Published in final edited form as:

Diabetes Metab Res Rev. 2010 November ; 26(8): 622–630. doi:10.1002/dmrr.1135.

Novel Insights into the Relationship between Diabetes and Osteoporosis

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Abstract

Only three decades ago adipose tissue was considered inert with little relationship to insulin resistance. Similarly bone has long been thought purely in its structural context. In the last decade, emerging evidence has revealed important endocrine roles for both bone and adipose tissue. The interaction between these two tissues is remarkable. Bone marrow mesenchymal stem cells give rise to both osteoblasts and adipocytes. Leptin and adiponectin, two adipokines secreted by fat tissue, control energy homeostasis, but also have complex actions on the skeleton. In turn, the activities of bone cells are not limited to their bone remodeling activities, but also to modulation of adipose sensitivity and insulin secretion. This review will discuss these new insights linking bone remodeling to the control of fat metabolism and the association between diabetes mellitus and osteoporosis.

Keywords

Osteoporosis; diabetes mellitus; obesity; leptin; osteocalcin

Introduction

Diabetes mellitus (DM) is a disorder that metabolically is more than a hyperglycemic syndrome [1,2]. Changes in protein and lipid metabolism coupled with chronic elevations in serum glucose have a profound effect on virtually all tissues [3]. The skeletal manifestations of DM were previously only considered in the context of disturbed glucose intolerance [4]. As such, imbalances in calcitropic hormones were the main focus of investigation. Indeed, changes in PTH, vitamin D and calcitonin can affect calcium, phosphorus and magnesium balance, and thereby impact the synthesis and release of metabolic hormones (e.g. insulin, glucagon, growth hormone and catecholamines) [5–9] (Figure 1). Primary hyperparathyroidism has classically been associated with insulin resistance and diabetes mellitus [6,8]. Similarly, vitamin D deficiency impairs insulin action and release and is recognized as a risk factor of diabetes mellitus (Figure 1) [5,9]. On the other hand, poorly controlled diabetic patients have urinary waste of phosphorus and magnesium which not only plays against metabolic improvement but also impacts the skeleton (Figure 1).

However, emerging evidence suggests that bone is metabolically active secreting growth factors and proteins that modulate insulin sensitivity and insulin secretion. [10–13]. For example, osteocalcin, a bone specific protein, can regulate peripheral insulin sensitivity and stimulate insulin synthesis [11,14]. Adipokines such as leptin [15] and adiponectin [16] have complex actions on bone cells. Leptin stimulates sympathetic tone by acting through the hypothalamus to cause bone loss as β adrenergic receptors on osteoblasts are activated. These newly discovered pathways reflect an integrative physiology where bone, formerly linked only by its mechanical properties (body support and organ protection) takes on an important role in regulating intermediary metabolism [11–13]. The intention of this review is to discuss the clinical implications of the relationship between bone/energy metabolism and diabetes mellitus/osteoporosis

Influence of Adiposity on Bone Mass and Bone Quality

Strength, the most obvious characteristic of hard tissue depends on a complex array of factors, which includes an organized deposition of protein, mainly collagen type I, and proper mineralization. Small deviations in the tertiary protein structure (e.g. osteogenesis imperfecta) or alterations in the physical properties of the mineral phase (e.g. decreased mineral in rickets/osteomalacia or increased mineral in osteopetrosis) as well as a reduction in overall mass can radically impair the structural capacity of bone [17–19]. The latter can be easily and accurately measured by Dual X-ray energy absorptiometry and provide risk assessments for susceptible individuals, whereas the former represents qualitative aspects of bone that are not easily determined. A combination of factors such as genetic, nutritional, hormonal, environmental, physiological and acquired diseases influence bone development and maintenance, and each has a different impact on bone quantity as well as quality [20].

Low body weight has long been established as an important risk factor for hip fracture [20]. In contrast obesity is often associated with high cortical bone mass [21]. Those long standing observations imply that adipose tissue not only insulates the skeleton, but may exert increased load that could enhance mechanical signaling to the osteocyte and hence the cortical bone. On the other hand, several lines of evidence suggest that excess body weight may be detrimental to the skeleton. For example, during aging, menopause and glucocorticoid therapy, fat mass is increased or redistributed at a time when bone mass is declining [22]. Goulding et al (2005) observed an increased fracture risk in obese children [23]. In older patients attending the Liason Fracture Service, in the United Kingdom, with fragility fractures more than half of these individuals were obese or morbidly obese and only ~ 40% had normal bone mass [24]. In addition, a recent clinical investigation showed an association between metabolic syndrome and osteoporotic non-vertebral fractures [25]. Thus, individuals harboring a set of predisposing conditions to cardiovascular disease (i.e., visceral obesity, high glucose, high triglycerides, hypertension and low HDL) all intimately linked to insulin resistance, are prone to fragility fracture [25].

There are typical differences in body weight for Type I (T1DM) and Type 2 diabetes mellitus (T2DM). Besides the difference in body mass index, there is a clear distinction in hormonal profile between diabetic type 1 and 2. While the former has an absolute deficiency of insulin, low serum levels of IGF-I and of steroid hormones, the second usually manifests hyperinsulinemia, estrogen and androgen excess and normal levels of IGF-I [26–28]. These differences impact bone mineral density (BMD) particularly in T1DM [26,27]. However, the bone mass phenotype in T2DM is quite heterogeneous [26,29,30]. The experimental models of diabetes, such as pharmacological diabetes, which simulates T1DM, and the spontaneous T2DM of Torii rat, show in common decreased rate of bone formation [31,32]. These results overlap with data obtained in humans indicating lower production of biochemical markers of bone formation in type 1 and 2 diabetic patients [26,28]. Several studies have recently

showed that even T2DM patients with high BMD have an increased fracture risk [33]. Both obesity and T2DM are striking examples of the inherent difficulties of using only BMD to determine bone integrity and fracture risk prediction [24,34,35]. Recently, T2DM has been included in algorithms for the clinical screening of fracture risk, adding this syndrome to a growing list of endocrine abnormalities associated with a greater fracture risk [34].

Osteoporosis in diabetes mellitus: role of adipose tissue in control of bone mass

Excess adipose tissue is an important factor in the induction of insulin resistance. It is not only the quantity but also the distribution of fat that predicts the onset of insulin resistance and the eventual predisposition to DM. Interestingly, the lack of adipose tissue, as in lipodystrophy, is at least as pernicious as adipose excess in triggering insulin resistance and glucose intolerance [36,37]. In addition, acanthosis nigricans and centripetal obesity are surrogate indicators of insulin resistance. As such, adipose tissue is an important source of peptides and cytokines which modulate metabolic homeostasis.

The relationship between fat and bone is complex and several factors dictate fracture risk in T2D with insulin resistance. Not surprisingly, bone remodeling requires energy; the intricate balance between energy consumption and bone mass maintenance implies that disorders in fuel metabolism can affect the skeleton. For example, as adipose tissue takes on a storage phenotype it also becomes an endocrine tissue. Adipokines and inflammatory cytokines released by large lipid filled adipocytes can alter bone remodeling by either stimulating resorption or suppressing bone formation [13,22] (Figure 2). In addition, excess subcutaneous fat with less lean mass may modify the mechanical impact on bone, alter balance and predispose the individual to falling [24,38]. Chronic complications of diabetes including retinopathy and neuropathy further increase the risk of falling and further enhance the possibility of fracture [39].

The distribution of adipose tissue impacts bone mass, such that visceral adipose tissue (VAT) has been found to be a negative predictor of lumbar spine and whole body BMD in obese girls [40]. In one study, circulatory levels of selectin and adiponectin were negative predictors of BMD, whereas leptin was found to be a positive predictor of BMD, most likely as a reflection of total body weight. VAT is metabolically active and through its actions as an endocrine tissue it secretes cytokines and adipokines that have negative effects on trabecular bone in a manner analogous to VAT's actions on the vasculature.

The relationship of leptin to bone mass has proven somewhat more controversial [12,14]. Leptin acts in rodents via hypothalamic receptors to inhibit feeding and increase thermogenesis through activation of the sympathetic nervous system [41]. While this feedback regulatory loop is well established in rodents, its role in humans is less clear. Notwithstanding, multiple signaling pathways may be activated by leptin which impact bone. Leptin-deficient *ob/ob* mice show increased cancellous bone mass in addition to an overt obesity [42]. The skeletal phenotype of *ob/ob* mice can be corrected by leptin administration [43]. The pattern of bone changes in leptin-deficient mice may be reproduced by chemical lesion of neurons in the region of the ventro-medial hypothalamus [44]. This neural damage also prevents the consequences of central administration of leptin in skeleton. Taken together, these evidences place the hypothalamic ventro-medial nucleus as the key site in the central nervous system for leptin control of bone mass [44]. From this nucleus, sympathetic fibers transmit stimuli, which will be recognized by the effector in osteoblasts, the β_2 adrenergic receptor (β_2 AR) [44] (Figure 2). The engineered β_2 AR disrupted-mice share with *ob/ob* and chemical-injured ventro-medial mice the same bone alteration.

Another peculiarity about the central action of leptin emerged recently, when it was demonstrated that the leptin receptor in hypothalamic ventro-medial neurons is not necessary for triggering leptin action [45]. These data indicate that leptin probably acts in other sites of the brain to regulate metabolism. Serotonergic neurons of the brainstem are a reasonable candidate to mediate this action, since the consequences of leptin deficiency on bone turnover and metabolism can be reversed by hampering serotonin production in the brainstem [46].

Leptin can influence bone metabolism through other pathways. For example, leptin enhances insulin sensitivity, possibly through induction of an insulin-like growth factor binding protein (IGFBP-2) and this may have positive effects on bone [47] (Figure 2). Leptin receptors have been cloned from osteoblasts and it has been hypothesized that leptin could directly stimulate osteoblast formation. On the other hand, leptin regulates bone metabolism indirectly through the hypothalamus by activating the sympathetic nervous system (SNS) and suppressing bone formation while stimulating bone resorption via skeletal adrenergic receptors on osteoblasts [43,48] (Figure 2). Targeted deletion of leptin receptors only in the hypothalamus leads to a high bone mass phenotype, suggesting that the predominant effect of leptin on bone is through the central nervous system. In addition to its indirect effects on the SNS, leptin also interacts with various hypothalamic neuropeptides, such as cocaine- and amphetamine regulated transcript, neuropeptide Y and/or neuromedin U, which also may impact skeletal remodeling [49]. In osteoblasts sympathetic signaling is also regulated by the circadian transcriptional factors *Per* and *Cry*. Mice lacking the gene *Per 2* have a high bone mass phenotype associated with increased bone formation [50]. Intracerebroventricular leptin infusion does not reverse the high bone mass phenotype in *Per2*-deficient mice, suggesting that the molecular clock acts downstream of the β 2-adrenergic receptor (β 2-AR) to modulate sympathetic signaling in osteoblasts [51]. Besides the interaction between the central and peripheral pathways, the effects of leptin may also depend on leptin serum concentrations. In a experimental model of osteoporosis (tail-suspended rats), low doses of leptin prevented bone loss, whereas high doses inhibited femoral growth and provoked both reduced bone formation and decreased bone resorption [52]. These experiments suggested that beneficial and detrimental effects of leptin depend on a threshold triggered by circulating leptin levels. In humans several studies were designed to evaluate the influence of serum leptin levels on bone mass. Although some data have indicated that leptin positively correlates with BMD [53,54] others verified that the correlation disappeared after adjustment for body weight [55]. Almost certainly this relationship is complex due to the direct and indirect actions of leptin on bone.

Serum leptin is decreased in T1DM but its contribution to bone loss or low bone mass is unclear. In a recent study, mice were treated with streptozotocin to induce Type I diabetes and leptin was then administered by pump [56]. Leptin prevented the increase of marrow adipocytes observed in diabetic mice receiving vehicle. However, leptin did not prevent diabetic decreases in trabecular bone volume fraction or bone mineral density in tibia or vertebrae [56]. In contrast to T1DM, serum leptin levels in T2DM are not significantly different from nondiabetic individuals [57]. The evaluation of leptin levels in a group of Japanese patients with T2DM showed a significant positive correlation between serum leptin and adiponectin levels as well as Z-scores at the distal radius, but not at the femoral neck or the lumbar spine. [54].

Bone cells and adipocytes reside within the bone marrow and the relative composition of marrow changes during different developmental stages of life. For example, during bone mass accrual in the appendicular skeleton, hematopoietic precursors that make up 'red' marrow are converted to 'yellow' marrow indicative of increased adipogenesis. These cells have the appearance of classic fat cells that store lipid, although assessing their function has

not been accomplished. The cross talk between bone cells and hematopoietic cells appears to be essential for the support of hematopoietic stem cell differentiation and bone remodeling [58–60]. Similarly, the presence of increased marrow adipocytes has been associated with impaired hematopoiesis [61]. During aging, the hematopoietic bone marrow in the vertebrae is replaced by adipose tissue and this phenomenon is coincident with bone loss, rather than gain. Although the causal relationship between morphologic changes of the bone marrow with the development of osteoporosis remains to be established, several lines of evidence support this possibility. First, it is widely believed that osteoblasts and adipocytes differentiate from a common multipotent precursor cell. Thus, in some circumstances, the preferential pathway to form one lineage appears to occur at the expenses of the other [14,22]. Second, in many of the secondary causes of osteoporosis, as well as during aging, the loss of trabecular bone is accompanied by progressive marrow infiltration with adipocytes. However, the true source of bone marrow adipocytes is yet to be confirmed while the physiologic function of these cells is complex and poorly defined.

Diabetes mellitus is often considered within the context of accelerated aging and the marrow exemplifies this feature. The apparent shift in lineage allocation from osteoblast to adipocyte is accompanied by enhanced peroxisome proliferator-activated receptor- γ (PPAR- γ) activation. Similarly, insulin sensitizers such as the thiazolidinediones (TZD), which are PPAR- γ agonists, are widely prescribed to patients with insulin resistance and cause marrow adiposity and bone loss, despite significant improvements in glycemic control. *In vitro* studies have repeatedly demonstrated that specific endogenous and exogenous PPAR- γ activators reallocate the fate of bone marrow mesenchymal stem cells to adipocytes. Rats and mice treated with PPAR- γ agonist show markedly decreased bone mass and reduced osteoblast activity [62–64]. In humans, rosiglitazone induces rapid reduction (14 weeks) in bone formation markers and, progressive bone loss [65]. Bone loss was also observed in a small group of female patients using rosiglitazone or pioglitazone during a period of 4 years [66]. In a study designed to compare the effect of metformin, glyburide and rosiglitazone on long term control of glucose levels, Kahn et al (2006) detected an increased incidence of fractures in female diabetics on rosiglitazone compared to other oral agents [67]. In experimental animals, T1DM is associated with progressive marrow adiposity, whereas insulin resistance and/or obesity alone have not been shown to affect marrow adiposity. Indeed, very recently, Devlin et al reported that calorie restriction in young mice is associated with progressive marrow adiposity [68].

Hyperglycemia and Osteoporosis

There are conflicting data about the direct association of hyperglycemia with low BMD independent of changes in adipose tissue. In particular, the stronger association has been observed between hyperglycemia and low bone mass in T1DM [27,28] but not T2DM [26], although very recent studies suggest that prolonged hyperglycemia itself, regardless of etiology is detrimental to bone. Several hypotheses could be considered for this including: 1) accelerated aging in the bone marrow compartment due to enhanced reactive oxygen species; [69,70] 2) direct glucose toxicity to osteoblasts; [70] 3) changes in circulating calcitropic hormones or growth factors. With respect to the latter, the tenet that poor metabolic control provokes urinary calcium wastage and secondary hyperparathyroidism has not been confirmed in a study designed to evaluate PTH secretion before and after EDTA-induced hypocalcemia in T1 and T2 DM [4]. Actually, patients with poor metabolic control had normal basal serum levels of PTH and decreased responses to hypocalcemia. The concomitant chronic hypomagnesemia presented by these patients could be the cause of the limited PTH response. Interestingly, higher PTH responses to physiological stimuli are often associated with high bone mass [71,72]. Also low serum levels of insulin-like growth factor

(IGF-I) in poorly controlled T1DM, may be a potential determinant of low bone mass, whereas in T2DM, circulating IGF-I is either normal or high [26–28].

The introduction of hemoglobin A1c (HbA1c) in the management of diabetics almost four decades ago highlighted the importance of the Maillard reaction *in vivo*. HbA1c the classical parameter for clinical follow up of diabetes mellitus, is now more consistently associated with chronic complications of this disease than any other parameter [73,74]. The Maillard reaction (nonenzymatic glycation) starts with the interaction of the carbonyl (aldehyde or ketone) of the reducing sugar and a protein or lipid, without the need for an enzyme to catalyze the reaction (Figure 3). Lipids have to first be converted into reactive carbonyl compounds, such as glyoxal and methylglyoxal then they react with protein. The first step is the formation of a reversible Schiff base (Figure 3). Protein glycation is common as a post-translational modification of proteins induced by the spontaneous condensation of glucose and metabolic intermediates (e.g. triose phosphate, glyoxal and methylglyoxal) with free amino groups in lysine or arginine residues [75]. Thereafter, the Schiff base can undergo a series of further rearrangements, dehydration, and condensation to form irreversible end products, which may be fluorescent and yellow-brown in color; some can form stable intermolecular and intramolecular cross-links. This process leads to an irreversible formation of advanced glycation end products (AGE) (Figure 3) from an array of precursor molecules [76]. Alfa-oxoaldehydes such as glyoxal, methylglyoxal and 3-deoxyglucosone occur at high levels in diabetic plasma and are significantly elevated in cells exposed to high glucose concentrations. The amount of AGEs on proteins is dependent on the inherent reactivity of specific amino groups, as determined by their micro-environment, the glucose concentration, and the half-life of protein. The reactivity of a sugar depends on the equilibrium between its open-chain and cyclic form, its chain length and its functional groups. The open-chain form is thermodynamically disfavored, shifting the equilibrium toward the cyclic and glycosylamine forms. Only 0.002% of glucose molecules exist in reactive open forms *in vivo*, which is significantly less compared to 0.02% for galactose and 0.7% for fructose [76]. However, the potential participation of glucose in the cross-linking process of protein should not be underestimated, as glucose is the most abundant sugar *in vivo* [77].

Several AGEs can bind to the receptor for advanced glycation end-products (RAGE), a transmembrane receptor of the immunoglobulin superfamily. The interaction between AGE and RAGE can activate proinflammatory genes and can contribute to higher blood sugars in a repetitive cycle [78]. Enhanced glycation favors the progression of diabetic macroangiopathic and microangiopathic complications [79]. This process may also be important in altering bone micro-architecture through changes in the bone matrix itself. Collagen cross-linking, a major post-translational modification of collagen, plays an important role in the biological and biomechanical features of bone. Collagen cross-links can be divided into lysyl hydroxylase and lysyl oxidase-mediated enzymatic immature divalent cross-links, mature trivalent pyridoline and pyrrole cross-links and glycation-or oxidation-induced non-enzymatic cross-links (advanced glycation end products) such as glucosepane and pentosidine (Figure 3). These types of cross-links differ in the mechanism of their formation and function, which in turn determines differences in the mineralization of bone as well as its ability to repair itself from microdamage. Pentosidine is one of the well-known AGEs, and its concentration in cortical and trabecular bone is negatively associated with bone strength. Previous studies showed that patients with femoral neck fractures had higher concentrations of pentosidine in cortical [80] and cancellous bone [81] than in controls. *In vitro* high glucose and AGEs synergistically inhibit the mineralization activity of MC3T3-E1 cells through glucose-induced increase in the receptor for AGE (RAGE) [82]. Diabetic patients have significantly higher levels of serum pentosidine than control individuals. Furthermore, in a recent clinical study, Yamamoto and cols. [83] observed in a

small group of patients that pentosidine serum levels were positively and significantly associated with the presence of vertebral fractures in postmenopausal women with DM and that this association was independent of BMD. The confirmation of these results in a large number of individuals would provide new insights into fracture prediction among diabetics.

Bone, Energy Metabolism and glucose control

Several lines of evidence now suggest an integration of the skeleton in overall energy metabolism due to the paracrine and endocrine-like properties of bone (Figure 2). As noted, adipocytes and osteoblast co-exist in the bone marrow and exert control over trabecular remodeling. Leptin and osteocalcin are important endocrine factors in this process (Figure 2). With respect to the former, the skeletal phenotype of *ob/ob* and *db/db* mice, which are leptin deficient and leptin receptor null [41] respectively, is very high cancellous bone mass and low or normal cortical bone volume, even in the face of impaired gonadotropin secretion [84–86]. In mice, the uncarboxylated form of osteocalcin, a bone specific matrix protein made by the osteoblast has recently been shown to affect adipocyte sensitivity to insulin and insulin secretion (Figure 2). Lee et al (2007) elegantly demonstrated that inactivation in osteoblasts of *Esp* a gene that encodes a receptor-like protein tyrosine phosphatase termed OST-PTP [87], causes uncarboxylated osteocalcin to rise. *Esp* null mice display an increase in β -cell proliferation, insulin secretion, and sensitivity that protect them from induced obesity and diabetes. These metabolic advantages are lost by the concomitant deletion of one allele of *osteocalcin*. Interestingly osteocalcin null mice are glucose intolerant, obese and hypoinsulinemic.

Osteocalcin undergoes posttranslational modification whereby three glutamic acid residues are carboxylated to form γ -carboxyglutamic acid residues. Carboxylated osteocalcin has a higher affinity for hydroxyapatite and this is thought to be involved in bone extracellular matrix mineralization, although conclusive data in humans are lacking. Recent studies suggested that ESP is involved in γ -carboxylation of osteocalcin. In studies by Lee *et al.* [87] and Ferron *et al.* [88], the uncarboxylated form appeared to mediate the metabolic effects of osteocalcin (i.e. increased β -cell proliferation, insulin secretion, insulin sensitivity and adiponectin and adiponectin expression). Other studies in cell cultures have suggested that both uncarboxylated and carboxylated forms increase basal and insulin-stimulated glucose transport, although the effect of the carboxylated form was less robust [89].

Additional biological evidence of osteoblast-mediated glucose homeostasis have been recently published [90]. FoxO1 belongs to the Forkhead family of transcriptional factors which is a major negative mediator of insulin receptor in β -cell (Figure 2), hepatocytes, myoblasts and adipocytes. For instance, in hepatocytes, FoxO1 promotes gluconeogenesis, at least in part, by stimulating key gluconeogenic enzymes. Rached et al. (2010) proposed that osteoblasts play a key role in FoxO1 mediated-actions on insulin. Mice lacking *Foxo1* only in osteoblasts had increased β -cell proliferation, insulin secretion and insulin sensitivity [90]. *Foxo1_{ob}^{-/-}* mice also have increased expression of *Foxa2* which regulates lipogenesis and ketogenesis, whereas expression of *G6Pase* and *Pck* were decreased as compared with control mice. Rached et al., suggested that these occurrences were secondary to increased insulin levels in *Foxo1_{ob}^{-/-}* mice [90]. Serum levels and expression of adiponectin, an insulin-sensitizing hormone, were also increased in *Foxo1_{ob}^{-/-}* mice, whereas the expression of resistin was not affected by the induced mutation. *Foxo1_{ob}^{-/-}* mice have an increase in 50% in the expression of osteocalcin and a 30% increase in the circulatory levels of osteocalcin. The removal of a single osteocalcin allele *Foxo1_{ob}^{-/-} Ocn^{+/-}* resulted in a complete reversal of the metabolic abnormalities of *Foxo1_{ob}^{-/-}* mice. Finally, the expression of *Esp* (the gene encoding OST-PTP, which mediates osteocalcin carboxylation) was reduced in 75% in *Foxo1_{ob}^{-/-}* mice. Taken together, the results obtained

by Rached et al. suggested that the osteoblast plays an important role in FoxO1 control of glucose homeostasis [90].

Bone also may play a role in the modulation of insulin sensitivity. Newly published studies suggest that osteoblasts which produce osteocalcin, express the insulin receptor and when activated by insulin trigger osteoclast mediated bone resorption that in turn leads to the undercarboxylation of osteocalcin [91,92]. Deletion of the insulin receptor in osteoblasts leads to insulin resistance and obesity. Interestingly, nearly a decade ago, it was demonstrated that the deletion of the insulin receptor in muscle, the most important site of glucose uptake after carbohydrate loading, was not associated with alterations in blood glucose, serum insulin and glucose tolerance [93]. At that time, the conclusion of the authors was that another tissue appears to be more involved in insulin-regulated glucose disposal than previously recognized [93]. The results obtained recently by Fulzele et al (2010) suggest bone may be that tissue [92]. The metabolic disturbances associated with deletion of the insulin receptor are rescued by the administration of osteocalcin, the osteoblast-derived peptide. Furthermore, mice harboring the insulin receptor deletion in osteoblast show an osteopenic phenotype, these data suggest that the bone and pancreas are linked in the control of energy metabolism and bone mass. Insulin and undecarboxylated osteocalcin are the molecules involved in this endocrine circuit. Additional pieces to this network are currently being investigated particularly in respect to whether osteoblasts require insulin for glucose mediated transport (Figure 2), and precisely how osteoclast-mediated bone resorption stimulates insulin secretion.

Conclusion

Chronic hyperglycemia profoundly affects multiple tissues and directly affects the frequency of complications in diabetes mellitus. Hypoinsulinemia is the primary hormonal disturbance leading to T1DM, whereas insulin resistance causing hyperglycemia is the principal event in T2DM. As discussed, bone mineral density is a relatively poor surrogate for defining bone structure during long standing hyperglycemia. Low bone mass is often detected in T1DM although the pathogenesis is likely to be multifactorial. On the other hand, BMD can be low, normal or increased in T2DM. Yet both forms of diabetes are associated with an increased risk of fracture. In part, higher rates of fracture can be related to neuropathic, nephropathic and retinopathic changes that lead to a greater risk of falling. In addition, low body weight, hypoinsulinemia, low serum levels of IGF-I and altered gonadal steroids favor a catabolic state in the skeleton of Type I diabetics. The presence of obesity and T2DM, although associated with increased cortical bone mass, does not translate to a lower fracture risk, and paradoxically may enhance risk. Hyperglycemia can lead to degenerative changes in bone quality through advanced end product glycation, which particularly affects collagen cross-linking. Not surprisingly, one of the classic late clinical features of diabetes mellitus, i.e. vascular calcification, is associated with lower bone mass and impaired bone strength. Those two processes may be linked to reduced renal function and aberrant deposition of calcium in blood vessels rather than in the appropriate collagen matrix. Notwithstanding the potential numerous insults associated with sustained hyperglycemia, several recent developments suggest there is now a greater awareness of the skeleton as both a target of diabetic complications, and a potential pathogenetic factor in the disease itself.

Acknowledgments

FJAP received financial support from the National Council for Scientific and Technological Development (CNPq), Brazil, 201650/2008-8. Writing this review and experimental work was enabled by support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute of Health grants RO1AR047342, RO1AR049190, RO1AR052690, R24DK084970 to MCH; the Yale Core Center for Musculoskeletal Disorders

P30AR046032; and the Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, CT. DK084970 and AR56404 Center for Clinical and Translational Research, Maine Medical Center Research Institute, Scarborough, ME.

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Figure 1. Interaction between mineral and energy metabolism

Calcitropic disorders impact on intermediary metabolism, contribute to insulin resistance, impair insulin secretion and ultimately lead to DM. In DM, Poor glucose control induces calcium, phosphorus and magnesium wastage, furthering disturbance in insulin resistance and sensitivity.

Figure 2. Endocrine connection between osteoblasts and adipocytes

Uncarboxylated osteocalcin increases insulin secretion and sensitivity. Osteocalcin, the bone-derived specific peptide, is negatively regulated by *Esp* a gene expressed in osteoblasts, through its product, protein tyrosine phosphatase (OST-PTP). OST-PTP induces osteocalcin carboxylation, thereby reducing its bioactivity. The transcriptional factor FoxO1 is also expressed in osteoblasts (OB). Osteoblast-specific FoxO1 deficiency is associated with an anabolic metabolism profile due to increased osteocalcin expression and decreased expression of *Esp*. In addition, osteocalcin may stimulate adipose tissue to secrete adiponectin, an insulin-sensitizing factor. Adipocytes (AD) affect bone and energetic metabolism by secreting leptin. In the CNS leptin stimulates the sympathetic nervous system (SNS) thereby activating the β_2 -adrenergic receptor ($\text{Adr}\beta_2$) in bone and subsequently decreasing OB proliferation. Leptin also improves insulin sensitivity and this effect may be, at least in part, mediated by IGFBP2.

Figure 3. Non-enzymatic cross-link formation in bone collagen

Glucosepane and pentosidine are cross-link derived-products formed by non-enzymatic glycation. The increment of this pathway in diabetes mellitus is a putative mechanism for emergence of bone fragility.