Bone Cells and Bone Turnover in Diabetes Mellitus

Mishaela R. Rubin

Abstract Substantial evidence exists that in addition to the well-known complications of diabetes, increased fracture risk is an important morbidity. This risk is probably due, at least in part, to altered bone remodeling and bone cell function in diabetes. Circulating biochemical markers of bone formation, including P1NP, osteocalcin and bone-specific alkaline phosphatase have been found to be decreased in type 2 diabetes (T2D) and may be predictive of fractures independently of bone mineral density (BMD). These findings have been corroborated by preliminary histomorphometric data. Reductions in the bone resorption marker serum CTx in T2D have also been reported. Serum sclerostin levels have been found to be increased in T2D and appear to be predictive of fracture risk independent of BMD. Other factors such as bone marrow fat saturation, advanced glycation endproduct (AGE) accumulation, and microarchitectural changes might also relate to bone cell function and fracture risk in diabetes.

Keywords Fracture risk · Altered bone remodeling · Bone cell function · Osteocalcin · Type 2 diabetes · Serum sclerostin

Introduction

Diabetes mellitus is the most common endocrine disorder with a prevalence of approximately 327 million worldwide [1]. Substantial evidence exists that in addition to the well-known complications of diabetes, such as neuropathy, nephropathy, and retinopathy, increased fracture risk is an im-

portant morbidity [2, 3]. Individuals with type 1 diabetes (T1D) have a very high risk of hip fracture, approximately six times greater than those without diabetes [2, 3]. Although the fracture risk is not as high in type 2 diabetes (T2D), it is nevertheless increased as well [4, 5]. A meta-analysis of 12 studies reported a relative risk of 1.7 (95 % CI: 1.3–2.2) for hip fracture in both men and women with T2D [2]. The risk of all clinical fractures was also increased, with a summary RR of 1.2 (95 % CI: 1.0–1.5) [2]. Subsequent studies have reported similar results [6, 7], with a direct association between the duration of diabetes and increased fracture risk [8]. Fractures in all diabetic individuals are particularly problematic because they are associated with poor fracture healing, greater morbidity [9, 10], and greater healthcare costs [11].

In T1D, hip and spine BMD are reduced compared with normative reference populations [3] or with healthy controls [12]. As in broader populations, reduced BMD is associated with higher fracture prevalence among those with T1D [13]. In contrast, BMD is generally higher in those with T2D compared to those without [3]. In a meta-analysis, Vestergaard reported an increased Z-score of +0.41 at the spine and +0.27 at the hip associated with T2D [3]. The paradox of higher BMD in association with increased fractures in T2D might be attributed to more frequent trauma, as diabetes is associated with an increased frequency of falls. However, in studies of diabetes and fracture that controlled for fall frequency, diabetes still remained independently associated with increased fracture risk [6, 14]. Thiazolidinedione (TZD) use might also be considered as an explanation, since it has been proposed that these agents divert mesenchymal stem cells from the osteogenic to the adipocytic lineage and are associated with bone loss and increased fracture risk, particularly in women [15]. However, TZD use cannot fully account for the increased risk of fracture observed with diabetes, since most studies included substantial observation time prior to the widespread use of these medications. Rather, it appears that

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other bone properties, which are undetectable by DXA, are probably contributing to fracture risk in both T1D and T2D.

Altered bone remodeling in diabetes may be one such factor. Bone remodeling depends upon a coordinated sequence of bone resorption by osteoclasts, followed by bone formation by osteoblasts. Diabetes appears to affect the function of both cell types, as well as that of osteocytes, the most abundant cells in bone.

Type 1 Diabetes

Levels of parathyroid hormone (PTH), a key regulator of bone remodeling, are altered with glycemia and diabetes. In healthy subjects, a glucose load leads to a slight decrease in ionized calcium and an increase in PTH, after an initial temporary decrease, as well as a decrease in markers of both bone formation and resorption [16]. In vitro data similarly show that exposure to high glucose levels impairs osteoblast function [17–19]. In T1D, blunted PTH responses have been observed [20]. In vitro data [18] and in vivo studies involving rodent models of T1D [21] indicate that bone formation is consistently impaired, as shown by the expression of osteoblastic transcription factors, including RUNX2, biochemical markers, and histomorphometric indices [22]. An association between T1D and low bone formation in clinical studies has also been shown [23–25]. In the largest histomorphometry study to date, iliac biopsies in 18 otherwise healthy subjects with T1D were compared with those from healthy age- and sex-matched non-diabetic control subjects [26]. Diabetic subjects, when compared to controls, had no significant differences in mineral apposition rate (MAR), mineralizing surface (MS/BS), osteoid maturation time (Omt), mineralizing osteoid (MS/OS), mineralization lag time (Mlt), bone formation rate (BFR/BS or BFR/BV), formation period (FP), remodeling period (Rm.P), or activation frequency (Ac.F) [26]. It is possible that the clinical data, in contrast to rodent models, showed no difference in bone formation rate for T1D as compared to controls because reduced bone formation emerges only with other complications, such as nephropathy and peripheral neuropathy, and these T1D subjects were otherwise healthy. In a subset of diabetic patients who had fractured, dynamic variables such as BFR/BS, BFR/BV, and Ac.F tended to be lower in the fracturing subjects, perhaps indicating lower remodeling in those T1D subjects [26].

Type 2 Diabetes

PTH and Biochemical Markers of Bone Turnover in T2D

Decreased bone remodeling in T2D has been demonstrated by a number of lines of evidence. Levels of PTH tend to be 20–

50 % lower in T2D subjects than in controls, even in the setting of reduced eGFR, suggesting a state of reduced PTH secretion in T2D [27–29]. Circulating biochemical markers of bone formation, including P1NP, osteocalcin [28, 29], and bone-specific alkaline phosphatase [30], have been found to be decreased in T2D. These decreases in formation measures are associated with reductions in the bone resorption marker serum CTx [27–30]. The decrease in bone remodeling in T2D appears to be predictive of fracture risk regardless of BMD. In a study of 255 T2D women and 240 controls, T2D women with the combination of the lowest PTH and osteocalcin levels had nearly a fivefold increased risk of vertebral fractures independent of lumbar spine BMD [29].

Dynamic Histomorphometry in T2D

Lower bone formation in T2D on biopsy was reported in one study, but the numbers were very small (n=6 T2D patients; 2 female), and the results were confounded by selecting for low BMD and a problematical control group [31]. In a more recent pilot study, low bone formation was observed in six T2D postmenopausal women as compared to six postmenopausal age-matched non-diabetic controls, where tetracycline double-labeled iliac crest bone biopsies showed virtually no uptake of label in diabetic subjects (Fig. 1), with reduced mineralizing surface, osteoid surface, and osteoblast surface (Fig. 2) [32]. These preliminary histological data corroborate the decrease in biochemical markers of bone turnover.

Other Bone Markers in T2D

IGF-1, an anabolic factor which stimulates osteoblast proliferation, has been inversely associated with the risk and number of vertebral fractures in diabetic women independent of BMD [28, 33]. Another marker which might reflect bone formation is that of circulating osteogenic precursor (COP) cells [34], which have been reported to be decreased in patients with T2D. COP cells can be detected in the peripheral blood by flow cytometry using antibodies specific for the osteoblast matrix protein osteocalcin (OCN) [35]. Peripheral blood mononuclear cells that were positive for osteocalcin were lower in postmenopausal women with T2D as compared to non-diabetic controls [32]. Moreover, within the decreased pool of overall OCN+ cells, the T2D subjects had an increased subpopulation of immature OCN+ cells, i.e., cells that also had early markers CD146 and CD34, subpopulations which diminish when osteoblasts mature [34]. An additional novel bone marker in T2D may be sphingosine 1-phosphate (S1P), a lipid mediator which increases osteoclastogenesis by increasing RANKL [36]. S1P was found to be increased in T2D women (n=482) as compared to controls and was associated with vertebral fractures. Interestingly, this marker
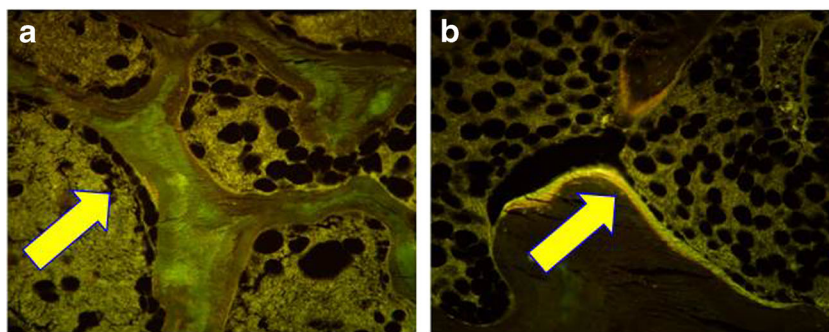
Fig. 1 Histomorphometric changes in bone formation. Tetracycline double-labeled bone biopsies in a 58-yr-old T2D Caucasian woman (**a**) and a 57-yr-old Caucasian female control (**b**). Bone formation is decreased in T2D with reduced mineralizing surface. The *arrows* highlight tetracycline uptake in the control subject and the absence of uptake in the diabetic subject. Adapted with permission from [32]

suggests an elevation in bone resorption in T2D, in contrast to the reports of decreased s-CTx levels [27–30].

Sclerostin in T2D

Sclerostin, an osteocyte product, is a negative regulator of bone formation which competes with the anabolic Wnt β-catenin pathway by binding to LRP5 or 6 [37]. In healthy adults, sclerostin levels are increased by factors including age, BMI, inactivity, bone mineral content, and possibly fractures [37]. It was first reported in 2012 that sclerostin levels were higher in 74 T2D women and men vs. 50 non-diabetic controls and that higher levels correlated with age, male gender, and BMD [38]. This observation was corroborated by another report in which sclerostin levels were found to be twofold higher in T2D than in controls or T1D, after adjusting for age and BMI [39]. A correlation between Wnt disruption and decreased osteoblast activity was further observed in 40 T2D postmenopausal women who, as compared to controls, had decreased β-catenin levels which correlated with lower BAP [30]. In the largest diabetes sclerostin study, higher sclerostin levels in 321 men and women with T2D were associated with an increased risk of vertebral fractures independent of lumbar spine BMD [40]. It could be posited from these data that the higher sclerostin levels in T2D reflect the presence of more deeply embedded osteocytes in older bone that has accumulated more microscopic damage.

Bone Marrow Fat Saturation in T2D

Recent data suggest that altered bone marrow fat composition is linked with diabetic fragility fractures independent of BMD [41]. In a study of 69 postmenopausal women, MR spectroscopy (MRS) of the lumbar spine quantified vertebral bone marrow fat content and composition in diabetic and non-diabetic subjects with and without fragility fractures. After adjustment for age, race, and spinal vBMD, diabetes was associated with −1.3 % (CI −2.3 to −0.2 %, $p=0.018$) lower

Fig. 2 Quantitative measures of bone formation were lower in T2D postmenopausal women than in controls. Adapted with permission from [32]
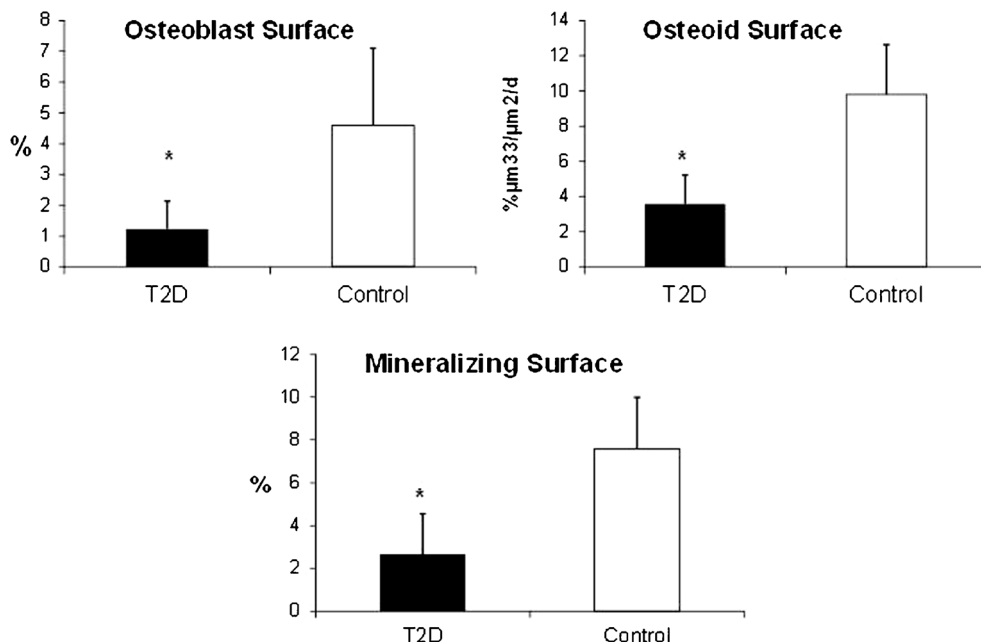
unsaturation and +3.3 % (CI 1.1 to 5.4 %, $p=0.004$) higher saturation levels, with fractured diabetics having the lowest marrow unsaturation and highest saturation. It is conceivable that this type of alteration in bone marrow fat might reflect a shift in stem cell lineage away from osteoblastogenesis toward adipogenesis [42]. In the AGES-Reykjavik cohort (115 men and 134 women; mean age 79; 7 % with diabetes), sclerostin levels were positively associated with marrow fat by MRS in men independent of BMD [42]. This positive relationship could be explained by a shift in precursor stem cell lineage away from osteoblastogenesis, as reflected by higher sclerostin levels, toward adipogenesis, as reflected by higher bone marrow fat [42].

AGEs and Bone Remodeling

Decreased bone formation might occur in part because of increased advanced glycation endproducts (AGEs) in bone collagen. In the setting of chronic hyperglycemia, AGEs accumulate in the organic bone matrix by a process known as non-enzymatic glycation (the Maillard reaction) [43–50]. AGEs interfere with normal osteoblast function [51] and attachment to the collagen matrix [52], as well as impair osteoblast development [53, 54]. Moreover, low bone formation also works in the opposite direction to further increase AGEs, as for example with high bisphosphonate dosages [44]. Accumulation of AGEs in the organic bone matrix leads to more biomechanically brittle bone that has lost its toughness and is less able to deform before fracturing [44]. Urinary pentosidine, the best studied AGE, was associated with a 42 % increase in clinical fracture incidence in T2D [55]. AGEs thus appear to be related to both low bone formation and increased bone fragility in T2D.

Architectural Properties in T2D

In addition to alterations in bone cells and remodeling, another factor that may contribute to the paradox of increased fractures despite normal areal BMD in T2D is microarchitectural abnormality. Increased cortical porosity, a key determinant of bone fragility [56], has been reported at the radius and tibia in female diabetics who have fractured, as measured by intracortical pore volume fraction via high-resolution peripheral quantitative computed tomography (HR-pQCT) [57]. In a recent community-based study of women and men, T2D and increased HbA1c levels were associated with deficits in cortical microstructure and density at the distal tibia [58]. Marcroarchitectural deficits in bone geometry might also explain reduced bone strength in T2D. Strength-to-load ratios (QCT) at the spine and femoral neck were not improved in older adults with T2D although areal BMD (DXA) was higher [59]. In a study of older men, volumetric BMD (pQCT) was higher but bone area was smaller at the distal radius and tibia

[60]. Smaller cross-sectional area suggests that stimulation of periosteal apposition, normally observed with greater loading, may be reduced in diabetes. These data seem to suggest that the higher areal BMD in diabetics does not result in biomechanical advantage.

Conclusions

At a time when classical complications of diabetes mellitus are becoming less common due to improved glucose control, the skeleton has emerged as a target organ for disease complications. Alterations in diabetic bone metabolism, including bone cells, remodeling, and other properties, could potentially contribute to this increase in fracture risk. Further investigation of skeletal parameters would shed light on the issue of greater bone fragility in diabetes and potentially offset serious challenges in this population as they age.

Compliance with Ethics Guidelines

Conflict of Interest   MR Rubin declares no conflicts of interest.

Human and Animal Rights and Informed Consent   All studies by MR Rubin involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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