

## Review

# Osteoporosis in Patients With Diabetes Mellitus

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**ABSTRACT:** Demographic trends with longer life expectancy and a lifestyle characterized by low physical activity and high-energy food intake contribute to an increasing incidence of diabetes mellitus and osteoporosis. Diabetes mellitus is a risk factor for osteoporotic fractures. Patients with recent onset of type 1 diabetes mellitus may have impaired bone formation because of the absence of the anabolic effects of insulin and amylin, whereas in long-standing type 1 diabetes mellitus, vascular complications may account for low bone mass and increased fracture risk. Patients with type 2 diabetes mellitus display an increased fracture risk despite a higher BMD, which is mainly attributable to the increased risk of falling. Strategies to improve BMD and to prevent osteoporotic fractures in patients with type 1 diabetes mellitus may include optimal glycemic control and aggressive prevention and treatment of vascular complications. Patients with type 2 diabetes mellitus may additionally benefit from early visual assessment, regular exercise to improve muscle strength and balance, and specific measures for preventing falls.

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**Key words:** diabetes mellitus, insulin, osteoblasts, osteoclast, osteoporosis

### INTRODUCTION

DIABETES MELLITUS IS a pandemic metabolic disease with substantial morbidity and mortality. Patients with diabetes mellitus have various skeletal disorders, including osteopenia or osteoporosis, Charcot's arthropathy, and the diabetic foot syndrome.<sup>(1)</sup> In principle, bone and mineral abnormalities in patients with diabetes mellitus may be caused by direct effects of insulin deficiency or resistance and hyperglycemia on the bone and bone marrow microenvironment, advanced glycation end products (AGEs) of bone matrix proteins, abnormal cytokine and adipokine production and their detrimental effects on bone cells, and impaired neuromuscular/skeletal interactions.<sup>(2,3)</sup>

Osteoporosis is the most important metabolic bone disease in patients with diabetes mellitus.<sup>(1–3)</sup> A survey of a prospective cohort of 32,089 postmenopausal women in the Iowa Women's Health Study revealed that women with type 1 diabetes mellitus (T1DM) were 12 times more likely to report hip fractures than women without T1DM.<sup>(4)</sup> However, women with type 2 diabetes mellitus (T2DM) also had a 1.7-fold higher risk for reporting hip fractures compared with women without T2DM.<sup>(4)</sup> It has been suggested that long-standing T2DM may predispose to a higher incidence of falls, thus increasing the likelihood of suffering fractures despite higher average BMD reported in these patients.<sup>(1)</sup> Finally, distinct syndromes with a combined osteoporosis-

diabetes mellitus phenotype such as Cushing's syndrome, hereditary hemochromatosis, or autoimmune polyglandular syndromes call for special clinical attention and therapy.

To provide optimal bone health care for the growing number of patients with diabetes mellitus, awareness of the epidemiology, careful clinical assessment, and appropriate prevention or treatment of skeletal diseases are pivotal. In this article, we summarize the epidemiology of osteoporosis in patients with diabetes mellitus, identify risk factors that are associated with BMD and osteoporotic fractures, discuss the underlying molecular and cellular mechanisms, and provide concise clinical recommendations.

### MATERIALS AND METHODS

Peer-reviewed, full-length articles up to March 2007 were identified using a PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) search strategy with the terms diabetes, diabetes mellitus, insulin, osteoporosis, bone, skeletal, bone mineral density, and falls. More than 500 articles were identified, and those judged to be relevant by the authors were further evaluated. Clinical studies that included BMD measurements in patients with diabetes mellitus were limited to those using DXA and being published in English. Except for pediatric or adolescent studies of bone metabolism in T1DM, only studies of >30 patients with T1DM or >50 patients with T2DM were considered relevant. Clinical recommendations were based on cited references and good clinical practice. For the section on syndromes with a com-

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The authors state that they have no conflicts of interest.

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TABLE 1. EVALUATION OF BMD IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

References [first author (year)]	n	Sex (F/M)	Age (mean or range in years)	Mean duration (years)	Major findings
Gunczler (1998) <sup>(5)</sup>	26	11/15	12/12	4	Lower LS BMD (mean Z-score, $-1.06 \pm 0.2$ ) in Venezuelan diabetic adolescents compared with 27 age- and sex-matched nondiabetic controls, 93% of patients with T1DM had a Z-score of $< -1.0$ . No correlation was present between BMD Z-scores and duration of disease or glycosylated hemoglobin levels. No differences were found for FN BMD.
Valerio (2002) <sup>(6)</sup>	27	12/15	13	7	Lower LS BMD (mean Z-score, $-0.44 \pm 1.02$ ) in Italian diabetic adolescents compared with 43 nondiabetic controls, negative correlation between LS BMD Z-score and age, duration of disease, and glycosylated hemoglobin.
Pascual (1998) <sup>(7)</sup>	55	29/26	11/10*	3	No LS and DR BMD differences between Spanish adolescents with T1DM and 282 age-matched controls, no correlation between glycemic control or duration of disease.
Liu (2003) <sup>(8)</sup>	72	72/0	16/28†	7/15‡	BMD values of U.S. teenage women with T1DM $> 20$ years of age were lower compared with 91 age-matched nondiabetic controls at the LS ( $-5.6\%$ ) and the FN ( $-8.7\%$ ). No such effect was observed at the DR or in women $< 20$ years of age. No correlation with glycemic control or duration of disease.

The diagnosis of osteopenia/osteoporosis was based on DXA-derived Z-scores.

Only studies evaluating  $>25$  patients are listed.

\* Mean age for girls/boys.

† Teenage/post-teenage females.

F, female; M, male; LS, lumbar spine; FN, femoral neck; DR, distal radius; IGF-1, insulin-like growth factor-1.

bined osteoporotic–diabetic phenotype, representative references describing the phenotype of the syndrome and/or its clinical management were chosen.

## OSTEOPOROSIS IN TYPE 1 DIABETES MELLITUS

### Epidemiology

The prevalence of osteopenia and osteoporosis varies widely in patients with T1DM. Studies on the prevalence of osteoporosis in T1DM can be categorized as (1) those of children or adolescents that assess BMD in a growing skeleton with recent onset of T1DM (Table 1), (2) those of young adults who have reached peak bone mass (mainly after the onset of T1DM) with stable diabetes mellitus, and (3) those of middle-aged patients with long-standing diabetes and mostly with associated diabetic complications (Table 2).

In children with T1DM (Table 1), decreased BMD values with Z-scores of  $-1.1$  and  $-0.4$  in the lumbar spine have been detected in two small studies on 26 and 27 patients, respectively.<sup>(5,6)</sup> The mean age of these patients were 12–13 years, and the mean duration of the disease was 4–7 years.<sup>(5,6)</sup> In one study, a negative correlation of lumbar BMD and glycosylated hemoglobin  $A_{1c}$  levels was noted,<sup>(6)</sup> underlining the negative impact of poor metabolic control on bone mass development. Of note, the study by Gunczler et al.<sup>(5)</sup> showed an adverse effect of T1DM on BMD at the lumbar spine where the Z-score was  $-1.1$  lower in 26 patients compared with 27 nondiabetic controls, but no differences at the femoral neck, suggesting that cancellous bone may be particularly vulnerable.

In contrast, the two largest pediatric studies that evaluated 55 children with a mean age of 10–11 years<sup>(7)</sup> and 39 girls with a mean age of 16 years<sup>(8)</sup> have shown no adverse effect of T1DM on BMD in a population that is yet to develop peak bone mass. In these studies, there was no correlation between BMD and the short duration of disease (3 and 7 years) or glycemic control as determined by glycosylated hemoglobin  $A_{1c}$  serum levels. However, cross-sectional comparison of these 39 teenage girls with T1DM (age range, 13–19 years) with a group of post-teenage women with T1DM (age range, 20–37 years) revealed BMD values that were 5.6% lower at the lumbar spine and 8.7% lower at the femoral neck in women  $>20$  years of age compared with age-matched healthy controls, indicating that T1DM may negatively affect accrual of peak bone mass.<sup>(8)</sup> Studies that assess BMD in children or young adolescents with T1DM by DXA are generally limited by the small sample size and seem to be largely underpowered. Whereas these studies<sup>(5–8)</sup> were adjusted for age and sex, they did not directly take bone size into account (Table 1).

In young adults who have reached peak bone mass and have stable T1DM of intermediate duration, the findings are somewhat heterogeneous, although the majority of studies point toward a negative effect of T1DM on BMD (Table 2). Two studies that evaluated 38 and 35 patients in their forties with a mean duration of T1DM of 33 and 20 years, respectively, detected no significant BMD differences at the lumbar spine and the femoral neck<sup>(9)</sup> or the distal radius.<sup>(10)</sup> Other studies that included between 31 and 56 patients with T1DM showed lower BMD values at the lumbar spine<sup>(11,12)</sup> and femoral neck.<sup>(11–14)</sup> A Spanish study found that BMD values were decreased (Z-score  $-0.61$

TABLE 2. EVALUATION OF BMD IN ADULT PATIENTS WITH TYPE 1 DIABETES MELLITUS

References [first author (year)]	n	Sex (F/M)	Age (mean or range in years)	Mean duration (years)	Major findings
Rozadilla (2000) <sup>(17)</sup>	88	43/45	29	11	Decreased LS BMD (Z-score -0.32), nonsignificant decrease of FN BMD in T1DM, osteoporosis present in 3%. Retinopathy associated with low BMD.
Munoz-Torres (1996) <sup>(18)</sup>	94	49/45	30	12	Decreased LS (Z-score -0.89) and FN (Z-score -0.99) BMD in T1DM, osteoporosis present in 19%. Retinopathy, nephropathy, and active smoking was associated with low BMD.
Lopez-Ibarra (2001) <sup>(11)</sup>	32	10/22	20-39	0*	Lower LS (Z-score -0.61) and FN (Z-score -0.38) BMD at the time of diagnosis, 44% with osteopenia, no correlation with glycemic control.
Campos Pastor (2000) <sup>(20)</sup>	57	30/27	35	17	Presence of retinopathy and poor glycemic control was associated with higher percentage of osteopenia/osteoporosis (72% vs. 53% without retinopathy), benefits of intensive insulin therapy.
Kemink (2000) <sup>(12)</sup>	35	14/21	38	9	Decreased LS (Z-score -0.56 in men) and FN (Z-score -0.42 in women) BMD in T1DM. Osteopenia associated with decreased IGF-1 serum levels and bone formation markers.
Lunt (1998) <sup>(23)</sup>	99	99/0	42	27	LS BMD was 13.1% lower in postmenopausal women with T1DM compared with matched controls. No significant differences in premenopausal women. LS BMD positively associated with oral contraceptive use, femoral BMD negatively with peripheral vascular disease.
Hampson (1998) <sup>(14)</sup>	31	31/0	42	20	Nonsignificant (-10.2%) decrease of FN BMD and lower 25-hydroxyvitamin D <sub>3</sub> levels in T1DM compared with controls, osteoporosis present in 13%.
Ingberg (2004) <sup>(9)</sup>	38	20/18	43	33	No significant LS and FN BMD differences between patients with or without diabetes, negative correlation of duration of disease with LS BMD only in men and FN BMD only in women.
Clausen (1997) <sup>(21)</sup>	36	0/36	48	27	Normal BMD (LS, FN, DR) in patients with long-term T1DM and normal renal function, decreased FN BMD (-15.1%) in patients with T1DM and with progressive microalbuminuria (>300 mg/d).
Bridges (2005) <sup>(10)</sup>	35	0/35	49	20	No DR BMD differences between patients with T1DM, T2DM, and normal controls.
Rix (1999) <sup>(19)</sup>	42	0/42	57/56 <sup>‡</sup>	28/27 <sup>†</sup>	Z-scores were -1.0 for LS, -0.94 for FN, and -1.1 for DR in patients with T1DM and peripheral neuropathy, and -0.60 for LS, -0.55 for FN, and -1.1 for DR in patients with T1DM only.
Tuominen (1999) <sup>(13)</sup>	56	27/29	62/61 <sup>‡</sup>	18/N.A.	FN BMD was 6.8% lower in women and 7.6% lower in men compared with matched controls.

The diagnosis of osteopenia/osteoporosis was based on DXA measurement.

The studies are listed in the order of increasing mean age. Only studies evaluating >30 patients are listed.

\* At diagnosis.

<sup>‡</sup> Mean age for women/men.

<sup>†</sup> With or without severe peripheral neuropathy.

F, female; M, male; N.A., not available; LS, lumbar spine; FN, femoral neck; DR, distal radius; IGF-1, insulin-like growth factor-1.

lower at the lumbar spine and -0.38 lower at the femoral neck) in 32 young adults between 20 and 39 years of age at the time T1DM was diagnosed, with 44% of the patients showing osteopenia.<sup>(11)</sup> Osteopenia was also detected in as many as 67% of men (*n* = 21) and 57% of women (*n* = 14) compared with 33 matched controls in a Dutch study, and osteoporosis was diagnosed in as many as 14% of men with T1DM with a mean duration of 9 years.<sup>(12)</sup> In this study, osteopenia was associated with low serum levels of IGF-1 and bone formation markers.<sup>(12)</sup> A similar prevalence rate

of 13% for osteoporosis was found in a female cohort (*n* = 31; mean age, 42 years) with a mean duration of T1DM of 20.2 years and was associated with lower 25-hydroxyvitamin D<sub>3</sub> serum levels.<sup>(14)</sup>

A Finnish study of 27 women and 29 men in their 60s with a mean duration of T1DM of 18 years showed that femoral neck BMD was 6.8% lower in women and 7.6% lower in men with T1DM compared with age-, sex-, and body mass index (BMI)-matched controls (*n* = 498).<sup>(13)</sup> A recent U.S. study evaluated bone metabolism by DXA (at

the femoral neck and at the lumbar spine) and quantitative ultrasound (at the calcaneus) in 67 postmenopausal women (age range, 5–55 years) with T1DM (mean duration of 32 years).<sup>(15)</sup> Compared with age-matched healthy women, BMD was 3–8% and broadband ultrasound attenuation was 15% lower in women with T1DM. The OR for self-reported fractures in this small cohort was 1.89 in women with T1DM.<sup>(15)</sup> Under the assumption that the site-specific BMD-fracture risk relationship according to Marshall et al.,<sup>(16)</sup> which is based on a meta-analysis of postmenopausal women, also applies to younger men and women with T1DM (Table 2), one can estimate that patients with T1DM have an increased fracture risk at the lumbar spine in the order of 1.3–2.3 (derived from  $2.3^{0.32}$ – $2.3^{1.0}$ ),<sup>(11,12,17–19)</sup> at the femoral neck of 1.4–2.6 (derived from  $2.6^{0.38}$ – $2.6^{0.99}$ ),<sup>(11,12,18,19)</sup> and at the distal radius of ~1.8 (derived from  $1.7^{1.1}$ ).<sup>(19)</sup> Importantly, the majority of studies on patients with T1DM reported no association between BMD and glycemic control determined by hemoglobin A<sub>1c</sub> serum levels.<sup>(5,7,8,11,12,14)</sup>

### Major risk factors

Several studies showed that the presence of micro- and macrovascular diabetic complications as a result of long-standing poor glycemic control rather than long duration per se predict low BMD in patients with T1DM. These include retinopathy,<sup>(17,18,20)</sup> peripheral neuropathy,<sup>(19)</sup> nephropathy,<sup>(18,21,22)</sup> and peripheral vascular disease.<sup>(23)</sup> Both diabetic retinopathy and peripheral neuropathy may lower BMD through impaired physical activity and neuromuscular/skeletal interactions, and enhance the propensity of falls. In one study of 57 patients with T1DM (mean age, 35 years; mean duration, 17 years), osteopenia or osteoporosis was present in 72% of patients with retinopathy, but only in 53% of patients without retinopathy.<sup>(20)</sup> Because the incidence of retinopathy is lower in patients with T1DM on intensive insulin therapy compared with conventional therapy, it was concluded that intensive insulin therapy had beneficial effects on bone metabolism. In addition, overt nephropathy (a microalbuminuria of >300 mg/d),<sup>(18,21)</sup> peripheral neuropathy based on biothesiometry to determine the vibration perception threshold,<sup>(19)</sup> and peripheral vascular disease based on pulse status<sup>(23)</sup> were found to be associated with low BMD in patients with T1DM.

Men with T1DM tend to be particularly prone to osteopenia or osteoporosis. One study showed that 14% of men, but no women, with T1DM had osteoporosis,<sup>(12)</sup> and there was a negative correlation of BMD with duration of T1DM only in men but not in women.<sup>(9)</sup> In part, this observation may be caused by the long mean duration of disease of 33 years in this study. In women with T1DM, the use of estrogen/gestagen-based oral contraceptives was positively associated with the BMD at the lumbar spine,<sup>(23)</sup> whereas smoking was associated with lower BMD in both women and men with T1DM.<sup>(18)</sup> It should be noted that the factors summarized in this section are risk factors for low bone mass, not for fractures.

### Potential mechanisms

The distinct finding of osteopenia and osteoporosis in young patients with T1DM, even shortly after the onset of diabetes mellitus, has led to the hypothesis that insulin serves as a bone anabolic factor.<sup>(24)</sup> Because T1DM typically occurs in children, adolescents, and young adults, the ensuing insulin deficiency coincides with relative skeletal immaturity, thus potentially affecting bone accrual and final peak bone mass.

Support for a direct bone anabolic effect of insulin comes from animal models. Streptozotocin-induced diabetic mice exhibited defects of bone mineralization based on a decreased calcium-to-phosphate ratio of the bone ash, a reduced ash content within the bone, and decreased hydroxyapatite crystal perfection.<sup>(25)</sup> In an immunohistochemical study, streptozotocin-induced diabetic mice expressed reduced IGF-1, IGF-1 receptor, and insulin receptor levels within the skeletal growth centers and exhibited severe histological changes and growth retardation.<sup>(26)</sup> Of note, insulin therapy normalized insulin receptor levels, whereas IGF-1 receptors only partially recovered.

Of interest, mice with variable cellular mosaicism for null insulin receptor alleles, in which the insulin receptor is absent in 98% of cells, displayed growth retardation, diabetes mellitus, and a 60-fold higher expression of hepatic IGF binding protein-1.<sup>(27)</sup> Mice that lack insulin receptor substrate that mediates insulin and IGF-1 signaling, had impaired bone formation and low bone turnover.<sup>(28,29)</sup> Thus, these animal models indicate that some of the skeletal effects of insulin may be mediated through the IGF-1 system. However, in animal models, IGF-1 has differential effects on the cortical versus trabecular bone, and the biological effects on the skeleton depend on whether IGF-1 is locally overexpressed in bone or systemically elevated. When overexpressed in osteoblasts under the collagen type I gene promoter, the femurs of transgenic animals were longer, had a larger cortical width, and an increased cross-sectional area, whereas cancellous bone was not significantly affected.<sup>(30)</sup> A congenic mouse strain with (up to 21%) lower systemic IGF-1 serum levels displayed 50% lower cancellous bone volume density and trabecular number at the femur because of an inhibition of osteoblastic differentiation compared with control mice with “normal” IGF-1 serum levels. In this study, differences of systemic IGF-1 levels affected cancellous bone more than cortical bone.<sup>(31)</sup>

Human data support the concept that insulinopenia in T1DM may impair osteoblast function. A large study conducted in >100 children and young adults with T1DM showed that IGF-1 serum levels (Z-score –0.8 in boys and –0.6 in girls) and biochemical markers of bone formation such as osteocalcin (Z-score –0.6 in boys and –0.7 in girls) were lower in patients with T1DM compared with healthy subjects.<sup>(32)</sup> In addition, IGF-1 serum levels were positively correlated with indices of bone formation (procollagen type I propeptides, alkaline phosphatase, osteocalcin) in subjects with T1DM but not in healthy controls.<sup>(32)</sup> Moreover, low IGF-1 serum levels were found to be associated with osteopenia in patients with T1DM.<sup>(12)</sup>

Consistent with the “insulin deficiency” hypothesis are

the positive skeletal effects of intensive insulin therapy on bone metabolism over the course of 7 years.<sup>(20)</sup> In this study, 57 patients with T1DM (mean age:  $29 \pm 9$  years) were started on intensive insulin therapy and followed for 7 years. Within this period, BMD at the lumbar spine and femoral neck remained stable, and bone resorption determined by serum activity of TRACP was decreased by 38%.<sup>(20)</sup> A potential confounding effect may have been a better glycemic control, because glycosylated hemoglobin levels dropped from 8.5% to 7.9%. Moreover, osteopenia or osteoporosis was present in 72% of patients with retinopathy, but in only 53% of patients without retinopathy.<sup>(20)</sup>

Amylin, a 37 amino acid peptide, is another osteotropic factor that is co-secreted by pancreatic  $\beta$  cells and absent in T1DM.<sup>(33)</sup> In a rat model of T1DM in which streptozotocin selectively destroys pancreatic  $\beta$  cells, the administration of amylin maintained bone mass, inhibited biochemical markers of bone resorption, and elevated biochemical markers of bone formation.<sup>(33)</sup> The phenotype of amylin-deficient mice is characterized by osteopenia and enhanced bone resorption, and amylin was found to inhibit osteoclastogenesis *in vitro*.<sup>(34)</sup>

The role of other pancreatic and enteric hormones in the regulation of bone turnover has recently been reviewed in this *Journal*.<sup>(35)</sup> In particular, glucagon-like polypeptide 2 (GLP 2) and gastric inhibitory peptide (GIP) seem to confer potent osteotropic effects. GLP 2 receptors have been located on osteoclasts, and the administration of physiological doses of GLP 2 reduced bone resorption.<sup>(36)</sup> GIP receptors are located on osteoblasts, and activation of GIP receptors is associated with an enhanced expression of alkaline phosphatase and secretion of type I collagen.<sup>(37)</sup> Whereas GIP administration has no acute effects in humans, it prevented ovariectomy-induced bone loss in mice.<sup>(38)</sup>

It is unclear whether the autoimmune process itself, which is characterized by the presence of activated T cells and an associated osteoclastogenic cytokine microenvironment, including increased RANKL,<sup>(39)</sup> is involved in impaired bone metabolism in patients with T1DM, even before the disease becomes clinically apparent.

### *Clinical recommendations*

The following recommendations are based on key findings of studies cited in this manuscript. Because of the low incidence of T1DM, high-grade evidence-based recommendations are not available. Patients with T1DM should be regarded as high-risk individuals to develop osteoporotic fractures.<sup>(4)</sup> Taking a family and fracture history, nutritional evaluation to identify a low body mass index, malnutrition, and lactose intolerance, and physical examination to assess the extent of retinopathy, neuropathy, nephropathy, and vascular disease may identify additional risk factors that predispose patients with T1DM to low BMD and osteoporotic fractures. In addition, early BMD measurement along with a high clinical index of suspicion for associated immune-mediated diseases (e.g., celiac disease, autoimmune thyroid diseases) is recommended. Despite limited

data, a healthy and physically active lifestyle, including cessation of cigarette smoking<sup>(18)</sup> should be recommended. In particular, men with T1DM are at increased risk for osteoporosis,<sup>(9,12)</sup> which calls for particular clinical attention. The use of oral contraceptives in women with T1DM seems to be protective.<sup>(23)</sup>

## OSTEOPOROSIS IN TYPE 2 DIABETES MELLITUS

### *Epidemiology*

Table 3 summarizes the major findings regarding the effects of T2DM on BMD. Because the onset of T2DM is gradual and may variably precede the actual diagnosis of T2DM by 5–10 years, “time since diagnosis” is more appropriate than the term “duration of disease.” The Rotterdam study, the largest study on BMD in T2DM, included DXA-based BMD data and fracture data on 792 elderly patients with T2DM (483 women and 309 men; mean age: 74 years) and 5863 nondiabetic controls and confirmed that the presence of treated T2DM carries an increased fracture risk (hazard ratio: 1.33; 95% CI, 1.00–1.77) despite a higher BMD at the femoral neck and the lumbar spine.<sup>(40)</sup> A subset analysis revealed an increased fracture risk only in treated T2DM patients (hazard ratio: 1.69; 95% CI, 1.16–2.46), but a lower fracture risk in patients with impaired glucose tolerance (hazard ratio: 0.80; 95% CI, 0.63–1.00).<sup>(40)</sup>

Similar, Strotmeyer et al.<sup>(41)</sup> evaluated 566 patients (243 women and 323 men) with T2DM in their mid-70s and reported a 4–5% higher BMD at the hip, regardless of sex and race. A smaller all-female population with a mean age of 75 years showed BMD values that were 11% higher at the femoral neck and 8% higher at the lumbar spine in women with T2DM compared with healthy controls.<sup>(42)</sup> Other studies with younger patients confirmed these findings. In a Korean study that assessed 185 women with T2DM, lumbar spine BMD was slightly higher compared with a healthy and age-matched control group, and BMD values were negatively correlated with age ( $r = -0.58$ ), years since menopause ( $r = -0.47$ ), and to a lesser degree, with disease duration ( $r = -0.19$ ).<sup>(43)</sup> In a study of 65 Italian women with T2DM (mean age: 63 years), mean BMD T-score at the femoral neck was  $-1.62 \pm 1.03$  compared with  $-2.24 \pm 0.97$  in 42 nondiabetic controls, whereas lumbar spine BMD was not significantly different.<sup>(44)</sup> This study proposed that different skeletal sites may variably be affected by T2DM. Another report suggested that sites mainly composed of cortical bone such as the distal radius may actually be decreased in Japanese patients with T2DM, with mean T-scores being 0.8 lower in 64 men and 1.1 lower in 81 women compared with 95 nondiabetic controls.<sup>(45)</sup>

As in T1DM, two studies suggested some degree of sexual dimorphism in BMD of patients with T2DM. Lumbar spine BMD was found to be 8% lower in 38 men with T2DM and normal renal function compared with 248 healthy controls, but no such differences were found in women with T2DM (40 patients and 916 controls).<sup>(46)</sup> Similar, calcaneal BMD was 10% higher in 56 women with

TABLE 3. EVALUATION OF BMD IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

References [first author (year)]	n	Sex (F/M)	Mean age (years)	Major findings
De Liefde (2005) <sup>(40)</sup>	792	483/309	74	LS and FN BMD higher in patients with T2DM regardless of sex 1.69-fold increased fracture risk in patients treated for T2DM despite higher BMD
Strotmeyer (2004) <sup>(41)</sup>	566	243/323	73/74*	Total hip BMD 4–5% higher in patients with T2DM regardless of sex and race
Kwon (1996) <sup>(43)</sup>	185	185/0	71	LS BMD higher in women with T2DM, BMD negatively correlated with duration of T2DM ( $r = -0.19$ )
Majima (2005) <sup>(45)</sup>	145	81/64	67/63*	DR BMD T-scores were 0.8 lower in men and 1.1 lower in women with T2DM compared with controls. No significant BMD differences at LS and F. Negative correlation between BMD and mean glycosylated hemoglobin A <sub>1c</sub> serum levels ( $r = -0.289$ at DR in men and $-0.314$ at FN and $-0.219$ at DR in women)
Perez-Castrillon (2004) <sup>(47)</sup>	92	56/36	63/65*	Calcaneal BMD 8% higher in women (but not men) with T2DM compared with healthy controls. Body mass index negatively associated with the presence of osteoporosis
Bridges (2005) <sup>(10)</sup>	90	0/90	63	DR BMD not significantly different between patients with T1DM or T2DM and healthy controls. BMD positively correlated with body mass index ( $r = 0.314$ )
Lenchik (2003) <sup>(49)</sup>	80	38/42	64/61*	Adiponectin serum levels negatively correlated with BMD ( $r = -0.22$ at LS, $-0.35$ at total hip, and $-0.26$ at DR)
Wakasugi (1993) <sup>(46)</sup>	78	40/38	62/63*	LS BMD 8% lower in men with T2DM compared with healthy controls, no such effect in women BMD positively correlated with body mass index, negatively with duration of T2DM
Tuominen (1999) <sup>(13)</sup>	68	34/34	64/63*	No significant differences of FN. BMD between patients with T2DM and healthy controls
Gerdhem (2005) <sup>(42)</sup>	67	67/0	75	FN BMD 11% and LS BMD 8% higher in women with T2DM compared with women without T2DM. No differences in osteoporotic fractures
Isaia (1999) <sup>(44)</sup>	66	66/0	63	FN BMD T-scores were 0.6 higher in women with T2DM, no such effect for LS BMD

The diagnosis of osteopenia and osteoporosis was based on T-scores between  $-1.0$  and  $-2.5$  and less than  $-2.5$  based on DXA measurement.

The studies are listed in the order of decreasing sample size. Only studies evaluating  $>50$  patients are listed.

BMD differences are reported as percentage increase or T-scores, if available.

\* Mean age for women/men.

F, female; M, male; LS, lumbar spine; FN, femoral neck; DR, distal radius.

T2DM compared with 56 healthy women, whereas BMD at this site was similar in 36 men with T2DM compared with 36 nondiabetic men.<sup>(47)</sup> A very small study (27 women and 29 men) detected no significant differences of femoral neck BMD between men or women with T2DM and sex-matched healthy controls.<sup>(13)</sup>

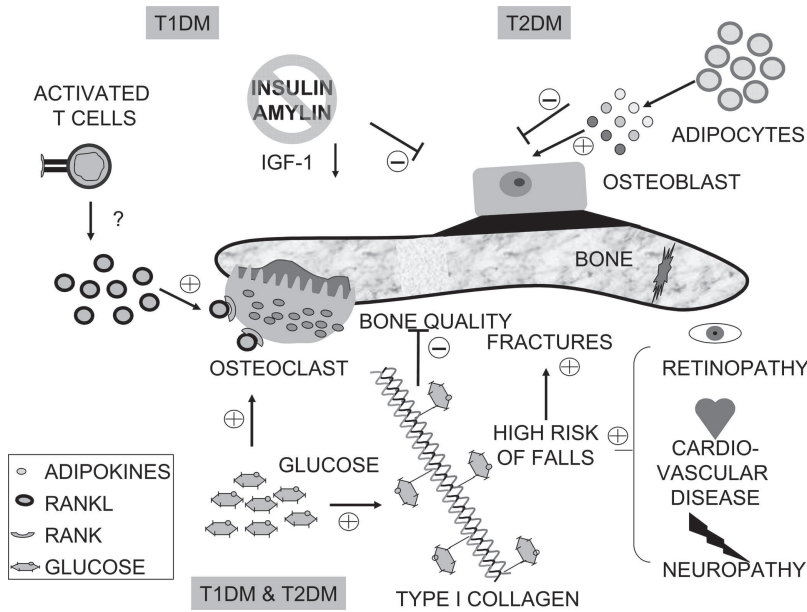
A recent bone ultrasound study from Austria revealed a higher bone mass in 583 elderly nursing home patients with T2DM compared with 1081 nondiabetic controls, even after adjustment for age, weight, and mobility.<sup>(48)</sup> Mean calcaneal stiffness scores were  $-0.03$  in T2DM versus  $-0.52$  in controls, and radial and phalangeal speed of sound scores were  $-0.49$  versus  $-0.81$  and  $-0.65$  versus  $-0.79$  in T2DM versus controls, respectively.<sup>(48)</sup> During a follow-up of 2 years, the hip fracture and nonvertebral fracture rates were comparable between the two groups, indicating that the positive effects of T2DM on bone mass may be counterbalanced by the increased likelihood of falls.<sup>(48)</sup>

#### Major risk factors

Several studies suggest that obesity protects against bone loss based on the finding that BMD and BMI are positively

correlated in patients with T2DM<sup>(10,46)</sup> and that the BMI in patients with T2DM is negatively associated with the presence of osteoporosis.<sup>(47)</sup> These observations indicate that, in addition to mechanical loading, adipose tissue and its cytokines (“adipokines”) such as leptin, resistin, and adiponectin may modulate BMD increases as discussed below. In fact, one study showed an inverse association between adiponectin serum levels and BMD at different sites in patients with T2DM.<sup>(49)</sup> Other studies have shown that axial BMD is negatively correlated with the duration of T2DM<sup>(46)</sup> and that cortical BMD is negatively correlated with mean hemoglobin A<sub>1c</sub> serum levels, an index of poor metabolic control.<sup>(45)</sup>

Despite a higher BMI (and a presumably higher BMD), postmenopausal women with T2DM ( $n = 1682$ ; mean age, 62 years) had a 1.7-fold (95% CI, 1.21–2.38) higher risk for self-reported hip fractures than women without T2DM ( $n = 30,377$ ) in the Iowa Women’s Health Study.<sup>(4)</sup> Data from the Rotterdam study (see details above) confirmed that patients with T2DM have an increased fracture risk despite a higher BMD.<sup>(40)</sup> The hazard ratio for fracture risk was 1.33 (95% CI, 1.00–1.76) for nonvertebral fractures,



**FIG. 1.** Potential mechanisms contributing to low bone mass and increased fracture susceptibility in diabetes mellitus. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. The figure represents a suggested model of potential deleterious effects of diabetes on bone based on in vitro findings, animal studies, and observational human data.

1.34 (95% CI, 0.79–2.28) for hip fractures, and 1.40 (95% CI, 0.81–2.41) for wrist fractures in patients with T2DM compared with nondiabetic individuals after adjustment for age, sex, BMD, and falling frequency. The most likely explanation for these findings is that the presence of T2DM may predispose to a higher incidence of falls, because 25% of patients with treated T2DM, but only 15% of nondiabetic subjects, reported falls.<sup>(40)</sup> In addition, factors other than BMD and falls seem to influence fracture risk.

In a large prospective cohort study of 9249 women as part of the Study of Osteoporotic Fractures, in which the presence of diabetes mellitus was assessed by a questionnaire, 629 women (6.8%) had diabetes that was classified as non-insulin-treated diabetes (530 women) or insulin-treated diabetes mellitus (99 women).<sup>(50)</sup> The majority of these women apparently suffered from T2DM. Insulin-treated women with diabetes mellitus constituted the group with the highest incidence of falls (age-adjusted OR: 2.78; 95% CI, 1.82–4.24), followed by non-insulin-treated women with diabetes mellitus (age-adjusted OR: 1.68; 95% CI, 1.37–2.07). This study did not assess fractures. A potential bias in this study may have been that those with more complicated T2DM may have been more likely to be switched from a diet and exercise or oral anti-diabetic drug regimen (which combined for the noninsulin-treated group) to insulin therapy. It is also possible that hypoglycemic episodes under insulin therapy may have contributed to the increased risk for falls. Women with diabetes mellitus who reported falls commonly had multiple established risk factors, including advanced age, impaired balance, a history of coronary heart disease or arthritis, and peripheral neuropathy.<sup>(50)</sup>

*Potential mechanisms*

In contrast to T1DM with autoimmune β-cell destruction and complete insulin and amylin deficiency, T2DM is characterized by peripheral insulin resistance with a variable degree of hyperinsulinemia and impaired insulin secretion

after metabolic challenge by glucose. Hyperglycemia may have several adverse effects on bone metabolism both in patients with poorly controlled T1DM and T2DM. Glucose is the principal energy source for osteoclasts and is able to dose-dependently enhance avian osteoclast activity in vitro.<sup>(51)</sup> In addition, hyperglycemia leads to nonenzymatic glycosylation of various bone proteins (Fig. 1), including type I collagen, which may impair bone quality.<sup>(52)</sup> In an animal study of a spontaneously diabetic WBN/Kob rat, the bone content of glycation-induced nonenzymatic cross-links (pentosidine) increased over the course of the disease, whereas the content of enzymatic cross-links, including pyridinoline and deoxypyridinoline, concurrently decreased.<sup>(53)</sup> Moreover, bones of diabetic rats with a high content of pentosidine showed impaired biomechanical properties on three-point bending compared with nondiabetic controls, despite similar BMD values,<sup>(53)</sup> indicating that diabetogenic overglycosylation may contribute to poor bone quality (Fig. 1).

Other indirect skeletal sequelae of hyperglycemia include hypercalciuria caused by glycosuria, and various interactions of hyperglycemia with the PTH/vitamin D system. An oral glucose load study in eight healthy women showed hypocalcemia and hypercalciuria, which was associated with suppression of PTH secretion.<sup>(54)</sup> Assessment of bone metabolism in 78 poorly controlled patients with T2DM that were hospitalized revealed that improvement of glycemic control reduced urinary excretion of calcium and phosphate and serum 1,25(OH)<sub>2</sub>D<sub>3</sub> levels and increased serum phosphate levels, but had no effect on serum calcium or PTH levels.<sup>(55)</sup> A cross-sectional study of 5677 New Zealanders (Polynesians and whites) revealed lower 25-hydroxyvitamin D<sub>3</sub> serum levels in subjects with newly diagnosed T2DM and impaired glucose tolerance (*n* = 238) compared with controls that were matched for age, sex, and ethnicity.<sup>(56)</sup> In a prospective population-based study of environmental factors in the etiology of T2DM, vitamin D

status was assessed in 142 elderly Dutchmen, of whom 39% were 25-hydroxyvitamin D<sub>3</sub> depleted.<sup>(57)</sup> Of interest, area under the glucose curve during a standard 75-g oral glucose tolerance test and total insulin concentrations were inversely associated with the serum concentration of 25-hydroxyvitamin D<sub>3</sub>.<sup>(57)</sup>

However, in T2DM, the adverse effects of hyperglycemia on the skeleton are largely counteracted by the positive effects of obesity on BMD. Both osteoblasts and adipocytes are derived from nonhematopoietic mesenchymal stem cells. Moreover, soluble factors released from adipocytes (adipokines) have recently emerged as crucial mediators in various human diseases,<sup>(58)</sup> including osteoporosis. Leptin is by far the best-characterized adipokine with regard to its skeletal effects, but more recently, adiponectin and resistin have also been implicated to mediate, at least part of the protective effects of obesity on the skeleton.

Based on *in vivo* studies, there may be two principal mechanisms involved in skeletal action of leptin, one central and one peripheral, which have divergent effects. The major central mechanism of leptin on the skeleton of animals is a suppression of bone formation by restraining osteoblast proliferation. In a series of elegant studies, the Karsenty group has convincingly shown that this effect depends on the sympathetic nerve system and involves molecular clock genes, which regulate circadian functions.<sup>(59–61)</sup> Of note, peripheral administration of leptin partially prevented ovariectomy-induced bone loss in rats.<sup>(62)</sup> Both adiponectin-deficient mice and transgenic mice overexpressing adiponectin had no overt skeletal phenotype.<sup>(63)</sup> The skeletal phenotype of resistin-deficient or transgenics has not been defined.

*In vitro* studies indicate that the peripheral action of leptin is mediated by specific receptors that are localized on osteoblastic lineage cells.<sup>(64)</sup> Leptin stimulates osteoblastic differentiation<sup>(64)</sup> and inhibits osteoclastogenesis.<sup>(65)</sup> Adiponectin receptors are expressed on osteoblastic and osteoclastic cells and adiponectin suppressed osteogenesis in cultured osteoprogenitor cells; however, in the presence of insulin, this suppression was blunted.<sup>(63)</sup> Resistin is expressed by osteoblastic and osteoclastic lineage cells. Resistin stimulated osteoclastogenesis and enhanced preosteoblastic proliferation without affecting osteoblastic differentiation.<sup>(66)</sup>

Clinical studies have implicated that serum levels of leptin are positively and serum levels of adiponectin are negatively correlated with BMD. In a random sample of a cohort of 645 subjects from the general population (302 women and 343 men) from the Mayo Clinic that did include some patients with T2DM, lean mass- and age-adjusted leptin serum levels were positively correlated with BMD at the hip ( $r = 0.42$ ), lumbar spine ( $r = 0.18$ ) and mid-distal radius ( $r = 0.27$ ) in postmenopausal women but not in men.<sup>(67)</sup> Moreover, a study on patients with T2DM (38 women and 42 men) showed that adiponectin serum levels after adjustment for age, sex, ethnicity, smoking, and diabetes status were negatively correlated with BMD at the lumbar spine ( $r = -0.22$ ), total hip ( $r = -0.35$ ), and distal radius ( $r = -0.26$ ).<sup>(49)</sup>

Taken together, adipokines have mixed effects on human

bone metabolism that do not fully explain increased BMD values of obese people. However, adipokines display several adverse effects on the cardiovascular system.<sup>(68)</sup> Specifically, leptin (1) contributes to a systemic inflammatory cytokine milieu, (2) is associated with atherosclerosis and arterial hypertension, and (3) mediates diet-induced neointimal thickening after vascular injury.<sup>(68)</sup> Adiponectin, which is decreased in obese and diabetic individuals, (1) has anti-inflammatory properties, (2) confers protection of endothelial and vascular smooth muscle cells, and (3) exerts positive effects on myocardial remodeling.<sup>(68)</sup> Thus, whereas adipokines seem to have a positive net effect on the skeleton in patients with T2DM, their adverse effects on the cardiovascular system may predispose to falls, which contributes to an elevated risk of osteoporotic fractures despite higher BMD.

### *Clinical recommendations*

The following recommendations are based on key findings of studies cited in this manuscript. Specific evidence-based recommendations are not available for diagnosis and treatment of osteoporosis in T2DM, although most osteoporosis treatment studies included patients with impaired glucose tolerance or frank T2DM. Patients with T2DM represent a diagnostic and prognostic dilemma because the value of BMD measurement in predicting osteoporotic fractures may be limited by two main factors: decreased bone quality and a higher risk of falls. Adequate glycemic control is pivotal to limit the degree of nonenzymatic (over) glycosylation of collagen. Moreover, glycemic control prevents or delays diabetogenic vascular complications. The frequency of falls and near-falls and the presence of established risk factors for falls (advanced age, impaired balance, coronary heart disease, peripheral neuropathy)<sup>(50)</sup> should be assessed. A recent review recommended systematic implementation of established methods such as a regular exercise program to improve muscle strength, balance, and proprioception, withdrawal of psychotropic medications, visual assessment and adequate cataract surgery, professional environmental hazard assessment and modification, and the use of hip protectors to reduce the risk of falls or fractures.<sup>(69)</sup> Importantly, vitamin D and calcium supplementation for 3 months has been shown to reduce the risk of falls by 49% in a cohort of 122 elderly nondiabetic women.<sup>(70)</sup> It remains to be shown whether such beneficial effects are also achieved in patients with T2DM.

### **SYNDROMES WITH A COMBINED OSTEOPOROTIC-DIABETIC PHENOTYPE**

Two common chromosomal abnormalities, Turner's syndrome caused by a 45, X karyotype and Klinefelter's syndrome caused by a 47, XXY karyotype, can result in osteoporosis and diabetes mellitus.<sup>(71–73)</sup> In both syndromes, osteoporosis is mainly caused by primary hypogonadism,<sup>(73)</sup> and can be prevented by appropriate sex hormone replacement. It is recommended to measure BMD in all adult patients with Turner's and Klinefelter's syndrome at

TABLE 4. SYNDROMES WITH A COMBINED OSTEOPOROSIS/DIABETES MELLITUS PHENOTYPE

<i>Syndrome</i>	<i>Reference</i>	<i>Cause/mechanism</i>	<i>Associated disorders</i>	<i>Treatment</i>
Cushing's syndrome	76	Glucocorticoid excess	Obesity, plethora, myopathy, amenorrhea, arterial hypertension, obesity, secondary diabetes	Avoid exogenous glucocorticoid excess, removal of ACTH or cortisol source
Hereditary hemochromatosis	74	<i>HFE</i> mutation, iron overload	Hepatomegaly, liver cirrhosis, arthropathy, hypogonadism, bronze diabetes, cardiomyopathy	Phlebotomy, chelation therapy, hormone replacement
Kearns-Sayre's syndrome	77	Mitochondrial myopathy	Ophthalmoplegia, retinal degeneration, cardiac conduction defects, short stature, gonadal failure, diabetes mellitus, hypoparathyroidism	Supportive ophthalmologic care, hormone replacement
Klinefelter's syndrome	73	47, XXY karyotype	Primary hypogonadism, tall stature, behavioural abnormalities, pulmonary diseases, type 2 diabetes	Testosterone replacement, diet, exercise
Lawrence-Seip's syndrome	78	Acquired generalized lipodystrophy	Voracious appetite, acanthosis nigricans, hypertriglyceridemia, atherosclerosis, osteopenia, bone cysts	Diet, insulin, fibrates
Pancreatic insufficiency		Endocrine and exocrine organ failure	Secondary diabetes mellitus, malabsorption, osteomalacia	Diet, insulin, calcium and vitamin D supplementation, enzyme replacement
Polyglandular autoimmune syndrome type II	75	Autoimmune destruction of endocrine organs	Adrenal insufficiency, autoimmune thyroid disease, type 1 diabetes mellitus, primary hypogonadism	Hormone replacement therapy for affected organs
Turner's syndrome	72	45, X karyotype	Short stature, gonadal dysgenesis, congenital heart defects, type 2 diabetes	Diet, exercise, cyclical estrogen and progestin
Werner's syndrome	80	<i>RecQ helicase</i> mutation	Progeria, atherosclerosis, type 2 diabetes, cataract, osteoporosis	Supportive care, statins, diet, exercise
Wolcott-Rallison's syndrome	79	<i>EIF2AK3</i> mutation	Epiphyseal dysplasia, osteoporosis, type 1 diabetes, growth retardation, mental retardation, cardiovascular abnormalities	Supportive care, insulin

The underlying mechanism, associated disorders that predispose to osteoporotic fractures, and the appropriate treatment are listed.

the initial visit and 3–5 years later.<sup>(72)</sup> The occurrence of T2DM is rare, and it is primarily managed by diet and exercise.

Multiorgan diseases caused by iron overload (in hereditary hemochromatosis) or autoimmune destruction (autoimmune polyglandular syndrome type 2) may result in pancreatic islet cell destruction resulting in secondary diabetes mellitus.<sup>(74,75)</sup> Osteoporosis in these disorders is mainly

caused by concurrent hypogonadism or hypopituitarism. Glucocorticoid excess in Cushing's syndrome may result in severe osteoporosis in up to 50% of patients and is characterized by a stimulation of bone resorption and an inhibition of bone formation.<sup>(76)</sup> A spectrum ranging from impaired glucose tolerance to frank insulin-dependent diabetes mellitus occurs in up to 90% of patients with Cushing's syndrome, and is caused by the insulin-antagonistic

effects of glucocorticoids. In long-standing Cushing's syndrome, myopathy, arterial hypertension, and impaired vision (caused by cataracts or glaucoma) may further increase the likelihood of falls.<sup>(76)</sup>

Other rare syndromes with an osteoporotic–diabetic phenotype include Kearns-Sayre's syndrome, a mitochondrial myopathy,<sup>(77)</sup> and Lawrence-Seip's syndrome, an acquired generalized lipodystrophy.<sup>(78)</sup> Two inherited diseases with defined mechanisms are Wolcott-Rallison's syndrome and Werner's syndrome. Wolcott-Rallison's syndrome is caused by a mutation of *eukaryotic translation initiation factor 2- $\alpha$  kinase 3* (*EIF2AK3i*, an essential regulator of protein translation) that is highly expressed in pancreatic  $\beta$  cells and results in T1DM.<sup>(79)</sup> Werner's syndrome is characterized by premature aging and is caused by mutations in *RecQL2* (*RecQ3; WRN*), coding for a RecQ helicase family member that is needed for DNA replication, which leads to a limited replicative capacity of mesenchymal cells.<sup>(80)</sup> Clinically, patients with Werner's syndrome develop osteoporosis, T2DM, and atherosclerosis at a premature age. The roles of *EIF2AK3* and *RecQL2* in bone metabolism have not been elucidated. Table 4 summarizes the underlying mechanisms, associated disorders, and treatment recommendations of combined osteoporotic–diabetic syndromes.

#### SUMMARY AND AREAS OF FUTURE RESEARCH

Diabetes mellitus and osteoporosis are two frequent medical conditions with an increasing prevalence in the aging population. Patients with T1DM are at high risk for osteoporotic fractures. Whereas the initial period of insulin deficiency results in impaired bone formation, poor glycemic control in long-standing disease is associated with retinopathy, peripheral neuropathy, nephropathy, and peripheral vascular disease, which are predictors of low bone mass and increased fracture risk. Prevention and aggressive treatment of these complications by intensive insulin therapy, screening for low BMD, and awareness of other associated diseases (e.g., celiac disease) is recommended in patients with T1DM. In contrast, patients with T2DM have an increased fracture risk despite a higher BMD, which is mainly caused by the increased risk of falls. Thus, normal BMD values may be misleading. Adequate glycemic control and prevention of diabetic complications are also the mainstay of therapy in T2DM. In addition, risk factors for falls (advanced age, impaired balance, cardiovascular disease, neuropathy) should be identified and minimized by implementing a program that combines regular exercise, vitamin D supplementation, withdrawal of psychotropic medications, visual assessment, environmental hazard assessment and modification, and the use of hip protectors.

Areas of future research should include characterization of rodent models with a combined diabetes–osteoporosis phenotype, analysis of involved cytokines and signaling pathways, and clarification of the determinants of poor bone quality in diabetes. Clinically, assessment of skeletal effects of novel anti-diabetic drugs, subset evaluation of patients with T1DM and T2DM in osteoporosis treatment trials, and intervention studies to reduce falls in patients

with T2DM will benefit patients suffering from osteoporosis and diabetes mellitus. The example of the glitazones, oral anti-diabetic drugs that act as insulin sensitizers for patients with T2DM, but are associated with bone loss and fractures,<sup>(81)</sup> shows that new drugs that benefit one component of the diabetes–osteoporosis syndrome may impair the other. Finally, evidence-based guidelines of how to manage osteoporosis in subjects with diabetes mellitus are warranted.

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