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Review

Bone disorders associated with diabetes mellitus and its treatments

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ABSTRACT

Both type 1 and type 2 diabetes mellitus are associated with bone disorders, albeit via different mechanisms. Early studies in patients with type 1 diabetes suggested a 10-fold increase in the hip fracture risk compared to non-diabetic controls. Meta-analyses published more recently indicate a somewhat smaller risk increase, with odds ratios of 6 to 7. Diminished bone mineral density is among the contributors to the increased fracture risk. Both types of diabetes are associated with decreased bone strength related to low bone turnover. The multiple and interconnected pathophysiological mechanisms underlying the bone disorders seen in type 1 diabetes include insulin deficiency, accumulation of advanced glycation end products, bone microarchitecture alterations, changes in bone marrow fat content, low-grade inflammation, and osteocyte dysfunction. The bone alterations are less severe in type 2 diabetes. Odds ratios for hip fractures have ranged across studies from 1.2 to 1.7, and bone mineral density is higher than in non-diabetic controls. The odds ratio is about 1.2 for all bone fragility fractures combined. The pathophysiological mechanisms are complex, particularly as obesity is very common in patients with type 2 diabetes and is itself associated with an increased risk of fractures at specific sites (humerus, tibia, and ankle). The main mechanisms underlying the bone fragility are an increase in the risk of falls, sarcopenia, disorders of carbohydrate metabolism, vitamin D deficiency, and alterations in cortical bone microarchitecture and bone matrix. The medications used to treat both types of diabetes do not seem to play a major role. Nevertheless, thiazolidinediones and, to a lesser extent, sodium-glucose cotransporter inhibitors may have adverse effects on bone, whereas metformin may have beneficial effects. For the most part, the standard management of bone fragility applies to patients with diabetes. However, emphasis should be placed on preventing falls, which are particularly common in this population. Finally, there is some evidence to suggest that anti-fracture treatments are similarly effective in patients with and without diabetes.

1. Introduction

Diabetes has adverse effects on bone that translate into an increased fracture risk. However, the mechanisms underlying the bone alterations differ markedly between type 1 and type 2 diabetes. Type 1 diabetes (T1D) affects bone more severely and via a simpler pathophysiological mechanism dependent on a decrease in bone mineral density (BMD). T1D usually starts during adolescence, at a time of accelerated skeletal growth. As a result, the bone becomes compromised at a younger age, and the adverse consequences are even more severe during the aging process. On the other hand, both the incidence and the prevalence of T1D are lower than those of type 2 diabetes (T2D). That T2D may adversely affect bone health was suggested more recently. The pathophysiology of the bone effects is more complex, in particular because T2D is often combined with obesity, which can also have detrimental effects on bone. In addition, BMD is variably elevated in T2D, an effect that would be expected to increase bone strength. Given these data, we will consider the bone effects of T1D and T2D separately in this review. However, the potential role for antidiabetic medications in bone disorders will be discussed for both types of diabetes simultaneously. Few data are available on the management of bone fragility in patients with diabetes. Overall, there are only a few differences from the standard treatment of bone fragility.

2. Effects of type 1 diabetes (T1D) on bone

That T1D is associated with bone disorders was demonstrated many decades ago. Thus, as early as 1934 several cases of verte-

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bral fracture were reported in patients with diabetes [1]. Autopsy data confirmed the association a few years later by showing greater severity of osteoporosis in patients with T1D compared to controls without diabetes [2]. Cohort studies were then carried out. Among them, a study from Israel found that the proportion of patients with diabetes who had at least one vertebral fracture was 20%, which was far higher than expected [3]. The development of BMD measurement techniques, i.e., single-energy then dual-energy X-ray absorptiometry, demonstrated that BMD values in patients with T1D were 30% to 50% lower than in non-diabetic controls [4,5].

2.1. Fracture risk in type 1 diabetes (T1D)

Several studies showed abnormal bone fragility in patients with T1D [1,2]. However, only several years after the publication of these studies was clear evidence of an increased fracture risk obtained. For instance, in an 11-year study in 32,089 postmenopausal women in Iowa, the hip fracture risk was increased 12-fold in participants with versus without T1D [6]. The risk of hip fracture may be even greater in males. Thus, a study from Norway in 25 159 males and females showed that males with T1D had a nearly 18-fold increase in the hip fracture risk compared to male controls without diabetes [7]. T1D was associated with a 6- to 7-fold increase in the hip fracture risk in two meta-analyses published in 2007 [8,9]. The risk increase was smaller for vertebral fractures, with an odds ratio (OR) of 2.5 (95% confidence interval [95% CI]: 1.3–4.6) [10].

More recently, studies have confirmed that the fracture risk is increased in T1D, albeit to a lesser extent than suggested earlier. According to a 2015 meta-analysis, the risk of any fracture was increased 3-fold and the risk of hip fracture in women 5-fold in patients with T1D [11]. These apparent discrepancies may be related to differences in study populations regarding age at cohort inclusion, ethnicity, diabetes duration, and the prevalence of diabetic complications. Furthermore, improvements in T1D management over time may have contributed to diminish the fracture risk. In general, and without entering into the pathophysiological considerations that are detailed below, several factors play a key role in the increased fracture risk, notably disease duration and quality of glycemic control [6]. In addition, conflicting data have been reported [12]. Finally, diabetic complications, notably those affecting the microvasculature, undeniably contribute to the fracture risk [6,9,10].

2.2. Bone mineral density (BMD) in patients with type 1 diabetes (T1D)

In most studies, patients with T1D had variable decreases in BMD at the spine, hip, and whole body compared to controls [13,14,15,16,17]. Nevertheless, a few studies found no BMD decrease [18,19]. Furthermore, the magnitude of the BMD decrease varied considerably across studies, from 8% to 67%. In a 2007 meta-analysis, the mean BMD decreases were 22% at the spine and 37% at the hip compared to age- and sex-matched controls [8]. As with the fracture risk increase, the magnitude of the BMD decline increased with disease duration in most studies. However, the same meta-analysis found no association between the glycated hemoglobin level (Hb1Ac) and BMD [8]. In general, achieving good glycemic control does not seem sufficient to prevent the BMD decline. As with fractures, diabetic microvascular disease is associated with aggravated bone loss [13,14,15,16,17]. Most of the current data indicate that the BMD decline is not the only contributor to the increased fracture risk and that bone quality is also adversely affected in T1D (see below).

2.3. Bone microarchitecture in type 1 diabetes (T1D)

A few studies used high-resolution peripheral quantitative computed tomography (HR-pQCT) to assess bone quality in T1D. Compared to controls, patients with T1D had lower total and trabecular volumetric BMD values at the ultradistal radius and tibia, and the differences were greatest in the patients with microvascular disease [20]. Thinning of the bone trabeculae and tibial cortex was also most marked in the group with microvascular disease [20]. However, and in contrast to observations often made in T2D, cortical porosity was not increased, even in the patients with microvascular disease.

2.4. Bone turnover in patients with type 1 diabetes (T1D)

An association of T1D with decreased bone turnover has been suggested by numerous animal studies [21,22]. Osteoblasts and mineralization seem consistently decreased in rodent models. The data on osteoclastogenesis and bone resorption, in contrast, vary somewhat across studies [21,22].Studies based on bone turnover markers have confirmed these findings in humans [23,24,25]. Thus, osteocalcin levels seem to be depressed in patients with T1D [23,24]. Furthermore, children and young adults with T1D may have abnormally low levels of procollagen type 1 amino-terminal propeptide (P1NP) [25]. However, these data may be biased due to the collagen reticulation alterations seen in T1D, which result in underestimation of levels of carboxy-terminal collagen cross-links (CTX). Few histological and histomorphometric data are available [26]. Given this caveat, the above-mentioned study supports a substantial decrease in bone formation. A more recent bone-biopsy study demonstrated increases in mineralization and collagen cross-links independent from enzyme activity in patients with T1D, notably those with a history of fractures, compared to non-diabetic controls [27]. These findings therefore also support a decrease in bone turnover.

Taken in concert, these data support the existence in T1D of bone quality alterations (affecting bone microarchitecture, bone turnover, and molecular structure) that decrease bone hardness and resistance to mechanical loads.

2.5. Pathophysiology of bone disorders in patients with type 1 diabetes (T1D)

Fig. 1 recapitulates the cellular and molecular mechanisms involved in the pathophysiology of bone disorders associated with T1D. A few factors may be directly involved in the quantitative and qualitative bone alterations.

2.5.1. Insulin, incretins

Insulin has anabolic effects on bone in vitro [28,29]. In animals with diabetes, insulin treatment corrects the bone turnover

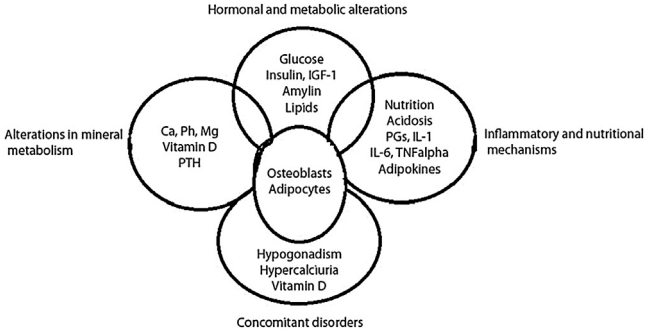

Fig. 1. Pathophysiology of bone disorders associated with type 1 diabetes. IGF-1: insulin-like growth factor-1; PTH: parathyroid hormone; PGs: prostaglandins; IL: interleukin; TNF: tumor necrosis factor.

Table 1
Main data on the fracture risk in patients with type 2 diabetes.

Authors	Fracture sites	Odds ratio or relative risk	95% CI
Janghorbani et al., 2007 [9]	Hip	1.7	[1.30–2.20]
Vestergaard et al., 2007 [8]	Hip, wrist	1.38	[1.25–1.53]
		1.19	[1.10–1.41]
Fan et al., 2016 [37]	Hip	1.34	[1.19–1.51]
Wang et al., 2016 [38]	Spine	2.03	[1.60–2.59]
Dytfield and Michalak, 2017 [39] [a]	Hip	1.296	[1.07–1.57]
Moayeri et al., 2017 [40]	Hip	1.20	[1.17–1.23]
	Spine	1.16	[1.05–1.28]
	Foot	1.37	[1.21–1.54]
	Any site	1.17	[1.15–1.20]

[a] Postmenopausal women.

abnormalities and improves some of the bone quality parameters, depending on the insulin dose and time to insulin initiation [30]. However, insulin deficiency is not the only factor involved in the bone disorders seen in T1D. Insulin-like growth factor-1 (IGF-1, also known as somatomedin) plays a pivotal role in bone mass accumulation and maintenance. Depressed IGF-1 levels have been reported in T1D and may, per se, contribute to the bone demineralization [15,31].

The main incretins are glucose-dependent insulinotropic peptide (GIP), also known as gastric inhibitory polypeptide, and glucagon-like peptide-1 (GLP-1). Both are hormones that are released by the gastrointestinal tract and potentiate the effect of insulin on carbohydrate metabolism. When evaluating bone disorders, their role seems far greater in T2D than in T1D. Thus, the GLP-1 agonists and dipeptidyl peptidase-4 (DDP-4) inhibitors used to treat T2D may exert substantial effects on bone (see below). In murine models of T1D, incretins can prevent bone microarchitecture alterations and preserve bone quality [32].

2.5.2. Hyperglycemia and advanced glycation end products (AGEs)

Hyperglycemia per se suppresses osteoblast differentiation and contributes to the signaling process involved in altering bone formation. Furthermore, chronic hyperglycemia results in nonenzymatic glycation of proteins, notably collagen, leading to increased levels of advanced glycation end products (AGEs).

AGEs and their receptors are involved in the development of many diabetic complications, including bone alterations. AGEs can affect bonds within the type 1 collagen triple helix, thereby causing alterations in intrinsic bone quality, of which one effect is increased bone rigidity. Pentosidine is the most extensively studied AGE. In a cross-sectional study, serum pentosidine levels were elevated in patients with T1D [33], although the large standard deviation warrants circumspection in interpreting this result.

2.5.3. Bone marrow fat content

Bone marrow contains an abundance of stem cells that can differentiate into osteoblasts, adipocytes, or chondrocytes. The development of bone marrow adipocytes is generating growing interest as a possible explanation to the bone loss seen in T1D. Thus, the bonemarrow fat content correlates negatively with BMD. An increase in bone marrow fat content at the lumbar spine may be associated with a higher fracture risk in the general population. Stem-cell differentiation to adipocytes involves the transcription factor known as peroxisome proliferator-activated receptor (PPARγ2) and is viewed as competing with osteoblastogenesis. The above-mentioned decrease in osteoblastogenesis in T1D has therefore turned research attention toward the development of bone marrow fat. In various murine T1D models, increased PPARγ2 levels and adipocyte counts were found in bone marrow; nevertheless, whether bone loss and increased bone marrow fat content are linked in this setting has not been proven [34,35]. Only limited data are available. Thus, whether fat accumulation within the bone marrow may explain the bone disorders seen in T1D remains to be investigated.

2.5.4. Inflammation

Low-grade inflammation is common in patients with T2D. However, T1D is also associated with overexpression of the main genes involved in inflammatory processes. Similarly, diabetic complications, notably microvascular disease, are partly related to inflammatory alterations. Additional data are needed to further evaluate this hypothesis in T1D.

2.5.5. Disorders in osteocyte function

As indicated above, osteoblast suppression may be a major factor in the genesis of bone disorders associated with T1D. Data also suggest alterations in osteocyte function involving sclerostin, a Wnt-pathway inhibiting factor released by osteocytes. The Wnt-pathway is crucial to osteoblast differentiation. Elevated sclerostin levels have been reported in patients with T1D [33]. The duration of T1D may influence the sclerostin levels.

3. Effects of type 2 diabetes (t2d) on bone

T2D is far more common than T1D. The number of patients with T2D is currently estimated at 422 million worldwide [36]. The T2D/T1D ratio is 0.9/0.1. In addition, the incidence of T2D has been climbing steadily in recent years, in large part due to the obesity epidemic. The mechanisms underlying the increased fracture risk are more complex in T2D than in T1D. In particular, BMD values, which are usually low in patients with T1D, are generally elevated in those with T2D.

3.1. Epidemiology

A fracture risk increase was demonstrated by several studies of patients with T2D. Overall, the risk increase is smaller than in T1D (Table 1). That the hip fracture risk is elevated has been convincingly demonstrated, with ORs ranging across studies from 1.2 to 1.7 [8,9,36,37,38,39,40]. Although the results vary somewhat, both longer diabetes duration and poor glycemic control seem associated with a higher fracture risk [41].

3.2. Pathophysiology of bone disorders in type 2 diabetes (T2D)

The fracture risk increase involves many causes or risk factors, which are more or less interconnected and differ in part from those relevant to T1D. As most studies showed no decline in BMD values,

the increased bone fragility is strongly believed to be related to alterations in bone quality.

3.2.1. Obesity

Higher body weight protects against bone loss up to a certain point. However, the relation is not linear. Thus, when body mass index (BMI) values enter the overweight zone, i.e., become greater than 25 kg/m^2, no further bone protection occurs with additional weight gain. In addition, patients with obesity are at increased risk for fractures at certain sites such as the humerus, leg, and ankle [42]. Given that many patients with T2D are also obese, the relative contributions of the two diseases may be difficult to tease apart.

3.2.2. Increased fall risk

An increased risk of falls has been demonstrated both in patients with T2D and in those with obesity [43]. The increase is multifactorial and involves visual loss due to cataract and retinopathy, cardiac arrhythmias, neuropathy, hypoglycemia, and other factors.

3.2.3. Sarcopenia

Sarcopenia increases the risk of falls in the general population. This effect seems particularly marked in patients with diabetes, particularly those who are also obese (sarcopenic obesity). In patients with diabetes, sarcopenia seems independent from the presence of neuropathy [44].

3.2.4. Alterations in carbohydrate metabolism

T2D is characterized by insulin resistance. There is sound evidence that insulin metabolism abnormalities influence bone turnover (see below). Furthermore, hyperglycemia leads to AGE accumulation within the bone matrix. The build-up of AGEs also contributes to alter bone tissue quality [45].

3.2.5. Vitamin D deficiency

Vitamin D deficiency is more marked in patients with T2D than in the general population. One contributor to this difference is obesity. In addition to its effects on bone, vitamin D may participate in maintaining glycemic control, as the pancreatic beta cells carry vitamin D receptors. However, vitamin D supplementation seems to have no effect on glycemic control [41].

3.2.6. Bone turnover

Few histomorphometric data from patients with T2D are available. In a study of 26 patients, decreases were found in osteoid thickness, osteoid volume, and osteoblast surface area compared to age-matched controls without diabetes [46]. Other studies suggest decreases in dynamic parameters associated with the level of bone turnover such as the bone formation rate, mineralized surface area, and bone mineralization rate. In keeping with these data, there is an overall decrease in bone turnover markers including CTX and osteocalcin [47].

3.2.7. Alterations in bone microarchitecture

HR-pQCT has been used to investigate bone microarchitecture in T2D [48,49,50], with conflicting results. One study, in only 19 patients with T2D, showed increased cortical porosity at the radius and tibia compared to healthy controls [48]. A larger study in 190 males with T2D demonstrated a decrease in total bone surface area at the radius and tibia combined with a decrease in bone strength (evaluated using the finite element method) confined to the cortices of these two bones [49]. Another study compared postmenopausal women with and without diabetes [50]. In both groups, some patients had a history of fractures. Within the T2D group, patients with fractures had moderate alterations in cortical bone microarchitecture, with an increase in cortical porosity, compared to those without fractures. Interestingly, no such difference was found between non-diabetic patients with versus without fractures. A more recent study used HR-pQCT to investigate 1069 males and females, among whom 12% had T2D [51]. After adjustments on multiple factors, T2D was associated with decreases in cortical bone density and tibial bone surface area and with an increase in cortical porosity. However, the differences were moderate. Furthermore, the trabecular parameters were better in the patients with than without diabetes. Patients with diabetes and a history of fracture had lower values of tibial volumetric BMD and radial cortical thickness [51]. Some of the data are conflicting, however. In a small study of 25 individuals, HR-pQCT parameters failed to demonstrate any differences between patients with T2D and controls. Other studies also showed no differences in bone microarchitecture and bone strength parameters between women with and without T2D [52,53].

The trabecular bone score (TBS) has been the focus of a few studies [54,55]. The results suggest that TBS values may be lower in patients with T2D, although their BMD values are usually elevated. These results may seem surprising since both the TBS and BMD are measured at the lumbar spine based on the same acquisitions.

3.2.8. Microindentation

Bone microindentation testing is a recently developed tool for measuring the resistance of subperiosteal bone to penetration at the proximal tibia. A probe is applied, and the depth of the indentation thus produced is then measured and used to determine the bone material strength index (BMSi), which reflects bone strength. The BMSi is decreased in patients with bone fragility, due for instance to postmenopausal osteoporosis. In addition, the results obtained using microindentation may be partly independent from the BMD values. Although the studies done so far in T2D involved only small numbers of patients, their results suggest a decrease in the BMSi [52,53,56]. In the earliest study, BMSi was significantly lower in 30 patients with T2D than in 30 controls. Furthermore, HbA1c values correlated negatively with the BMSi. Similar results have been obtained in larger studies [53,56].

3.2.9. Bone matrix alterations: role for advanced glycation end products (AGEs)

As indicated above, AGEs include several groups of compounds produced by nonenzymatic glycation of various proteins (including type 1 collagen). AGEs inhibit osteoblastic differentiation. The build-up of AGEs within the bone matrix alters the biomechanical properties of bone. AGE levels are elevated in patients with T2D [57]. Thus, a role for AGEs in the bone disorders associated with T2D is a plausible pathogenic hypothesis that deserves further investigation.

4. Effects of antidiabetic medications on bone tissue

Overall, data are scant. Table 2 reports the main available evidence. It is worth noting that the medications listed in Table 2 are not, or no longer, reimbursed by the French statutory healthcare system. Thus, thiazolidinediones are no longer reimbursed and sodium-glucose cotransporter inhibitors have never been reimbursed. Hypoglycemic sulfonamides have no direct effect on bone (Table 2). However, they may increase the fall risk by causing hypoglycemic episodes. In vitro data on metformin suggest a protective effect on bone, but studies in humans are less conclusive [58]. Thiazolidinediones activate PPARγ, thereby adversely affecting bone and increasing the fracture risk [10,59]. As mentioned above, thiazolidinediones are no longer available in France. Incretins seem to protect bone in vitro, but their in vivo effects are more difficult to interpret [60,61,62]. Among the sodium-glucose cotransporter inhibitors, canagliflozine may exert deleterious effects on bone,

Table 2
Effects of antidiabetic medications on bone.

Medication	Mechanism of action	Effect on BMD	Effect on the fracture risk
Hypoglycemic sulfonamides [58]	No direct effect on bone tissue	No data	No change
Metformin [58]	Stimulates osteoblastogenesis and decreases bone resorption	No change	Decrease (or no change)
Thiazolidinediones [10,59]	Activates PPARγ (inhibit osteoblastogenesis and increase bone resorption)	Decrease	Increase
Incretins [60,61,62]	Inhibit bone resorption (preclinical data)	No change	Decrease (or no change)
Sodium-glucose cotransporter inhibitors [63,64]	Increase phosphate reabsorption by the renal tubule	Decrease (canagliflozine)	Possible increase (canagliflozine)

causing an increase in the fracture risk [63,64]. This drug class is not reimbursed in France.

5. Management of bone disorders in patients with type 1 or 2 diabetes

Very few data specific of patients with T1D or T2D are available. Therefore, the measures are derived from common sense rather than from scientific evidence. In general, fall prevention is important, as falls are common in patients with either type of diabetes. Preventing hypoglycemic episodes is a major factor in avoiding falls. Weight loss is a key priority in patients with T2D, since obesity is an independent risk factor for falls. Bariatric surgery has been proven beneficial in patients with severe T2D. However, the well-documented adverse effects of the procedure on bone require close monitoring and appropriate vitamin D supplementation, as the malabsorption induced by the procedure promotes vitamin D deficiency. Data are extremely scant on the use of osteoporosis medications in patients with diabetes. Post hoc analyses of data from the main pivotal trials of alendronate and raloxifene suggest comparable BMD gains with both drugs in patients with and without diabetes [65,66]. Similarly, in a nationwide registry study from Denmark, bisphosphonates and raloxifene were similarly effective in preventing fractures in patients with T1D, patients with T2D, and patients without diabetes [67]. Finally, a post hoc analysis of data from the DANCE study of teriparatide suggested similar antifracture effects in patients with and without diabetes [68].

In conclusion, both T1D and T2D are associated with bone fragility, although the underlying mechanisms differ. The pathophysiological mechanisms responsible for bone alterations are less complex in T1D than in T2D. In T1D, the insulin deficiency combined with many other factors lead to a decrease in BMD values and to alterations in bone quality. The situation is more complex in T2D, as BMD is elevated and the bone quality alterations are multifactorial. The contribution of antidiabetic medications, if any exists, seems limited, except perhaps via the induction of hypoglycemic episodes responsible for falls. Finally, data are scarce on the management of bone fragility in patients with diabetes. Consequently, common sense measures should be applied, with special attention to fall prevention. The few available data suggest that osteoporosis medications are similarly effective in patients with and without diabetes.

Disclosure of interests

B. Cortet has received honoraria or fees in the framework of research contrasts with Amgen, Expanscience, Ferring, Lilly, Medtronic, MSD, Mylan, Novartis, Roche Diagnostics, and UCB.

Stéphanie Lucas, Guillaume Penel, Christophe Chauveau declare that they have no competing interest.

I. Legroux-Gérot has received honoraria or fees in the framework of research contrasts with Amgen and Lilly.

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