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Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues

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Abstract

Diabetic osteoporosis is increasingly recognized as a significant comorbidity of type 1 diabetes mellitus. In contrast, type 2 diabetes mellitus is more commonly associated with modest increases in bone mineral density for age. Despite this dichotomy, clinical, in vivo, and in vitro data uniformly support the concept that new bone formation as well as bone microarchitectural integrity are altered in the diabetic state, leading to an increased risk for fragility fracture and inadequate bone regeneration following injury. In this review, we examine the contribution that insulin, as a potential anabolic agent in bone, may make to the pathophysiology of diabetic bone disease. Specifically, we have assimilated human and animal data examining the effects of endogenous insulin production, exogenous insulin administration, insulin sensitivity, and insulin signaling on bone. In so doing, we present evidence that insulin, acting as an anabolic agent in bone, can preserve and increase bone density and bone strength, presumably through direct and/or indirect effects on bone formation.

Keywords

type 1 diabetes mellitus; type 2 diabetes mellitus; osteoblasts; osteoporosis; insulin receptors; hyperinsulinism

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IN A RECENT REVIEW by Riggs and Parfitt (94) the authors propose specific criteria for classifying an agent, be it drug or hormone, as an anabolic agent for bone. They provide the following definition:

[An anabolic drug] increases bone strength by increasing bone mass substantially as a result of an overall increase in bone remodeling [more BMUs (bone multicellular units) are formed] combined with a positive BMU balance (the magnitude of the formation phase is more than that of the resorption phase). Although some anabolic drugs also may induce renewed modeling, increased periosteal apposition, and repair of trabecular microstructure, these are not required properties.

In this review, we will evaluate the literature to apply these criteria to insulin to determine whether this hormone is indeed an anabolic agent in bone.

Insulinopenia as occurs in type 1 diabetes (T1DM) or resistance to the metabolic actions of insulin as occurs in type 2 diabetes (T2DM), are both associated with several deleterious consequences for skeletal health. Skeletal defects that are observed in conjunction with T1DM include *1*) diminished linear bone growth during the pubertal growth spurt in adolescents with

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diabetes, *2*) decreased adult bone density, *3*) an increased risk for adult osteoporosis, *4*) an increased risk of fragility fracture, and *5*) poor bone healing and regeneration characteristics. In contrast, T2DM, a state of hyperinsulinemia and insulin resistance, is typically associated with increased bone density, yet seemingly decreased bone strength contributing again to an increased risk of fracture. Recognizing that these two clinical entities are typically characterized by differences in insulin secretion, insulin sensitivity, and/or exogenous insulin administration, we present a review of clinical, in vivo and in vitro evidence examining whether insulin, as both a drug and hormone, qualifies as an anabolic agent for bone.

CLINICAL DICHOTOMY BETWEEN T1DM AND T2DM AND BONE HEALTH

Clinical Definitions

The World Health Organization (WHO) defines osteopenia as a bone mineral density (BMD) of between 1 and 2.5 SD below that of a young normal adult (i.e., *T*-score between −1 and −2.5). Osteoporosis is defined by the WHO as a BMD ≥ 2.5 SD below that of a young normal adult (i.e., *T*-score of ≤ −2.5) (143). Definitions put forth by the National Osteoporosis Foundation (NOF) differ slightly, in that the NOF recommends initiation of therapy to reduce fracture risk in individuals with a *T*-score ≤ −2 SD or, for individuals with additional risk factors for osteoporosis (including diabetes), a *T*-score ≤ −1.5 SD (84). Both definitions are focused on the Caucasian postmenopausal female population, providing no specific definitions for men or younger age groups. This review has incorporated literature spanning dates from 1968 to 2005 and examined populations from pediatric to geriatric. Although the majority of citations were published within the past 10 years, some clinical references also predate the current diagnostic use of the terms osteopenia and osteoporosis. Therefore, wherever possible, we have quoted the terminology utilized by the original authors of quoted publications, recognizing that this approach will not uniformly align with currently accepted standard diagnostic terminology.

Osteopenia and Osteoporosis: T1DM

A number of historical studies demonstrate that osteopenia and osteoporosis are frequent complications of T1DM (7,49,76), in both children (98,103) and adults (77). However, such studies reflect periods of significantly less stringent glucometabolic control, less efficacious treatment options, and older densitometric techniques (specifically, photon absorptiometry techniques and radiogrammetry). It is relevant, therefore, that more recent studies confirm that T1DM is associated with decreased bone density (39,60,82,127) and a state of low bone turnover (60). For example, Kemink et al. (60) found that, among a population of 35 middle-aged patients with uncomplicated T1DM (duration of DM, 8.5 ± 3.5 yr), 57% of females and 67% of males had osteopenia (*T*-score ≤ −1 SD) of the femoral neck and/or lumber spine and 14% of males met criteria for osteoporosis (*T*-score ≤ −2.5). Low bone density was associated with lower mean plasma insulin-like growth factor-I (IGF-I), serum alkaline phosphatase, and serum osteocalcin levels, suggesting decreased bone formation among these individuals (60). Similarly, Kayath et al. (58) studied 90 T1DM patients, ages 18−54 yr, and found that 34% had osteopenia (*Z*-score = −1 SD), whereas Muñoz-Torres et al. (82) reported that 19% of 94 T1DM patients, ages 20−56 yr, met WHO diagnostic criteria for osteoporosis. A study by Tuominen et al. (127) of 56 type 1 DM patients, all of whom had developed T1DM after 30 yr of age, also demonstrated a significant decrease in BMD compared with age-matched controls. A review of studies of BMD in adult subjects with T1DM conducted over the past 10 yr is presented in Table 1 (see Ref. nos. in table). Of these 15 studies, 13 studies report some decrement in BMD in the T1DM study population.

Classically, osteoporosis has been considered a disease of the aging adult population. In T1DM, however, the situation may be quite different, with either insufficient bone accrual or bone loss occurring at a very young age. The timing of the onset of diabetic bone disease remains

somewhat controversial. Many studies have suggested that low BMD is already apparent at the time of diagnosis (71). Other work suggests that neither indexes of bone formation (6) nor BMD (15) are impaired in the recently diagnosed child with T1DM, indicating that metabolic consequences of the disease over time may be more important than a predisposing genotypic covariant. In any event, it is well supported that lower bone mass usually develops within the first few years of T1DM (35,77,98). A review of pediatric studies of bone density and T1DM conducted in the past 10 years is presented in Table 2. Six of nine reports demonstrate a significant decrement in BMD in adolescent patients compared with age-matched control subjects in at least one skeletal site. For example, as reported by Gunczler et al. (35), significant deficits in lumbar spine BMD were already apparent in >50% of 26 children with T1DM, mean age 12.1 ± 3.1 yr, and a mean duration of DM of only 4.3 ± 2.9 yr, implying a relatively rapid impact of T1DM on bone health. Similar findings have subsequently been confirmed by others (22,43). The clinical relationship between diminished BMD and glycemic control remains unclear in these pediatric studies; some report a clearly negative correlation between BMD and Hb A_{1c} (43,66,129), whereas other studies demonstrating an impact of T1DM on BMD show no association between BMD and metabolic control (22,35).

There are several potential explanations for the inconsistencies noted among these pediatric studies. It is expected that the earliest changes in BMD induced by diabetes would be noted in metabolically active trabecular bone. Of note, two of six studies demonstrating an effect of T1DM on BMD utilized peripheral quantitative computed tomography (pQCT) either alone (66) or in conjunction with dual-energy X-ray absorptiometry (DEXA) (43), which provided distinct assessments of the trabecular bone BMD. Duration of disease was also variable among these studies, and two of three reports showing no change in BMD examined subjects with the shortest mean duration of T1DM (15,88). Of those studies demonstrating a significant correlation of BMD with metabolic control, two utilized a “long-term” assessment of glycemic control [i.e., 12 months of serial Hb A_{1c} measurements (43) or the mean of Hb A_{1c} measurements from the onset of disease to the last measurement (129)] rather than a single point-in-time Hb A_{1c}, and one study utilized pQCT techniques for measurement of BMD. Although other literature suggests that the effects of diabetes on BMD may be partially independent of metabolic control, the “diabetes impact index” (129) or the combined contribution of lifetime glycemic control coupled with duration of disease might prove to be more influential than is currently appreciated. Finally, the use of DEXA among pediatric populations has several limitations that have been reviewed elsewhere (4) but could contribute to inconsistencies noted when one is comparing pediatric clinical studies.

Pediatric studies as a whole, however, suggest that the impact of T1DM on skeletal health may be especially pertinent during adolescence. Adolescence is a developmental period characterized by physiological, hormonal, nutritional, cognitive, and psychological changes, all of which can have an impact on diabetes management and disease morbidity. With respect to bone health, numerous diabetes-associated perturbations in adolescence are particularly detrimental to bone (for detailed review, see Ref. 125). Studies suggest that type 1 diabetics, during adolescence, experience *1*) exaggerated dysregulation of the growth hormone/IGF-I/IGF-binding protein (IGFBP) axis, contributing to a puberty-associated deterioration in glycemic control and/or worsening of insulin resistance (17); *2*) noncompliance with medical management recommendations (56,140), again leading to poorer metabolic control; *3*) insufficient dietary calcium intake, particularly among females (2,61); *4*) an increase in daily urinary calcium excretion (8); and *5*) a higher incidence of subclinical eating behavior disorders, contributing to poor weight maintenance and/or relative malnutrition (125). All of these confounding variables may have independent negative impacts upon bone mineral acquisition in T1DM and, ultimately, on peak bone mass.

Osteopenia and Osteoporosis: T2DM

In contrast to T1DM, T2DM is typically not associated with osteopenia or osteoporosis, and among women is most often associated with higher measurements of bone mineral density. A review of studies of bone density and T2DM conducted in the past 10 years is presented in Table 3. To date, our review has identified only studies of adult subjects with T2DM, with the majority of these representing the postmenopausal female population (Table 3). However, Strotmeyer et al. (117) recently confirmed an association of higher BMD in T2DM by examining a multiracial, male and female elderly population. In that study, they demonstrated that T2DM "was associated cross-sectionally with 2−8% higher regional and whole body BMD, both areal and volumetric measures, even with adjustment for body composition variables of lean mass, fat mass, and abdominal visceral fat and other confounding factors." Of note, however, T2DM was associated in this study with the unique finding of lower spine bone volume. Parkinson and Fazzalari (87) have demonstrated that at low bone volume the structural integrity of cancellous bone is rapidly compromised. Consistent with this, Strotmeyer et al. suggest that a finding of lower bone volume in diabetes may account for presumed deficits in bone strength, leading to the paradoxically increased fracture risk noted in this same population (see *Fracture Risk*, below).

The etiology of the increased BMD in T2DM remains unclear, as evidence of decreased bone resorption (19,21), increased bone resorption (53), decreased bone formation (63), and increased bone formation (19) have all been reported. Krakauer et al. (63), examining histological data from transiliac bone biopsies in six subjects with T2DM, demonstrated low bone turnover, hypothesizing a protective effect of a low bone turnover state over time in aging type 2 diabetics. In addition, some contribution of concurrent obesity to BMD is likely, independent of hyperinsulinemia (37).

Studies in subjects with T2DM frequently do not specify and/or analyze results on the basis of treatment type (diet vs. oral hypoglycemic agent vs. insulin), which could also account for the inconsistencies in studies of bone density in T2DM. Animal studies illustrate these differences. Specifically, in mice, rosiglitazone administration results in a significant decrease in BMD, bone volume, and bone formation rate associated with a decrease in osteoblast-specific gene expression (100), and increased apoptotic death of osteoblasts (114). In contrast, insulin administration to the point of hyperinsulinemia stimulates osteoblast activity and mineral apposition rates (135). Differences in treatment modalities also likely imply differences in disease severity, further confounding the outcome of such studies. Thus the impact of endogenous insulin production, insulin sensitivity, and exogenous insulin administration as an anabolic agent for bone in T2DM has not been clarified.

Fracture Risk

In contrast to the discrepancy between the T1DM and T2DM populations and bone mineral density, diabetic populations with either disease uniformly appear to have a higher risk for bone fracture. Several large prospective clinical studies conducted in the US (59,85) and Norway (29,80) have demonstrated that a history of T1DM is associated with an increased risk of hip (29,80,85) and upper extremity fracture (80), with a reported relative risk ranging from 5.81 (80) to 12.25 (85). In a comprehensive review of the literature from 1982 to 1997, including 94 cohort and 72 case-controlled studies of risk factors associated with increased fracture rates, T1DM was among the top 10 factors associated with the highest risk of fracture (23). An increased incidence of calcaneal fracture has also been reported (44). To date, only a few studies dispute this association (78).

An increase in fracture risk is also reported among older patients with T2DM (29,85,90,106, 119), despite frequently reported normal or increased BMD among type 2 diabetics (40,52,

106,127). Age-adjusted relative risk ratios (RR) for fracture among individuals with T2DM ranged from 1.4 to 2.9 in these studies (typically 1.7 to 1.9) and frequently demonstrated an increasing RR with longer duration of disease.

The increase in fracture risk in both T1DM and T2DM, despite variations in BMD, would suggest that factors independent of BMD might also contribute to the increased relative risk for fractures. For example, among patients with diabetes, fracture risk is exacerbated by the concurrent risk for falls (93,107) and traumatic injury among these individuals, which can result from several diabetes-related comorbidities. Specifically, hypoglycemia unawareness and hypoglycemic seizures (45), visual impairment (55), peripheral neuropathy and gait disturbance secondary to lower-extremity abnormalities or insensate feet (79,137), and nocturnal polyuria (3a) all contribute to a higher risk of falling. Moreover, peripheral neuropathy appears to be an independent risk factor leading to further reduction in BMD among T1DM patients (90,96). Among patients with T2DM, discrepancies between increased BMD, yet decreased bone strength, have also been proposed.

Prolonged fracture union time and prolonged healing are also seen in patients with diabetes (70). Specifically, the presence of diabetes is associated with an increased risk of wound complications following surgical treatment of fractures (25) and non-union or mal-union of healing fracture sites (108,122).

HYPOINSULINEMIA vs. HYPERINSULINEMIA

Among the T1DM population, numerous factors may contribute to the development of osteopenia (progressing to osteoporosis) over the lifetime of an individual with T1DM, including *1*) insufficient skeletal mineralization during critical periods of bone mass accrual; *2*) increased urinary calcium excretion coupled with diminished calcium absorption, leading to chronic calcium deficiency; *3*) lifelong effects of chronic hyperglycemia on osteoblast function; *4*) detrimental effects of accumulated glycated end products on bone formation; *5*) insulinopenia; *6*) diabetes-induced dysregulation of the GH-IGF axis (123); and 7) a disproportional representation of the Caucasian population among disease demographics. When contrasted with the T2DM population and an associated increased BMD, however, *factors 2, 3, 4,* and *7* listed above do not appear to explain the discrepancies between the T1DM and T2DM populations, since chronic hyperglycemia, hypercalciuria, accumulation of advanced glycation end products, and multiracial uniformity of these findings are common to both groups. What does emerge, however, as clearly divergent are the differences in insulin concentrations (insulinopenia vs. hyperinsulinism) and IGF concentrations (decreased vs. normal or increased) between T1DM and T2DM (123). This suggests that either direct effects of insulin or indirect effects of insulin (e.g., hyperandrogenism secondary to hyperinsulinism, increased hepatic IGF-I production, and/or increased IGF-I bioavailability through reduction in IGFBP-1 production, etc.) may play a significant role in bone health in diabetes. In fact, several studies have demonstrated a positive correlation between BMD and insulin dose (31, 139), or 24-h urinary C-peptide excretion (31) among patients with T2DM, suggesting that hyperinsulinemia per se (either endogenous or exogenous) may prevent age-related declines in BMD. Dennison et al. (14) demonstrated a higher BMD, after adjustment for BMI, among newly diagnosed type 2 diabetics, compared with euglycemic individuals and noted a positive association with insulin resistance and hyperinsulinemia, suggesting a causal anabolic effect of insulin on bone. Similarly, in studies of nondiabetic postmenopausal women, Barrett-Conner et al. (5) found a positive association between bone density of the radius and spine and fasting insulin levels, whereas Reid et al. (92) demonstrated a correlation between bone density throughout the skeleton and both fasting and glucose-stimulated insulin levels. Taken together, these studies again suggest that clinical hyperinsulinemia may preserve and maintain bone

mass. We next examine in vivo and in vitro data relating to the role of insulin as an anabolic agent in bone.

IN VIVO EVIDENCE OF INSULIN AS AN ANABOLIC AGENT IN BONE

Impaired fracture healing is observed not only clinically but also in experimental models of both T1DM and T2DM (32,46,70,74). In support of a role for insulin in various stages of fracture repair, experimental studies show that the diabetic fracture callus demonstrates impaired biomechanical properties, reduced cell proliferation, and reduced collagen content (32,74,116,126).

Several investigators have studied bone healing and regeneration using T1DM rat models. The diabetic BB (BioBreeding) rat has been the most studied model of spontaneous diabetes among rodent models. The other model most commonly studied is the chemically induced [i.e., streptozotocin (STZ)] T1DM model, which causes destruction of the insulin-producing β-cells in the pancreas. Studies using these models suggest that several potential underlying mechanisms may contribute to bone pathology in insulin-deficiency. STZ-induced diabetes in rats, as in poorly controlled T1DM in humans, causes nonosmotic hypercalciuria, which can lead to a negative Ca^{2+} balance (138). Advanced glycation end products (AGEs) may also contribute to poor bone strength (68,89), and increased receptors for AGEs (RAGEs) are manifested in a fracture-healing model in chemically-induced diabetes in mice (102). In the skeletal growth centers of diabetic animals, levels of IGF-I, IGF-I receptors, and insulin receptors (IRs) are reduced (75), implying dysregulation of IGF action on bone in the diabetic state. And, during fracture healing, diabetic rats exhibit alterations in the timing and/or quantity of type II and type X collagen mRNA expression (33).

The degree of glycemic control (which is directly related to insulin sufficiency) has been shown to strongly correlate with bone integrity in T1DM rodent models. By use of the BB rat as a model, it has been shown that the degree of overall glycemic control correlates with fracture healing (26,28). In rats experiencing poorly controlled diabetes, severe mineralization defects have been noted and remain evident up to 6 wk after the fracture event (26). In contrast, animals with improved glycemic control showed much improved fracture healing. Additionally, the size of the fracture also was an independent variable in predicting successful repair, irrespective of the diabetic state (27). Other models using titanium implants in chemically induced diabetes (113), bacterial infection in STZ-treated mice (42), and distraction osteogenesis in nonobese diabetic mice (124) have all shown deficits in new bone formation, suggesting that the diabetic metabolic state has a negative impact on bone-forming cells. Indeed, it has been postulated that diabetes can revert osteoblasts into reticent bone-lining cells, and this is supported by recent studies showing that the diabetic state influences infiltrating cells in a marrow ablation model to behave as immature mesenchymal cells and not differentiate into mature osteoblasts, likely due to altered gene expression of proosteoblastic proteins (72). These reports share two conclusions: *1*) bone regeneration is impaired in insulin deficiency; and *2*) regeneration can be restored by insulin treatment, even in the face of moderate hyperglycemia, suggesting a primary role for insulin in bone formation.

Evidence for a direct link between insulin action and bone formation in vivo is scant. Newer studies in transgenic models have helped elucidate a potential role for insulin as an anabolic agent in osteoblastogenesis. The IR is a tyrosine kinase receptor and signals intracellularly through insulin receptor substrate (IRS) molecules, termed IRS-1 to IRS-4. Knockout mice null for IRS-1 and IRS-2 result in unique bone phenotypes: in vivo, IRS-2 appears to maintain dominance of bone formation over bone resorption, whereas IRS-1 regulates bone turnover (1,86). Recently, it has been shown that bone healing is impaired in IRS-1-deficient mice and can be corrected with reexpression of IRS-1 within the fracture site (111). IRS molecules also

mediate IGF receptor signaling, so some cross talk through IRS may take place via insulin and IGF signaling in osteoblasts; however, knowing that levels of IGF-I, IGF-I receptors, and IRs are all reduced in the skeletal growth centers of diabetic animals (75), it could be speculated that impaired insulin signaling in bone-forming cells results in a secondary and local IGF-I deficiency. Indeed, ablation of 80−98% of the IR in mosaic mice results in extreme growth retardation, suggesting a primary role for the IR in promoting normal skeletal development (62). Because IRs are also present on osteoclasts and insulin has been shown to inhibit osteoclastic activity in vitro (121), the net effect of insulin on bone, as suggested by in vivo models, is one of proformation and possibly of decreased resorption, both attributes of an anabolic agent for bone.

EFFECTS OF INSULIN ON THE BIOMECHANICAL AND MICROARCHITECTURAL QUALITY OF BONE: IN VIVO STUDIES

Recent studies examining rat models of diabetes have demonstrated detrimental effects of insulin deficiency on various biomechanical properties of bone. Many studies performed in animal models, and in rat models in particular, suggest that insulin deficiency can result in decreased bone integrity. Measurements of bone strength in T1DM models have revealed that diabetes and insulin deficiency can have a negative impact on bone strength and bone composition. In a long-term T1DM model, Einhorn et al. (18) showed that diabetic bones display specific defects of bone mineralization, including decreased hydroxyapatite crystal perfection, decreased calcium-to-phosphate composition of the ash, and decreased ash content in certain bones such as the tibial metaphysis. These authors also found that the bones from diabetic animals exhibited reduced strength-related properties, along with a compensatory increase in stiffness, suggesting a possible alteration in bone crystal structure. Bone strength has also been shown to be diminished in T1DM rats at the femur and the femoral neck (16, 48). In a number of T1DM animal studies, histomorphometric analyses have shown that, irrespective of the model used, insulin-deficient rats may exhibit reduced or absent bone formation and this decline is appreciated in relation to all bone surfaces examined, i.e., trabecular, periosteal, and endocortical (132–134). The major deficits in these insulin-deficient models appear to be related to a deficit in mineralized surface area, a decrement in the rate of mineral apposition, deceased osteoid surface, depressed osteoblast activity, and decreased numbers of osteoclasts (34,104,112,135), leading to an overall depression in remodeling of bone in the untreated insulin-deficient state. These data are supported by surrogate markers, such as the osteoblast marker osteocalcin, which is also generally depressed in the untreated diabetic rat (20,131), as is urinary deoxypyridinoline, an index of bone resorption (136). In keeping with the attributes of an anabolic bone agent, insulin therapy appears to reverse these histomorphometric, biomechanical, and biochemical abnormalities and improves bone strength (26,28,48).

IN VITRO EVIDENCE OF INSULIN AS AN ANABOLIC AGENT IN BONE

Several lines of evidence from in vitro bone cell cultures support the idea that insulin can exert direct anabolic effects on bone cells. For example, primary calvarial osteoblasts and multiple osteoblast-like cell lines express a significant number of IRs on the cell surface and have a high capacity for insulin binding (67, 91, 120). In response to physiological doses of insulin, cultured osteoblasts show increased rates of proliferation (41,141), collagen synthesis (10,91,97), alkaline phosphatase production (11,64), and glucose uptake (38,54). How insulin signaling might promote osteoblastogenesis is speculative; however, studies examining pancreatic β-cells suggests a direct action of insulin to inactivate p27, a cyclin-dependent kinase inhibitor that could attenuate cell proliferation in osteoblasts (128). In addition, a direct signaling sequence from the IR to PI 3-kinase to protein kinase B (PKB) to Bcl-2-associated death promoter (BAD) causes inhibition of apoptosis and increases cell survival in various cell

systems (142). Therefore, possible direct actions of insulin on bone cells may include mitogenic stimulation of bone-forming cells, coupled with inhibition of apoptosis.

In addition to the direct effects of insulin on bone cells, insulin may exert synergistic effects with other anabolic agents in bone, such as IGF-I and parathyroid hormone (PTH). IGFBP-1 is acutely downregulated by insulin in a variety of tissues and is similarly suppressed by insulin in bone cells (13). Therefore, insulin, by decreasing IGFBP-1, may allow bone cells to be more sensitive to IGFs in the pericellular environment. With respect to PTH, pretreatment of UMR-106−01 osteoblast-like cells with a physiological concentration of insulin has been shown to increase the level of PTH-stimulated cAMP production compared with cAMP production generated by PTH alone (47). Another report shows that, although PTH decreases and insulin slightly increases DNA synthesis in UMR-106−01 cells, chronic exposure of cells to PTH followed by an acute exposure to insulin increases DNA synthesis more than tenfold over stimulation by insulin alone (24). These studies are consistent with the recent finding that insulin plus PTH results in greater bone recovery in diabetic rats compared with insulin or PTH treatment alone (118). Other in vitro studies have reported inhibitory effects of insulin on second messenger generation by PTH when insulin is added prior to or alongside PTH (50, 51). Therefore, it will be necessary to explore further the potential anabolic interrelationships between insulin and PTH on bone cells, as synergism may be an important feature of insulin's actions on bone.

FUTURE DIRECTIONS

Although both clinical and animal data, as well as in vitro studies, strongly suggest an anabolic role for insulin in bone, future studies are needed to address mechanisms underlying the observations and outcomes herein reviewed. The IR has been deleted in a tissue-specific manner in a number of tissues (83); however, bone cells have not been studied in this regard. Therefore, a systematic approach to delete the IR in bone marrow precursors, in early and late osteoblasts, and/or in osteoclasts could refine the understanding of how insulin signaling works in the various skeletal compartments in bone modeling and remodeling. It is also unclear how systemic insulin administration may differ in its impact on the skeleton compared with local delivery, which would have much less impact on glycemic response and metabolism. Thus studies looking at local insulin delivery on bone formation will be needed to sort between insulin's direct effects on skeletal cells versus the more complex metabolic reaction to insulin administered peripherally. Also in need of clarification is how bone cells might remain sensitive to the anabolic effects of insulin even when other organs may be resistant to insulin action (e.g., hepatic tissue in T2DM). Studies designed to look at “selective” insulin-resistant pathways in bone cells need to be pursued, as two separate signaling pathways have been described for insulin action: *1*), a metabolic pathway that involves glucose uptake and is mediated via IRS-1 and -2 phosphorylation and subsequent activation of PI 3-kinase (110); and *2*), a mitogenic pathway that occurs through phosphorylation of Shc and downstream activation ultimately of mitogen-activated protein kinases (105). Resistance in one pathway and simultaneous sensitivity in the other pathway have been well described and therefore may also be applicable to bone cells in the insulin-resistant state.

SUMMARY

We propose that the combination of data presented in this review should qualify insulin as an anabolic agent for bone formation for the following reasons. *1*) Clinical studies demonstrating a decreased adolescent growth velocity, and a relatively rapid onset of demonstrable deficits in bone density in pediatric patients with T1DM, suggest a role for insulin sufficiency in periosteal surface bone modeling (i.e., bone growth). *2*) The clinical dichotomy between T1DM and T2DM with respect to bone density is consistent with the opposing insulin-secretory states

(i.e., hypoinsulinemia vs. hyperinsulinemia) in these two diseases, suggesting a preferential effect of insulin on bone formation. *3*) The insulin-signaling apparatus is clearly present and involved in bone growth and bone formation. *4*) Clinical, in vivo, and in vitro studies all suggest that insulin improves bone formation via proosteoblastic mechanisms. And *5*) insulin deficiency in animal models is associated with abnormalities of bone microarchitecture, which can be prevented with insulin replacement. Taken together, these findings suggest that insulin, as an anabolic agent, can preserve and increase bone strength through its effects on bone formation. The persistence of fracture risk in certain hyperinsulinemic states (i.e., T2DM), however, underscores the multifactorial nature of the effects of diabetes on bone and may suggest a threshold for insulin in promoting healthy bone.

To unravel and isolate insulin's actions on diabetic and normal bone formation and repair will not be an easy task. Fortunately, the tools available to study the underlying mechanisms (e.g., recombinant proteins, signal transduction inhibitors, genetic mouse models, etc.) are becoming increasingly available. Despite the underlying complexity, understanding and dissecting the unique anabolic actions of insulin in bone should facilitate the development of interventions to improve bone health in states of insulin dysregulation.

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REFERENCES

1. Akune T, Ogata N, Hoshi K, Kubota N, Terauchi Y, Tobe K, Takagi H, Azuma Y, Kadowaki T, Nakumura K, Kawaguchi H. Insulin receptor substrate-2 maintains predominance of anabolic function over catabolic function of osteoblasts. J Cell Biol 2002;159:147–156. [PubMed: 12379806]
2. Albertson AM, Tobelmann RC, Marquart L. Estimated dietary calcium intake and food sources for adolescent females 1980−1992. J Adolesc Health 1997;20:20–26. [PubMed: 9007655]
3. Al-Maatouq MA, El-Desouki MI, Othman SA, Mattar EH, Babay ZA, Addar M. Prevalence of osteoporosis among postmenopausal females with diabetes mellitus. Saudi Med J 2004;25:1423–1427. [PubMed: 15494815]

3a. Asplund R. Nocturia, nocturnal polyuria, and sleep quality in the elderly. J Psychosom Res 2004;56:517–525. [PubMed: 15172208]

4. Bachrach LK. Dual-energy x-ray absorptiometry (DEXA) measurements of bone density and body composition: promise and pitfalls. J Pediatr Endocrinol Metab 2000;13(Suppl 2):983–988. [PubMed: 11086651]
5. Barrett-Connor E, Kritz-Silverstein D. Does hyperinsulinemia preserve bone? Diabetes Care 1996;19:1388–1392. [PubMed: 8941469]
6. Bonfanti R, Mora S, Prinster C, Bognetti E, Meschi F, Puzzovio M, Proverbio MC, Chiumello G. Bone modeling indexes at onset and during the first year of follow-up in insulin-dependent diabetic children. Calcif Tissue Int 1997;60:397–400. [PubMed: 9115153]
7. Bouillon R. Diabetic bone disease. Calcif Tissue Int 1991;49:155–160. [PubMed: 1933578]
8. Brown IR, McBain AM, Chalmers J, Campbell IW, Brown ER, Lewis MJ. Sex differences in the relationship of calcium and magnesium excretion to glycaemic control in type 1 diabetes mellitus. Clin Chim Acta 1999;283:119–128. [PubMed: 10404736]
9. Campos Pastor MM, Lopez-Ibarra PJ, Escobar-Jimenez F, Serrano Pardo MD, Garcia-Cervigon AG. Intensive insulin therapy and bone mineral density in type 1 diabetes mellitus: a prospective study. Osteoporos Int 2000;11:455–459. [PubMed: 10912849]
10. Canalis EM, Dietrich JW, Maina DM, Raisz LG. Hormonal control of bone collagen synthesis in vitro. Effects of insulin and glucagon. Endocrinology 1977;100:668–674. [PubMed: 401359]
11. Canalis E. Effect of hormones and growth factors on alkaline phosphatase activity and collagen synthesis in cultured rat calvariae. Metabolism 1983;32:14–20. [PubMed: 6217395]

12. Christensen JO, Svendsen OL. Bone mineral in pre- and postmenopausal women with insulin dependent and non-insulin-dependent diabetes mellitus. Osteoporos Int 1999;10:307–311. [PubMed: 10692980]
13. Conover CA, Lee PD, Riggs BL, Powell DR. Insulin-like growth factor-binding protein-1 expression in cultured human bone cells: regulation by insulin and glucocorticoid. Endocrinology 1996;137:3295–3301. [PubMed: 8754754]
14. Dennison EM, Syddall HE, Sayer AA, Craighead S, Phillips DIW, Cooper C. Type 2 diabetes mellitus is associated with increased axial bone density in men and women from the Hertfordshire Cohort Study: evidence for an indirect effect of insulin resistance? Diabetologia 2004;47:1963–1968. [PubMed: 15565368]
15. De Schepper J, Smitz J, Rosseneu S, Bollen P, Louis O. Lumbar spine bone mineral density in diabetic children with recent onset. Horm Res 1998;50:193–196. [PubMed: 9838239]
16. Dixit PK, Ekstrom RA. Decreased breaking strength of diabetic rat bone and its improvement by insulin treatment. Calcif Tissue Int 1980;32:195–199. [PubMed: 6775788]
17. Dunger DB, Acerini CL. IGF-I and diabetes in adolescence. Diabetes Metab 1998;24:101–107. [PubMed: 9592633]
18. Einhorn TA, Boskey AL, Gundberg CM, Vigorita VJ, Devlin VJ, Beyer MM. The mineral and mechanical properties of bone in chronic experimental diabetes. J Orthop Res 1988;6:317–323. [PubMed: 3258636]
19. El Miedany YM, el Gaafary S, el Baddini MA. Osteoporosis in older adults with non-insulin-dependent diabetes mellitus: is it sex related? Clin Exp Rheumatol 1999;17:561–567. [PubMed: 10544839]
20. Epstein S, Takizawa M, Stein B, Katz IA, Joffe II, Romero DF, Liang XG, Li M, Ke HZ, Jee WS. Effect of cyclosporine A on bone mineral metabolism in experimental diabetes mellitus in the rat. J Bone Miner Res 1994;9:557–566. [PubMed: 8030444]
21. Erbagci AB, Araz M, Erbagci A, Tarakcioglu M, Namiduru ES. Serum prolidase activity as a marker of osteoporosis in type 2 diabetes mellitus. Clin Biochem 2002;35:263–268. [PubMed: 12135686]
22. Ersoy B, Goksen D, Darcan S, Mavi E, Ozturk C. Evaluation of bone mineral density in children with diabetes mellitus. Indian J Pediatr 1999;66:375–379. [PubMed: 10798085]
23. Espallargues M, Sampietro-Colom L, Estrada MD, Sola M, del Rio L, Setoain J, Granados A. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. Osteoporos Int 2001;12:811–822. [PubMed: 11716183]
24. Felsenfeld AJ, Iida-Klein A, Hahn TJ. Interrelationship between parathyroid hormone and insulin: effects on DNA synthesis in UMR-106−01 cells. J Bone Miner Res 1992;7:1319–1325. [PubMed: 1466257]
25. Folk JW, Starr AJ, Early JS. Early wound complications of operative treatment of calcaneus fractures: analysis of 190 fractures. J Orthop Trauma 1999;13:369–372. [PubMed: 10406705]
26. Follak N, Kloting L, Wolf E, Merk H. Delayed remodeling in the early period of fracture healing in spontaneously diabetic BB/OK rats depending on the diabetic metabolic state. Histol Histopathol 2004;19:473–486. [PubMed: 15024708]
27. Follak N, Kloting I, Wolf E, Merk H. Histomorphometric evaluation of the influence of the diabetic metabolic state on bone defect healing depending on the defect size in spontaneously diabetic BB/OK rats. Bone 2004;35:144–52. [PubMed: 15207750]
28. Follak N, Kloting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. Diabetes Metab Res Rev 2005;21:288–296. [PubMed: 15693070]
29. Forsen L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. Diabetologia 1999;42:920–925. [PubMed: 10491750]
30. Forst T, Pfutzner A, Kann P, Schehler B, Lobmann R, Schafer H, Andreas J, Bockisch A, Beyer J. Peripheral osteopenia in adult patients with insulin dependent diabetes mellitus. Diabet Med 1995;12:874–879. [PubMed: 8846677]
31. Fukunaga Y, Minamikawa J, Inoue D, Koshiyama H. Does insulin use increase bone mineral density in patients with non-insulin-dependent diabetes mellitus? Arch Intern Med 1997;157:2668–2669. [PubMed: 9531243]

32. Funk JR, Hale JR, Carmines D, Gooch HL, Hurwitz SR. Biomechanical evaluation of early fracture healing in normal and diabetic rats. J Orthop Res 2000;18:126–132. [PubMed: 10716288]
33. Gooch HL, Hale JE, Fujioka H, Balian G, Hurwitz SR. Alterations of cartilage and collagen expression during fracture healing in experimental diabetes. Connect Tissue Res 2000;41:81–91. [PubMed: 10992154]
34. Goodman WG, Hori MT. Diminished bone formation in experimental diabetes. Relationship to osteoid maturation and mineralization. Diabetes 1984;33:825–831. [PubMed: 6381178]
35. Gunczler P, Lanes R, Paz-Martinez V, Martins R, Esaa S, Colmen-ares V, Weisinger JR. Decreased lumbar spine bone mass and low bone turnover in children and adolescents with insulin dependent diabetes mellitus followed longitudinally. J Pediatr Endocrinol Metab 1998;11:413–419. [PubMed: 11517957]
36. Gunczler P, Lanes R, Paoli M, Martinis R, Villaroel O, Weisinger JR. Decreased bone mineral density and bone formation markers shortly after diagnosis of clinical type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2001;14:525–528. [PubMed: 11393573]
37. Haffner SM, Bauer RL. The association of obesity and glucose and insulin concentrations with bone density in premenopausal and post-menopausal women. Metabolism 1993;42:735–738. [PubMed: 8510518]
38. Hahn TJ, Westbrook SL, Sullivan TL, Goodman WG, Halstead LR. Glucose transport in osteoblast-enriched bone explants: characterization and insulin regulation. J Bone Miner Res 1988;3:359–365. [PubMed: 2463740]
39. Hampson G, Evans C, Petitt RJ, Evans WD, Woodhead SJ, Peters JR, Ralston SH. Bone mineral density, collagen type 1 alpha 1 genotypes and bone turnover in premenopausal women with diabetes mellitus. Diabetologia 1998;41:1314–1320. [PubMed: 9833939]
40. Hanley DA, Brown JP, Tenenhouse A, Olszynski WP, Loannidis G, Berger C, Prior JC, Pickard L, Murray TM, Anastassiades T, Kirkland S, Joyce C, Joseph L, Papaioannou A, Jackson SA, Poliquin S, Adachi JD, Canadian Multicentre Osteoporosis Study Research Group. Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study. J Bone Miner Res 2003;18:784–790. [PubMed: 12674340]
41. Hashizume M, Yamaguchi M. Stimulatory effect of beta-alanyl-L-histidinato zinc on cell proliferation is dependent on protein synthesis in osteoblastic MC3T3-E1 cells. Mol Cell Biochem 1993;122:59–64. [PubMed: 8350864]
42. He H, Liu R, Desta T, Leone C, Gerstenfeld LC, Graves DT. Diabetes causes decreased osteoclastogenesis, reduced bone formation, and enhanced apoptosis of osteoblastic cells in bacteria stimulated bone loss. Endocrinology 2004;145:447–452. [PubMed: 14525917]
43. Heap J, Murray MA, Miller SC, Jalili T, Moyer-Mileur LJ. Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr 2004;144:56–62. [PubMed: 14722519]
44. Hedlund LJ, Maki DD, Griffiths HJ. Calcaneal fractures in diabetic patients. J Diabetes Complications 1998;12:81–87. [PubMed: 9559485]
45. Hepburn DA, Steel JM, Frier BM. Hypoglycemic convulsions cause serious musculoskeletal injuries in patients with IDDM. Diabetes Care 1989;12:32–34. [PubMed: 2653747]
46. Herbsman H, Powers JC, Hirschman A, Shaftan GW. Retardation of fracture healing in experimental diabetes. J Surg Res 1968;8:424–431. [PubMed: 5673338]
47. Hickman J, McElduff A. Insulin sensitizes a cultured rat osteogenic sarcoma cell line to hormones which activate adenylate cyclase. Calcif Tissue Int 1990;46:401–405. [PubMed: 2163743]
48. Hou JC, Zernicke RF, Barnard RJ. Effects of severe diabetes and insulin on the femoral neck of the immature rat. J Orthop Res 1993;11:263–271. [PubMed: 8483039]
49. Hui SL, Epstein S, Johnston CC Jr. A prospective study of bone mass in patients with type 1 diabetes. J Clin Endocrinol Metab 1985;60:74–80. [PubMed: 3964795]
50. Iida-Klein A, Varlotta V, Hahn TJ. Protein kinase C activity in UMR-106−01 cells: effects of parathyroid hormone and insulin. J Bone Miner Res 1989;4:767–74. [PubMed: 2683593]

51. Iida-Klein A, Hahn TJ. Insulin acutely suppresses parathyroid hormone second messenger generation in UMR-106−01 osteoblast-like cells: differential effects on phospholipase C and adenylate cyclase activation. Endocrinology 1991;129:1061–1024.
52. Ingberg CM, Palmer M, Aman J, Arvidsson B, Schvarez E, Berne C. Body composition and bone mineral density in long-standing type 1 diabetes. J Intern Med 2004;255:392–398. [PubMed: 14871464]
53. Isaia GC, Ardissone P, Di Stefano M, Ferrari D, Martina V, Porta M, Tagliabue M, Molinatti GM. Bone metabolism in type 2 diabetes mellitus. Acta Diabetol 1999;36:35–38. [PubMed: 10436250]
54. Ituarte EA, Halstead LR, Iida-Klein A, Ituarte HG, Hahn TJ. Glucose transport system in UMR-106 −01 osteoblastic osteosarcoma cells: regulation by insulin. Calcif Tissue Int 1989;45:27–33. [PubMed: 2504460]
55. Ivers RC, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: The Blue Mountains Eye Study. Diabetes Care 2001;24:1198–1203. [PubMed: 11423502]
56. Johnson SB, Silverstein J, Rosenbloom A, Carter R, Cunningham W. Assessing daily management in childhood diabetes. Health Psychol 1986;5:545–564. [PubMed: 3542527]
57. Kao WH, Kammerer CM, Schneider JL, Bauer RL, Mitchell BD. Type 2 diabetes is associated with increased bone mineral density in Mexican-American women. Arch Med Res 2003;34:399–406. [PubMed: 14602507]
58. Kayath MJ, Dib SA, Vieiaa JG. Prevalence and magnitude of osteopenia associated with insulin-dependent diabetes mellitus. J Diabetes Complications 1994;8:97–104. [PubMed: 8061353]
59. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. Am J Epidemiol 1992;135:477–489. [PubMed: 1570814]
60. Kemink SA, Hermus AR, Swinkels LM, Lutterman JA, Smals AG. Osteopenia in insulin-dependent diabetes mellitus: prevalence and aspects of pathophysiology. J Endocrinol Invest 2000;23:295–303. [PubMed: 10882147]
61. Key JD, Key LL Jr. Calcium needs of adolescents. Curr Opin Pediatr 1994;6:379–382. [PubMed: 7951657]
62. Kitamura T, Kitamura Y, Nakae J, Giordano A, Cinti S, Kahn CR, Efstratiadis A, Accili D. Mosaic analysis of insulin receptor function. J Clin Invest 2004;113:209–219. [PubMed: 14722613]
63. Krakauer JC, McKenna MJ, Buderer NF, Rao DS, Whitehouse FW, Parfitt AM. Bone loss and bone turnover in diabetes. Diabetes 1995;44:775–782. [PubMed: 7789645]
64. Kream BE, Smith MD, Canalis E, Raisz LG. Characterization of the effect of insulin on collagen synthesis in fetal rat bone. Endocrinology 1985;116:296–302. [PubMed: 3880543]
65. Kwon DJ, Kim JH, Chung KW, Kim JH, Lee JW, Kim SP, Lee HY. Bone mineral density of the spine using dual energy X-ray absorptiometry in patient with non-insulin-dependent diabetes mellitus. J Obstet Gynaecol Res 1996;22:157–162. [PubMed: 8697346]
66. Lettgen B, Hauffa B, Mohlmann C, Jeken C, Reiners C. Bone mineral density in children and adolescents with juvenile diabetes: selective measurement of bone mineral density of trabecular and cortical bone using peripheral quantitative computed tomography. Horm Res 1995;43:173–175. [PubMed: 7782045]
67. Levy JR, Murray E, Manolagas S, Olefsky JM. Demonstration of insulin receptors and modulation of alkaline phosphatase activity by insulin in rat osteoblastic cells. Endocrinology 1986;119:1786–1792. [PubMed: 3530724]
68. Like AA, Rossini AA. Streptozotocin-induced pancreatic insulitis: new model of diabetes mellitus. Science 1976;193:415–417. [PubMed: 180605]
69. Liu EY, Wactawski-Wende J, Donahue RP, Dmochowshi J, Hovey KM, Quattrin T. Does low bone mineral density start in post-teenage years in women with type 1 diabetes? Diabetes Care 2003;26:2365–2369. [PubMed: 12882863]
70. Loder RT. The influence of diabetes mellitus on the healing of closed fractures. Clin Orthop 1988;232:210–216. [PubMed: 3289812]
71. Lopez-Ibarra PJ, Pastor MM, Escobar-Jimenez F, Pardo MD, Gonzalez AG, Luna JD, Requena ME, Diosdado MA. Bone mineral density at time of clinical diagnosis of adult-onset type 1 diabetes mellitus. Endocr Pract 2001;7:346–351. [PubMed: 11585369]

72. Lu H, Kraut D, Gerstenfeld LC, Graves DT. Diabetes interferes with the bone formation by affecting the expression of transcription factors that regulate osteoblast differentiation. Endocrinology 2003;144:346–352. [PubMed: 12488363]
73. Lunt H, Florkowski CM, Cundy T, Kendall D, Brown LJ, Elliot JR, Wells JE, Turner JG. A population-based study of bone mineral density in women with longstanding type 1 (insulin dependent) diabetes. Diabetes Res Clin Pract 1998;40:31–38. [PubMed: 9699088]
74. Macey LR, Kana SM, Jingushi S, Terek RM, Borretos J, Bolander ME. Defects of early fracture-healing in experimental diabetes. J Bone Joint Surg Am 1989;71:722–733. [PubMed: 2659600]
75. Maor G, Karnieli E. The insulin-sensitive glucose transporter (GLUT4) is involved in early bone growth in control and diabetic mice, but is regulated through the insulin-like growth factor I receptor. Endocrinology 1999;140:1841–1851. [PubMed: 10098523]
76. Mathiassen B, Nielsen S, Johansen JS, Hartwell D, Ditzel J, Rodbro P, Christiansen C. Long-term bone loss in insulin-dependent diabetic patients with microvascular complications. J Diabetes Complications 1990;4:145–149.
77. McNair P, Christiansen C, Christensen MS, Madsbad S, Faber OK, Binder C, Transbol I. Development of bone mineral loss in insulin-treated diabetes: a 1½ years follow-up study in sixty patients. Eur J Clin Invest 1981;11:55–59. [PubMed: 6783430]
78. Melchior TM, Sorensen H, Torp-Pedersen C. Hip and distal arm fracture rates in peri- and postmenopausal insulin-treated diabetic females. J Intern Med 1994;236:203–208. [PubMed: 8046320]
79. Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. Arch Phys Med Rehabil 2004;85:245–252. [PubMed: 14966709]
80. Meyer HE, Tverdal A, Falch JA. Risk factors for hip fracture. I. Middle-aged Norwegian women and men. Am J Epidemiol 1993;137:1203–1211. [PubMed: 8322761]
81. Miazgowski T, Czekalski S. A 2-year follow-up study on bone mineral density and markers of bone turnover in patients with longstanding insulin-dependent diabetes mellitus. Osteoporos Int 1998;8:399–403. [PubMed: 9850345]
82. Muñoz-Torres M, Jódar E, Escobar-Jiménez F, López-Ibarra J, Luna JD. Bone mineral density measured by dual x-ray absorptiometry in Spanish patients with insulin-dependent diabetes mellitus. Calcif Tissue Int 1996;58:316–319. [PubMed: 8661964]
83. Nandi A, Kitamura Y, Kahn CR, Accili D. Mouse models of insulin resistance. Physiol Rev 2004;84:623–647. [PubMed: 15044684]
84. National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: NOF [Online] http:// www.nof.org/physguide [2003]
85. Nicodemus KK, Folsen AR. Iowa Women's Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care 2001;24:1192–1197. [PubMed: 11423501]
86. Ogata N, Chikazu D, Kubota N, Terauchi Y, Tobe K, Azuma Y, Ohta T, Kadowaki T, Nakamura K, Kawaguchi H. Insulin receptor substrate-1 in osteoblast is indispensable for maintaining bone turnover. J Clin Invest 2000;105:935–943. [PubMed: 10749573]
87. Parkinson IH, Fazzalari NL. Interrelationships between structural parameters of cancellous bone reveal accelerated structural change at low bone volume. J Bone Miner Res 2003;18:2200–2205. [PubMed: 14672355]
88. Pascual J, Argente J, Lopez MB, Munoz M, Martinez G, Vazquez MA, Jodar E, Perez-Cano R, Hawkins F. Bone mineral density in children and adolescents with diabetes mellitus type 1 of recent onset. Calcif Tissue Int 1998;62:31–35. [PubMed: 9405730]
89. Paul RG, Bailey AJ. Glycation of collagen: the basis of its central role in the late complications of ageing and diabetes. Int J Biochem Cell Biol 1996;28:1297–1310. [PubMed: 9022289]
90. Piepkorn B, Kann P, Forst T, Andreas J, Pfutzner J. Bone mineral density and bone metabolism in diabetes mellitus. Horm Metab Res 1997;29:584–591. [PubMed: 9479561]
91. Pun KK, Lau P, Ho PW. The characterization, regulation, and function of insulin receptors on osteoblast-like clonal osteosarcoma cell line. J Bone Miner Res 1989;4:853–862. [PubMed: 2692404]

92. Reid IR, Evans MC, Cooper GJS, Ames RW, Stapleton J. Circulating insulin levels are related to bone density in normal postmenopausal women. Am J Physiol Endocrinol Metab 1993;265:E655–E659.
93. Reyes-Ortiz CA, Al Snih S, Loera J, Ray LA, Markides K. Risk factors for falling in older Mexican Americans. Ethn Dis 2004;14:417–422. [PubMed: 15328944]
94. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res 2005;20:177–184. [PubMed: 15647810]
95. Rishaug U, Birkeland KI, Falch JA, Vaaler S. Bone mass in non-insulin-dependent diabetes mellitus. Scand J Clin Lab Invest 1995;55:257–262. [PubMed: 7638560]
96. Rix M, Andreassen H, Eskildsen P. Impact of peripheral neuropathy on bone density in patients with type 1 diabetes. Diabetes Care 1999;22:827–831. [PubMed: 10332690]
97. Rosen DM, Luben RA. Multiple hormonal mechanisms for the control of collagen synthesis in an osteoblast-like cell line, MMB-1. Endocrinology 1983;112:992–999. [PubMed: 6337052]
98. Rosenbloom AL, Lezotte DC, Weber FT, Gudat J, Heller DR, Weber ML, Klein S, Kennedy BB. Diminution of bone mass in childhood diabetes. Diabetes 1977;26:1052–1055. [PubMed: 913894]
99. Rozadilla A, Nolla JM, Montana E, Fiter J, Gomez-Vaquero C, Soler J, Roigand Escofet D. Bone mineral density in patients with type 1 diabetes mellitus. Joint Bone Spine 2000;67:215–218. [PubMed: 10875321]
100. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology 2004;145:401–406. [PubMed: 14500573]
101. Sahin G, Bagis S, Cimen OB, Ozisik S, Guler H, Erdogan C. Lumbar and femoral bone mineral density in type 2 Turkish diabetic patients. Acta Medica (Hradec Kralove) 2001;44:141–143. [PubMed: 11836850]
102. Santana RB, Xu L, Chase HB, Amar S, Graves DT, Trackman PC. A role for advanced glycation end products in diminished bone healing in type 1 diabetes. Diabetes 2003;52:1502–1510. [PubMed: 12765963]
103. Santiago JV, McAlister WH, Ratzan SK, Bussman Y, Haymond MW, Shackelford G, Weldon VV. Decreased cortical thickness & osteopenia in children with diabetes mellitus. J Clin Endocrinol Metab 1977;45:845–848. [PubMed: 914988]
104. Sasaki T, Kaneko H, Ramamurthy NS, Golub LM. Tetracycline administration restores osteoblast structure and function during experimental diabetes. Anat Rec 1991;231:25–34. [PubMed: 1836318]
105. Sasaoka T, Rose DW, Jhun BH, Saltiel AR, Draznin B, Olefsky JM. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. J Biol Chem 1994;269:13689–13694. [PubMed: 7513704]
106. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauler JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR. Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab 2001;86:32–38. [PubMed: 11231974]
107. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, Schreiner PJ, Margolis KL, Cauley JA, Nevitt MC, Black DM, Cummings SR. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25:1749–1754. [PubMed: 12351472]
108. Segalman KA, Clark GL. Un-united fractures of the distal radius: a report of 12 cases. J Hand Surg [Am] 1998;23:914–919.
109. Sert M, Tetiker T, Kirim S, Soyupak S, Canataroglu A, Kocak M. Type 2 diabetes mellitus and osteopenia: is there an association? Acta Diabetol 2003;40:105–108. [PubMed: 12861410]
110. Shepherd PR, Kahn BB. Glucose transporters and insulin action: implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:248–257. [PubMed: 10413738]
111. Shimoaka T, Kamekura S, Chikuda H, Hoshi K, Chung U, Akune T, Maruyama Z, Komori T, Matsumoto M, Ogawa W, Terauchi Y, Kadowaki T, Nakamura K, Kawaguchi H. Impairment of bone healing by insulin receptor substrate-1 deficiency. J Biol Chem 2004;279:15314–15322. [PubMed: 14736890]

112. Shires R, Teitelbaum SL, Bergfeld MA, Fallon MD, Slatopolsky E, Avioli LV. The effect of streptozotocin-induced chronic diabetes mellitus on bone and mineral homeostasis in the rat. J Lab Clin Med 1981;97:231–240. [PubMed: 6450254]
113. Siqueira JT, Cavalher-Machado SC, Arana-Chavez VE, Sannomiya P. Bone formation around titanium implants in the rat tibia: role of insulin. Implant Dent 2003;12:242–251. [PubMed: 14560485]
114. Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC. Rosiglitazone impacts negatively on bone by promoting osteoblast/ osteocyte apoptosis. J Endocrinol 2004;183:203–216. [PubMed: 15525588]
115. Sosa M, Dominguez M, Navarro MC, Segarra MC, Hernandez D, de Pablos P, Betancor P. Bone mineral metabolism is normal in non-insulin-dependent diabetes mellitus. J Diabetes Complications 1996;10:201–205. [PubMed: 8835919]
116. Spanheimer RG. Correlation between decreased collagen production in diabetic animals and in cells exposed to diabetic serum: response to insulin. Matrix 1992;12:101–107. [PubMed: 1603033]
117. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB, for the Health ABC Study. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health, Aging, and Body Composition Study. J Bone Miner Res 2004;19:1084–1091. [PubMed: 15176990]
118. Suzuki K, Miyakoshi N, Tsuchida T, Kasukawa Y, Sato K, Itoi E. Effects of combined treatment of insulin and human parathyroid hormone (1–34) on cancellous bone mass and structure in streptozotocin-induced diabetic rats. Bone 2003;33:108–114. [PubMed: 12919705]
119. Taylor BC, Schreiner PJ, Stone KL, Fink HA, Cummings SR, Nevitt MC, Bowman PJ, Ensrud KE. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc 2004;52:1479–1486. [PubMed: 15341549]
120. Thomas DM, Hards DK, Rogers SD, Ng KW, Best JD. Insulin receptor expression in bone. J Bone Miner Res 1996;11:1312–1320. [PubMed: 8864906]
121. Thomas DM, Udagawa N, Hards DK, Quinn JM, Moseley JM, Findlay DM, Best JD. Insulin receptor expression in primary and cultured osteoclast-like cells. Bone 1998;23:181–186. [PubMed: 9737339]
122. Thompson RC Jr, Clohisy DR. Deformity following fracture in diabetic neuropathic osteoarthropathy. Operative management of adults who have type-I diabetes. J Bone Joint Surg Am 1993;75:1765–1773. [PubMed: 8258546]
123. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects and potential clinical utility. Diabetes Technol Ther 2000;2:69–80. [PubMed: 11467325]
124. Thrailkill KM, Liu L, Wahl EC, Liu Z, Bunn RC, Hogue W, Suva LJ, Perrien DS, Fowlkes JL, Aronson J, Lumpkin CK Jr. New bone formation is impaired in a model of Type 1 diabetes mellitus. ASBMR 25th Annual Meeting (Abstract). J Bone Miner Res 2003;18:S169.
125. Thrailkill, KM. Diabetes care for adolescents.. In: Reece, EA.; Coustan, DR.; Gabbe, SG., editors. Diabetes in Women. Lippincott Willimas & Willkins; Philadelphia, PA: 2004.
126. Topping RE, Bolander ME, Balian G. Type X collagen in fracture callus and the effects of experimental diabetes. Clin Orthop 1994;2:220–228. [PubMed: 7955687]
127. Tuominen JT, Impivaara O, Puukka P, Ronnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. Diabetes Care 1999;22:1196–2000. [PubMed: 10388989]
128. Uchida T, Nakamura T, Hashimoto N, Matsuda T, Kotani K, Sakaue H, Kido Y, Hayashi Y, Nakayama KI, White MF, Kasuga M. Deletion of Cdkn1b ameliorates hyperglycemia by maintaining compensatory hyperinsulinemia in diabetic mice. Nat Med 2005;11:175–182. [PubMed: 15685168]
129. Valerio G, del Puente A, Esposito-del Puente A, Buono P, Mozzillo E, Franzese A. The lumbar bone mineral density is affected by long-term poor metabolic control in adolescents with type 1 diabetes mellitus. Horm Res 2002;58:266–272. [PubMed: 12446989]
130. Van Daele PL, Stolk RP, Burger H, Algra D, Grobbee DE, Hofman A, Birkenhager JC, Pols HA. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med 1995;122:409–414. [PubMed: 7856988]

131. Verhaeghe J, Van Herck E, van Bree R, Moermans K, Bouillon R. Decreased osteoblast activity in spontaneously diabetic rats. In vivo studies on the pathogenesis. Endocrine 1997;7:165–175. [PubMed: 9549042]

132. Verhaeghe J, Suiker AM, Nyomba BL, Visser WJ, Einhorn TA, Dequek J, Bouillon R. Bone mineral homeostasis in spontaneously diabetic BB rats. II. Impaired bone turnover and decreased osteocalcin synthesis. Endocrinology 1989;124:573–582. [PubMed: 2643507]

133. Verhaeghe J, van Herck E, Visser WJ, Suiker AM, Thomasset M, Einhorn TA, Faierman TA, Bouillon R. Bone and mineral metabolism in BB rats with long-term diabetes. Decreased bone turnover and osteoporosis. Diabetes 1990;39:477–482. [PubMed: 2180758](a)

134. Verhaeghe J, Visser WJ, Einhorn TA, Bouillon R. Osteoporosis and diabetes: lessons from the diabetic BB rat. Horm Res 1990;34:245–248. [PubMed: 2100283](b)

135. Verhaeghe J, Suiker AM, Visser WJ, Van Herck E, Van Bree R, Bouillon R. The effects of systemic insulin, insulin-like growth factor-I and growth hormone on bone growth and turnover in spontaneously diabetic BB rats. J Endocrinol 1992;143:485–492. [PubMed: 1402554]

136. Verhaeghe J, Thomsen JS, van Bree R, van Herck E, Bouillon R, Mosekilde LI. Effects of exercise and disuse on bone remodeling, bone mass and biomechanical competence in spontaneously diabetic female rats. Bone 2000;27:249–256. [PubMed: 10913918]

137. Wallace C, Reiber GE, LeMaster J, Smith DG, Sullivan K, Hayes S, Vath C. Incidence of falls, risk factors for falls, and fall-related fractures in individuals with diabetes and a prior foot ulcer. Diabetes Care 2002;25:1983–1986. [PubMed: 12401743]

138. Ward DT, Yau SK, Mee AP, Mawer EB, Miller CA, Garland HO, Riccardi D. Functional, molecular, and biochemical characterization of streptozotocin-induced diabetes. J Am Soc Nephrol 2001;12:779–90. [PubMed: 11274239]

139. Weinstock RS, Goland RS, Shane E, Clemens TL, Lindsay R, Bilezikian JP. Bone mineral density in women with type II diabetes mellitus. J Bone Miner Res 1989;4:97–101. [PubMed: 2718784]

140. Weissberg-Benchell J, Glasgow AM, Tynan WD, Wirtz P, Turek J, Ward J. Adolescent diabetes management and mismanagement. Diabetes Care 1995;18:77–85. [PubMed: 7698052]

141. Wergedal JE, Baylink DJ. Characterization of cells isolated and cultured from human bone. Proc Soc Exp Biol Med 1984;176:60–69. [PubMed: 6324225]

142. White, M. Insulin signaling pathway. Science's STKE [Online] http:// stke.sciencemag.org/cgi//cm/stkecm;CMP_12069 [Dec. 2003]

143. World Health Organization. Prevention and Management of Osteoporosis. Technical Report Series, No. 921. WHO Marketing and Dissemination; Geneva: 2003.

Table 1

Adult studies of bone density in type 1 DM (1995−2004)

Study	Ref. No.	*n* (F/M)	Age, yr, (range or means ± SD)	Comparison	DM Duration, yr (means ± SD)	Method	Findings	CGC
Ingberg et al.	52	38 (20/18)	33−55	Age-matched controls	33	DEXA	No change in BMD	
Liu et al.	69	33 (33/0)	20−37	Age-matched controls	14.5±5.7	DEXA (Hologic QDR 4500A)	↓ LS BMD, ↓ FN BMD; no change in APS BMD, W BMD, WB BMD	No
Lopez-Ibarra et al.	71	32 (10/22)	20−39	Z-score	At diagnosis	DEXA (Hologic QDR 1000)	↓ LS BMD, ↓ FN BMD, ~40% with osteopenia	No
Campos Pastor et al.	9	57 (30/27)	35.1±10.5	Z-score	16.9±8.1	DEXA (Hologic QDR 1000)	69% with ↓ LS, FN, or WT BMD at baseline. After 7 yr of intensive insulin treatment, 66% with ↓ BMD at 1 site	No
Kemink et al.	60	35 (14/21)	37.6±9.9	Age-matched controls	8.5±3.5	DEXA	↓ FN BMD, ↓ LS BMD, osteopenia in 67% of men, 57% of women	No
Rozadilla et al.	99	88 (43/45)	28.9±8.8	Z-score	11.2±6.4	DEXA (Hologic QDR 1000)	Small ↓ in LS BMD, no change in FN BMD	No
Tuominen et al.	127	56 (27/29)	52−72	Age-matched controls	~18 yr (all developed DM after age 30)	DEXA (Norland XR-26 Mark II)	↓ FN/trochanter BMD	NS
Christensen et al.	12	53 (53/0)	31 pre-MP 22 post-MP	*T*-score	15.3±1.7 (pre-MP) 27.8±3.6 (post-MP)	DEXA (Hologic QDR 2000), SPA	↓ BMD in post-MP women with type 1 DM; no difference in pre-MP	No
Hampson et al.	39	31 (31/0)	42.4±8.9	Age-matched controls	20.2±10.5	DEXA (Hologic QDR 1000)	↓ FN BMD vs, controls (P = 0.08)	No
Lunt et al.	73	99 (99/0)	42 (median)	Z-score	27 (median)	DEXA	No difference from normal	
Miazgowski et al.	81	54 (23/31)	36.9±8 (F) 40.5 ±8 (M)	Age-matched controls	~16±8	DEXA (Lunar DPX-L)	LS BMD, ↓ WB BMD; ↑ incidence of osteopenia/ osteoporosis	No
Kayath et al.	58	23 (NS)	21−53	Z-score	2−20	DEXA	↓ LS BMD, 11 of 23 points with osteopenia	No
Muñoz-Torres et al.	82	94 (49/45)	20−56	Z-score	12±8	DEXA (Hologic QDR 1000)	↓ LS BMD, ↓ FN BMD, ↓ WT BMD; osteoporosis in ~19%	No
Krakauer et al.	63	46 (NS)	51.7 ±11.3 to 55.9 ±11.5	Z-score for BMD Reference data for bone biopsy	14.4 ±10.2 to 15.8 ±11.7	SPA, DEXA (Hologic QDR 1000), Transiliac bone Bx.	↓ Radial BMD, normal rate of further bone loss over time	No
Forst et al.	30	41 (21/20)	36±15	Age-matched controls	19±7	DPA	↓ FN BMD, ↓ distal lower limb BMD, no change in LS BMD	No

DM, diabetes mellitus; FN, femoral neck; LS, lateral spine; APS, anterior-posterior spine; W, wrist, WT, Ward's triangle; WB, whole body; BMD, bone mineral density; pre/post-MP, pre/post-menopausal; CGC, correlation with glycemic control; NS, not specified; DEXA, dual-energy X-ray absorptiometry; SPA, single-photon absorptiometry; DPA, dual-photon absorptiometry.

Table 2

Pediatric studies of bone density in type 1 DM (1995−2004)

Study	Ref. No.	*n* (F/M)	Age, yr, (range or means ± SD)	Comparison	DM Duration, yr	Methods	Findings	CGC
Heap et al.	43	55 (25/30)	12−17	Age-matched controls	~3.8−6.7	DEXA + pQCT	↓ Tibia trabecular BMD, ↓ FN BMD, ↓ WB BMD, ↓ WB BMC	Yes
Liu et al.	69	39 (39/0)	13−19	Age-matched controls	7.1±3.9	DEXA (Hologic QDR 4500A)	No change	
Valerio et al.	129	27 (12/15)	9−17	Z-score	6.9±3.0	DEXA (Hologic QDR 1000)	Negative correlation between LS BMD *X*-score & Hb A_{1c}	Yes
Gunczler et al.	36	23 (16/7)	9.5±2.2	Z-score	~0.5	DEXA	↓ LS BMD, no change in FN BMD or WB BMD	NS
Ersoy et al.	22	30 (14/16)	11−16	Age-matched controls	“varying”	DPA	↓ LS BMD	No
Gunczler et al.	35	26 (11/15)	7−14	Age-matched controls	4.3±2.9	DEXA	↓ LS BMD; no change in FN BMD, WB BMD	No
De Schepper et al.	15	23 (8/15)	12.5±3.7	Z-score	2.8±1.5	DEXA (Hologic QDR 1000)	Normal LS BMD	
Pascual et al.	88	55 (29/26)	10.4±4.1	Age-matched controls	3.1±2.6	DEXA (Hologic QDR 1000)	Normal axial and appendicular BMD	No
Lettgen et al.	66	21 (8/13)	6.2−19.9	Age-matched controls	5.2±4.3	pQCT	↓ Trabecular, cortical, and total BMD	Yes

pQCT, peripheral quantitative computed tomography; BMC, bone mineral content.

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Table 3

Studies of bone density in type 2 DM (1995−2004)

Study	Ref. No.	*n* (DM) (F/M)	Age Range, yr	Comparison	DM Duration, yr	Methods	Findings	CGC
Strotmeyer et al.	117	566 (243/323)	70−79	Age-matched (HEALTHY ABC Study)	Variable, <5 to >20 yr	DEXA + spine QCT	↑ BMD of the hip, whole body and volumetric spine	No = BMD; Yes = bone vol.
Al-Maatouq et al.	3	104 (104/0)	Post-MP	Age-matched controls	NS	DEXA (Lunar)	↓ BMD in FN and LS	
Dennison et al.	14	65 (32/33)	59−71	Age-matched controls and IGT	Newly diagnosed	DEXA (Hologic QDR 4500)	↑ BMD in newly diagnosed women (P<0.001) and men (P<0.05)	NS
Kao et al.	57	153 (98/55)	54.8±12.5 (F) 54.3±13.3 (M)	Age-matched controls	Variable—newly diagnosed and previously diagnosed T2DM	DEXA (Hologic QDR 1500)	↑ BMD in women, no different in men	No
Sert et al.	109	277 (176/101)	30−60	Age-matched controls	6.5±5.3	DEXA (Hologic QDR 1500)	↑ BMD in FN in F/M, 51−60 yr ↓ BMD in LS in M, all ages	No
Sahin et al.	101	161 (161/0)	Post-MP	Age-matched controls	≥2 years	DEXA (Hologic QDR 4500)	↑ BMD in FN and LS	NS
Christensen and Svenden	12	32 (32/0)	11 pre-MP, 21 post-MP	*T*-score	3.0±1.2 (pre-MP) 7.0±1.7 (post-MP)	DEXA (Hologic QDR 2000), SPA	↑ BMD in post-MP	No
el Miedany et al.	19	60 (40/20)	F = all post-MP	Age-matched controls	NS	QCT of lumbar spine	↑ BMD in women, no difference in men	No
Isaia et al.	53	66 (66/0)	63.2 ±7.4 all post-MP	Age-matched controls	≥2 yr	DEXA (Hologic QDR 1000)	↑ BMD in FN	NS
Tuominen et al.	127	68 (34/34)	52−72	Age-matched controls	NS all developed DM after age 30)	DEXA	No change in BMD at FN, male or female	
Hampson et al.	39	21 (21/0)	42.5±5.5	Age-matched controls	7.6±5.0	DEXA (Hologic QDR 1000)	No change in BMD at any site; increased bone resorption markers	No
Sosa et al.	115	47 (47/0)	61.3±7.0	Available healthy control data (n = 252)	NS	DEXA (Hologic QDR 1000) + QCT	Normal BMD by DEXA and QCT	NS
Kwon et al.	65	185 (185/0)	35−74	Age-matched controls	0 to >16	DEXA (Lunar)	Slight ↑ BMD	NS
Krakauer et al.	63	63 (NS)	51.7 ±11.3 to 55.9 ±11.5	*Z*-score for BMD Reference data for bone biopsy	14.4±10.2 to 15.8 ±11.7	SPA, DEXA (Hologic QDR 1000), Transiliac bone Bx	Radial BMD *Z* -scores improved over time, indicating slower than expected rate of bone loss	No
Rishaug et al.	95	36 (15/21)	49−69	Age-matched controls	3−15 yr	DEXA (Lunar) + ultrasound	↑ Total body BMD in men only	NS
van Daele et al.	130	578 (335/243)	≥55 yr	Age-matched nondiabetics	NS	DEXA (Lunar)	↑ BMD at FN and LS	NS

IGT, impaired glucose tolerance.