 and DMT1	Mean f/n years	Age ^d	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
Increased Risk									
<i>Janghorbani et al. 2006[5]</i>		Older Females n= 83/48/101,343	DMT2 if diagnosed at age >30, DMT1 if diagnosed at age <30 and on insulin or ketosis prone.	20±3	69±7	OR ♀:2.2*	NE	NE	Adjusted variables: Multivariate adjusted incl. age, BMI, smoking, & estrogen use (not adj. for BMD). Control group: Non-diabetic women from the Nurses' Health Study who in general had a lower BMI, younger age, and were more likely to be on postmenopausal hormones.
<i>Nicodemus et al. 2001[4]</i>		Postmenopausal females n=1682/30377	DMT2 if diagnosed with diabetes after age 30 regardless of treatment type.	306,900 person years	62	OR ♀:1.7*	NE	NE	Adjusted variables: Multivariate adjusted incl. age, BMI, smoking, estrogen use (not adj. for BMD). Control group: Non-diabetic postmenopausal female residents of Iowa, who in general had a lower BMI than DMT2 subjects and were more likely to be smokers or users of estrogen.
<i>Schwartz et al. 2001[5]</i>		Elderly Women Non-insulin Rx: n=551/8997 Insulin Rx: n=106/8997	DMT2 if age at Dx >40 regardless of treatment type.	9±2	72±5 71±5	RR 1.82* NS	RR NS NS	RR Proximal humerus: 1.94* All nonvertebral: 1.3* Foot: 2.66*	Adjusted variables: Multivariate adjusted including BMD. Control group: Non-diabetic subjects from the study of osteoporosis fractures (SOF) cohort. The SOF is comprised of community dwelling non-black women who are 65 years or older.
<i>Stromeyer et al. 2005[6]</i>		DM + IFG ♀ 243+71 ^b /1209 ♂ 323+106 ^b /1027	DMT2 and IFG Dx based on labs & medication history.	4.5±1	♀:73 ^c ♂:74 ^c	OR ♀&♂: 1.6*	NE	NE	Adjusted variables: Multivariate adjusted for hip BMD, lean mass, fat mass, and abdominal visceral fat. *One of only 2 studies that studied black race.

	n Case/controls	Distinguishing criteria between DM T2 and DMT1	Mean f/u years	Age ^d	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
<i>Forsen et al. 1999[7]</i>	DMT2 >5yrs ♀ 274/13685 ♂ 220/13210 DMT2 < 5yrs ♀ 144/3831 ♂ 95/2868	DMT2 defined as diabetics on diet or oral therapy or if on insulin therapy onset of DM above age 40.	9 ^c	50-75 ♀: 72 ♂: 70 75+ ♀: 82 ♂: 81	RR ♀ 1.8 [*] ♂ NS ♀ NS ♂: 2.1 [*]	NE	NE	Control group: Non-diabetic older male and female participants of the Health, Aging, and Body Composition study (Health ABC). Controls had a significantly lower hip BMD compared to those with IFG or DMT2. Adjusted variables: Multivariate adjusted incl. age, BMI, stroke, and smoking among others. (not adj. for BMD) Control group: Men and women without DM, who in general had less impaired vision, motor impairment, stroke and lower BMI compared to DMT2 group.
<i>Ahmed et al. 2005[8]</i>	♀ 198/14065 ♂ 175/12639	DMT1 differentiated from DMT2 based on clinician's judgment using C-peptide levels & presence of DKA at diagnosis.	6 ^c	♀: 68 ♂: 64	OR ♀: 1.9 [*] ♂: NS	NE NE	OR All Nonvert Fx ♀: NS ♂: NS	Adjusted variables: Age, BMI, & smoking (not adj. for BMD). ^a Radiographically confirmed fractures. Control group: Male and female residents of Tromsø, Sweden without diabetes. Compared to DMT2 subjects, controls were significantly younger, had less strokes, were in better health and more physically active.
<i>De Liefde et al. 2005[9]</i>	♀ 483/3481 ♂ 309/2382	DMT2 if positive OGTT and diagnosis at age >30.	7±2	74±9	OR ♀: NS ♂: NS ♂ & ♀ on DM Rx: 1.69 [*]	NE NE	OR ♀: NS ♂: NS <i>Wrist</i> ♂ & ♀ on DM Rx: 2.14 [*]	Adjusted variables: Multivariate adjusted for falls, age, BMI, lower limb disability, visual acuity, smoking and BMD. Control group: Non-diabetic male and female residents age 55 and older of the Omoord district in Rotterdam, Netherlands. Controls had significantly lower BMDs at both the femoral neck and spine and had significantly less falls, less lower limb disability, better visual acuity, and

	n Case/controls	Distinguishing criteria between DM T2 and DMT1	Mean f/u years	Age ^d	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
<i>Bonds et al., 2006[10]</i>	Postmenopausal females 5285/88,120	DM was determined based on self-report. DMT1 was excluded and defined as onset at age <20 or admission for "diabetic coma."	7 ^c	65±7	OR ♀:1.2 *	NS	OR Foot 1.32	were younger than DMT2 subjects. Adjusted Variables: Age, ethnicity, weight, hx of falls, previous fracture, osteoporosis, medication use (bisphosphonates, estrogen, steroids, etc.). Control group: Non- diabetic postmenopausal women from the Women's health initiative study. Controls were significantly younger, had less frequent falls, lower visual impairment, greater use of bisphosphonates (2.6 vs. 1.6%), estrogens, calcium and vitamin D compared to DMT2 subjects. Controls also had a much lower black population (7 vs. 21%)
<i>Vestergaard, P 2005[11]</i>	Case/control 124,655 ^a /373,962	WHO criteria.	N/A	43±27	DMT2 vs. ctrl OR 1.38 *	OR 1.34 NS	OR Forearm 1.21 *	Adjusted Variables: Multivariate adjusted incl. prior fractures, corticosteroids, alcoholism, antiepileptics, stroke, sedatives etc. (not adj. for BMI or BMD) <i>*Retrospective Study</i> Control group: Three age- & sex- matched controls were chosen, per case, from the general Danish population.
No increased risk								
<i>Van Daele et al. 1995[13]</i>	♀ 335/3450 ♂ 243/2481	DMT2 if on OADs but no insulin or diet treatment and BS >11.1 mmol/L after 2hr-OGT	5 ^c	♀: 72 ♂: 70	NE	NE	OR ♀: 0.63 * ♂: NS	Adjusted variables: BMD, BMI and age. <i>*Retrospective study.</i> Control group: Non- diabetic male and female residents age 55 and older of the Omoord district in Rotterdam, Netherlands. Controls had lower spine and hip BMD compared to DMT2 subjects.

	n Case/controls	Mean f/u years	Age ^d	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
<i>Sosa et al. 2009[14]</i>	Postmenopausal females n=111/91	N/A	72/70			OR All Fx 9:0.93	Adjusted variables: Age only. *Cross-sectional design, radiologically confirmed vertebral fx and chart confirmed hip fractures. Control group: Non-diabetic, Caucasian postmenopausal females from Spain. Controls had a lower BMD at the lumbar spine.
<i>Dobnig et al. 2006[15]</i>	Elderly Nursing home patients 583/1081	2	83±6	OR 0.97* Adjusted for weight.	NS	NS	Adjusted variables: Weight, subgroup was adjusted for calcaneal stiffness. Control group: Non-diabetic male and female nursing home residents age >70.
<i>Gerthm et al.[17]</i>	74/1058	4.6 ^c	75	NE when adjusted for calcaneal stiffness	NR	OR for any fracture 0.7 NS	Adjusted variables: Weight, BMD, visual acuity, use of walking aid. Control group: Non-diabetic women aged 75 or older who were residents of Malmo, Sweden. Controls were significantly leaner, had lower BMD at the hip and spine, and had higher 25(OH)D levels.

^a n and age show number and age of cases (all fractures in Denmark in 2000 in both diabetics and non-diabetics) vs. controls (3 randomly selected controls, see comment section).

^b Number of patients with DMT2 + IFG.

^c Standard deviation not reported, **DM Rx**= treatment with OADs or insulin, **NE**=Not Evaluated, **NR**= Not reported, **NS**= Not Significant.

* Statistically significant.

Follow-up years and age shown for T2DM only and not for the control group.

Table 2

Studies of fracture risk in type 1 diabetic adults compared to non-diabetic adults.

	N case/controls	DM T2 Distinguished from T1?	Mean f/u years	Age	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
Increased Risk								
<i>Janghorbani, M 2006[3]</i>	Older Females ♀= 292/101,343	DMT1 defined as on insulin or ketosis-prone and dx at age <30	18±5	65±7	OR ♀: 6.4 *	NE	NE	Adjusted variables: Multivariate adjusted incl. age, BMI, smoking, estrogen use (not adj. for BMD). Control group: Age-adjusted non-diabetic women from the Nurses' Health Study who in general had a lower BMI, younger age, and were more likely to be on postmenopausal hormones.
<i>Nicodemus, KK 2001[4]</i>	Postmenopausal females n=47/30377	DMT1 if diagnosed at age <40 and on insulin.	306,900 person years	61 ^a	OR ♀: 12.25 *	NE	NE	Adjusted variables: Multivariate adjusted incl. age, BMI, smoking, & estrogen use (not adj. for BMD). Control group: Non-diabetic postmenopausal female residents of Iowa, who in general had lower intake of alcohol compared to DMT1 subjects, and were more likely to be smokers or users of estrogen.
<i>Forsen, R 1999[7]</i>	♀ n=23/13685 ♂ n=28/2868		9 ^c	♀: 59 ^a ♂: 60 ^a	RR ♀: 6.9 * ♂ NS			Adjusted Variables: Multivariate adjusted incl. age, BMI, stroke, and smoking among others. Control group: Men & women w/o DM (not adj. for BMD) who in general had less impaired vision, motor impairment, and stroke but similar BMI to DMT1 group.
<i>Ahmed, L 2005[8]</i>	♀ 29/14065 ♂ 52/12639	DMT1 differentiated from DMT2 based on clinician's judgment using C-peptide levels & presence of DKA at diagnosis.	6 ^c	♀: 43 ^a ♂: 45 ^a	OR ♀: 9.03 * ♂: 18.43 *	NE NE	OR All Nonvert. Fx ♀: NS ♂: 3.05 *	Adjusted variables: Age, BMI, & smoking (not adj. for BMD). *Radiographically confirmed fractures. Control group: Male and female residents of Tromsø, Sweden without diabetes. Controls were not significantly different from DMT1 subjects.
<i>Vestergaard, P 2005[11]</i>	Case/control 124,655 ^b /373,962 NR for DMT1	WHO criteria.	N/A	43±27	DMT1 vs. ctrl OR ♂+♀: 1.7 *	OR 2.5 *	OR ♂+♀: 1.2 *	Adjusted Variables: Multivariate adjusted incl. prior fractures, corticosteroids, alcoholism, antiepileptics, stroke, sedatives etc. (not adj. for BMI or BMD) Control group: Three age- & sex-matched controls were chosen, per case, from the general Danish population.

	N case/controls	DM T2 Distinguished from T1?	Mean f/u years	Age	Hip Fx	Vertebral Fx	Non-vertebral Fx	Comments
Miao et al. 2005/25/	9 12,054/NR σ 12,551/NR	Age <30 at time of hospital admission for insulin dependent DM	9.9	9.43 \pm 9 σ 41 \pm 11	SHR 9.9.8* σ : 7.6*	NE	NE	Control group: Age-, sex-, and calendar-period- matched general population from the entire Swedish inpatient registry.

^a Standard deviation not given

^b n and age show number and age of cases (all fractures in Denmark in 2000 in both diabetics and nondiabetics) vs. controls (3 randomly selected controls, see comment section), **DM Rx**= treatment with OADs or insulin, **NE**=Not Evaluated, **ND**= No difference between those with and those without type 2 diabetes, **NR**: Information *not reported* in paper, **NS**= Not Significant, **SHR**: Standardized hospitalization ratios,

* Statistically significant.

Follow-up years and age shown for T1DM only and not for the control group.