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Effects of Type 1 Diabetes on osteoblasts, osteocytes and osteoclasts

Evangelia Kalaitzoglou, MD[a,b], **Iuliana Popescu, PharmD, PhD**[a], **R. Clay Bunn, PhD**[a,b], **John L. Fowlkes, MD**[a,b], and **Kathryn M. Thrailkill, MD**[a,b]

[a] University of Kentucky Barnstable Brown Diabetes Center, University of Kentucky College of Medicine, Lexington KY, 40536

[b] Department of Pediatrics, University of Kentucky College of Medicine, Lexington KY 40536

Abstract

Purpose of review—To describe the effects of Type 1 diabetes on bone cells.

Recent findings—Type 1 diabetes (T1D) is associated with low bone mineral density, increased risk of fractures and poor fracture healing. Its effects on the skeleton were primarily attributed to impaired bone formation, but recent data suggests that bone remodeling and resorption are also compromised. The hyperglycemic and inflammatory environment associated with T1D impacts osteoblasts, osteocytes and osteoclasts. The mechanisms involved are complex; insulinopenia, pro-inflammatory cytokine production and alterations in gene expression are a few of the contributing factors leading to poor osteoblast activity and survival and, therefore, poor bone formation. In addition, the observed sclerostin level increase accompanied by decreased osteocyte number and enhanced osteoclast activity in T1D results in uncoupling of bone remodeling.

Summary—T1D negatively impacts osteoblasts and osteocytes whereas its effects on osteoclasts are not well characterized, although the limited studies available indicate increased osteoclast activity, favoring bone resorption.

Keywords

Type 1 diabetes; bone cells; osteoblasts; osteocytes; osteoclasts

Introduction

Type 1 diabetes (T1D), caused by autoimmune destruction of beta-cells in the pancreas with resulting insulin deficiency, is a chronic condition often diagnosed in childhood or early adult life. Long-standing T1D is associated with a variety of complications such as

Corresponding author: Evangelia Kalaitzoglou, MD, University of Kentucky, UK Barnstable Brown Diabetes Center, 830 S. Limestone St., Lexington, KY 40536, evangelia.kalaitzoglou@uky.edu.

Compliance with Ethics Guidelines

Conflict of Interest

Iuliana Popescu, Kathryn Thrailkill, Robert Bunn, John Fowlkes, Evangelia Kalaitzoglou declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

nephropathy, neuropathy and retinopathy, especially when glycemic control is poor. In addition to these complications, studies have shown an increase in the risk of bone fractures and low bone mineral density in patients with T1D, even in early stages of the disease [1], and particularly in the presence of uncontrolled hyperglycemia [2]. This insult to the skeleton involves impairments in bone metabolism, both in terms of formation and resorption of bone which depends on normal function and communication of bone cells. In this review we will focus on specific findings and underlying mechanisms of the effects of T1D on three groups of bone cells: osteoblasts, osteocytes and osteoclasts.

Literature search and selection methodology

PubMed was used as the search engine to find the literature relevant to this review and for the selection process of the articles included in this paper. The search terms included, but were not limited to, the following: “bone” AND “diabetic mice” AND/OR “STZ” OR “streptozotocin” OR “streptozotocin-induced diabetic”, “osteoblasts” AND “Type 1 diabetes”, “insulin” AND/OR “IGF-1” AND “osteoblasts” AND “ Type 1 diabetes”, “gene expression” AND/OR “hyperglycemia” AND “osteoclasts” OR “osteoblasts”, “Type I diabetes” AND “bone loss” OR “bone turnover”, “gene expression” AND/OR “hyperglycemia” AND “osteoclasts” OR “osteoblasts”, “bone” AND “diabetes” AND “mechanical loading”, “osteocyte” AND “Type 1 diabetes”, “Sclerostin” AND “diabetes”, “bone” OR “osteoblast” OR “osteocyte” OR “osteoclast” AND “cytokine” OR “cytokines” OR “inflammation” AND “t1d” OR “type 1 diabetes”. Each author independently reviewed the literature that resulted from the search and selected articles of significant interest and importance. The articles were then discussed amongst authors and the final selection occurred based on authors’ agreement. Most of the cited articles are original articles, although a few are review papers.

Effects of Type 1 Diabetes on Osteoblasts

The increased risk of fractures and osteopenia that has been observed in patients with T1D is thought to occur, partially, due to poor bone formation [3]. Osteoblasts (OBs) are essential to bone formation; they synthesize collagen, mineralize osteoid and participate in bone remodeling. T1D effects on OBs and their progenitor cells have been studied extensively and appear to involve various mechanisms that synergistically act to cause osteoblast dysfunction.

Effects of Type 1 Diabetes on osteoblast progenitor cells

Gene expression of transcription factors involved in osteoblast differentiation is modified in T1D [4, 5]. Runt-related transcription factor 2 (Runx2), the master regulator of bone development, directs differentiation of mesenchymal cells into pre-osteoblasts, promotes the formation of the immature osteoblast and inhibits differentiation of mesenchymal cells into adipocytes and chondrocytes [6]. At early stages, it regulates the expression of major genes necessary for bone matrix protein synthesis, such as collagen (Col1a), osteopontin, integrin binding sialoprotein (Ibsp) and osteocalcin (OC). Runx2 is positively regulated by Dlx (drosophila distal less gene) and β-catenin and is inhibited by other transcription factors (CCAAT/Enhancer Binding Protein Delta (C/EBPδ), Distal-Less Homeobox 3 (Dlx3), Msh

Homeobox 2 (Msx2), Peroxisome Proliferator Activated Receptor Gamma (PPARγ), Signal Transducer and Activator Of Transcription 1 (Stat1), SMAD Family Member 3 (Smad3), etc.) [6, 7]. In animal models of insulin deficiency, Runx2 transcripts are reduced in bones early in the course of diabetes, and correction of hyperglycemia with insulin partially reverses this decrease in expression and the associated bone loss [4, 5]. In a streptozotocin (STZ)-induced diabetes-bone marrow ablation model, diabetic animals failed to adequately express Runx2 and its regulator, distal-less homeobox 5 (Dlx-5) [4]. In a mouse distraction osteogenesis model of bone regeneration, STZ-induced hyperglycemia resulted in downregulation of Runx2 and several of its targets in the regenerated bone, including matrix metallopeptidase 9 (MMP-9), matrix metallopeptidase 13 (MMP-13), Ibsp, Col1, phosphate regulating endopeptidase homolog, X-Linked (Phex), dentin matrix acidic phosphoprotein 1 (DMP-1), osteopontin and OC, as well as other osteoblast regulatory genes osterix (Osx), alkaline phosphatase (ALP), ameloblastin and vitamin D receptor [5]. However, other studies have shown no modification of Runx2 expression in insulinopenic conditions; for instance, studies using non-obese diabetic (NOD) mice (a model of spontaneous autoimmune diabetes) and a cohort of STZ-induced diabetic mice did not show differences of Runx2 or ALP expressions, between control and diabetic animals [8, 9]. The Wnt/beta catenin pathway, which is essential for osteoblast differentiation and regulation of bone formation in differentiated osteoblasts, has also been shown to be down regulated in the bone of STZ-induced diabetic animals [10], partly due to increased expression of sclerostin and dickkopf-related protein 1 (Dkk1), two inhibitors of Wnt signaling. Interestingly, several studies describing altered expression of osteoblast regulating genes, such as Runx2, Dlx5, Osx, ALP, OC, Col1 and osteoclast genes, including osteoprotegerin (OPG), MMP9 and receptor activator of nuclear factor kappa-B ligand (RANKL) in diabetic bones, found that zinc supplementation can prevent these dysregulations and protect bones from diabetes induced damage [11, 12].

In addition to decreased gene expression of osteoblast promoting genes, the expression of adipocyte differentiation markers, such as PPARγ 2, resistin and aP2 is increased in STZ-induced hyperglycemia models, indicating that marrow adiposity could contribute to the bone defects that accompany T1D [8]. In contrast to this hypothesis, a study involving treatment of diabetic mice with a PPARγ antagonist showed that although the number of marrow adipocytes was decreased as a result of the antagonist, the bone phenotype was not altered [13].

IGF-1 and insulin as trophic factors for osteoblasts

T1D is associated with low systemic insulin and insulin like growth factor-1 (IGF-1) levels in humans [14], whereas diminished gene expression of IGF-1, IGF-1 receptor (IGF-1R) and insulin receptor (IR) in bone marrow stromal cells (BMSCs) and low protein levels of IGF-1 and IGF-1R have been observed in STZ-induced diabetic rats [15]. IGF-1 is fundamental for growth and maturation of OBs; it has been shown to stimulate growth and differentiation of OBs from mesenchymal stem cells both *in vivo* and *in vitro* [16, 17] and it is essential for bone mineralization [18, 19]. IGF-1 actions on bone are mediated through the IGF-1 receptor [20]. Due to the fact that insulin and IGF-1 have significant molecular homology, insulin has the ability to bind to and activate the IGF-1R, albeit with approximately 100-fold

lower affinity, in addition to signaling through its own receptor, known as the insulin receptor (IR). Moreover, IRs are present in OBs and, when activated with insulin, osteoblast collagen production is increased [21, 22]. More recent studies have shown that mice lacking the IR in OBs have lower number of OBs, decreased trabecular bone formation, as well as lower osteocalcin levels [23], whereas mice lacking the IR in osteoprogenitor cells have post-natal growth restriction and decreased bone strength [24]. These data suggest that poor osteoblast activity and bone formation in T1D could be explained, at least in part, by the absence or decrease of IGF-1 and insulin signaling in cells of the osteoblast lineage.

Effects of Type 1 Diabetes on number and survival of osteoblasts

Low numbers of osteoblasts accompanied by low osteoid formation and mineralization have been documented in bones of rats and mice with autoimmune- or STZ-mediated diabetes [18, 25]; insulin and IGF-1 were found to partially reverse these findings [18]. The reduced numbers of osteoblasts observed could be secondary to apoptosis of osteoprogenitor cells in STZ-induced diabetic animals, perhaps due to oxidative stress present in diabetic bone [26, 27]. Parathyroid hormone, a hormone associated with anabolic effects on bone, is found to be low in children and adolescents with T1D [28], and when given intermittently, it improves bone density in diabetic mice by increasing mineralization and preventing osteoblast apoptosis [29].

Effects of Type 1 Diabetes on osteoblast activity

Several markers of osteoblast activity are altered in T1D, reflecting the negative effects of diabetes on osteoblast function. Osteocalcin (OC), a marker of late-stage osteoblast differentiation, is produced by the mature osteoblasts and is the main non-collagenous protein responsible for the development of bone inorganic matrix. OC has been shown to be decreased in animal models of spontaneous [30] or STZ-induced diabetes [31] and in humans with long-standing T1D [1, 32, 33], and is particularly affected by poor glycemic control [1, 34]. Both OC transcripts and serum levels are decreased, and they are partially restored with insulin treatment [35]. Amylin, which is co-secreted with insulin by the pancreas, has been shown to improve bone density in an STZ-induced diabetes animal model by affecting osteocalcin levels and bone formation, among other mechanisms [31]. Collagen production is also affected by insulinopenia; human osteoblasts, when cultured with sera from children with T1D, show decreased collagen synthesis [36]. Skeletal alkaline phosphatase, another late marker of osteoblast activity, has been found to be low in diabetic children and adults, confirming poor osteoblast function [32, 33], as well as in most animal models of STZ-induced diabetes [10, 8, 27]. Expression of other key genes important for osteoblast bone metabolism and remodeling such as proteolytic members of the metalloproteinase family MMP2 (matrix metallopeptidase 2) and MMP9 were found to be increased in an animal model of STZ-induced diabetes [11], whereas in a model pairing STZ-induced diabetes with distraction osteogenesis, MMP9 and MMP13 were decreased [5]. Interestingly, *in vitro* studies have suggested that some of the hyperglycemic effects on the expression of genes encoding extracellular matrix proteins such as osteonectin, osteopontin, and collagen I can be attributed to osmotic changes [37-39].

Hyperglycemic and inflammatory effects of Type 1 Diabetes on Osteoblasts

The toxic effects of hyperglycemia on osteoblasts have also been studied. Advanced glycation end products (AGEs) acting on the receptor for advanced glycation end products (RAGE) have been implicated in poor bone healing in diabetic animals [40]. Specifically, AGEs impair mineralization when present in a high glucose environment *in vitro* [41] and they increase bone marrow stromal cells (BMSC) apoptosis through inflammatory and oxidative stress-inducing mechanisms [42].

In addition to metabolic factors potentially regulating osteoblast activity, upregulation of inflammatory cytokines likely plays a major role in reducing osteoblast activity in T1D. Autoimmune destruction of the pancreatic beta cells by infiltrating immune cells triggers pancreatic and systemic upregulation of inflammatory cytokines in humans [43-45] and in animal models of STZ-induced diabetes [46]; moreover, T1D subjects with poor glycemic control exhibit higher levels of inflammation compared to well-controlled subjects [45]. Inflammatory cytokines that are systemically upregulated in T1D subjects, such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) have been demonstrated to have negative effects on osteoblast proliferation and differentiation *in vitro*, as well as inhibition of bone healing *in vivo* [47-50].

Although systemic elevations in cytokine levels and resulting inhibition of osteoblast proliferation, differentiation and function could explain the osteopenia observed in T1D subjects, inflammatory cytokine production by cell types present within the bone may have more direct negative effects on osteoblasts. Indeed, local production of inflammatory cytokines in bone tissue has been described in mouse models of STZ-induced diabetes [46, 51, 52]. Coe *et al* [52] demonstrated that bone marrow from diabetic mice stimulated osteoblast apoptosis in *ex vivo* cultures, an effect that was blocked by the addition of a TNF-α neutralizing antibody.

The cellular source of inflammatory cytokines in bone marrow is not clear; however, the number of bone marrow adipocytes increases in the long bones of NOD mice and mice with STZ-induced diabetes [9], and marrow adipocytes were shown to accumulate adjacent to a healing bone defect [5] in an STZ-induced diabetic mouse model. Marrow fat from rodents and humans, like white adipose tissue, is capable of secreting numerous cytokines [53]. Bone marrow adipocytes have been shown to have higher TNF-α gene expression when compared to white adipose tissue [54]. These results should be interpreted with caution however, as one study failed to detect a relationship between increased bone marrow adipose tissue and T1D [55].

Summary

The state of insulin and IGF-1 deficiency associated with T1D causes alterations in transcription of osteoblast promoting genes, and an inflammatory and hyperglycemic environment that ultimately affects osteoblast differentiation, activity and survival. Insulin and IGF-1, as well as other bone anabolic factors (PTH, zinc) appear to reverse some of these effects and could prove beneficial in the treatment of T1D related bone disease.

Effects of Type 1 Diabetes on Osteocytes

As new bone mineralizes, terminally differentiated osteoblasts become embedded within lacunae of mineralized tissue transforming into osteocytes, the most abundant of bone cells. These embedded cells maintain their intercellular communication by multiple filopodial cellular processes which extend throughout the lacunar-canalicular pore system, linked by gap junctions [56]. These mature bone cells function to support bone structure, to detect changes in the mechanical loading of bone, and to communicate remodeling needs to other cell types. Their role in mechano-sensation is paramount to inducing skeletal shape, density and size adjustments that are needed to respond to changing biomechanical forces. However, osteocytes also participate in osteolytic activities, promoting mineral release from the skeleton via perilacunar remodeling, in certain circumstances such as lactation. Unfortunately, due to their relative inaccessibility, data regarding the effects of T1D, specifically, on osteocyte activity or cell survival is more limited than with other cell types.

Osteocyte activity, sclerostin and T1D

Sclerostin, a product of osteocytes and an inhibitor of the Wnt signaling pathway, impedes bone formation and promotes osteoblast apoptosis; it is, therefore, a negative regulator of bone mass. Osteocyte secretion of sclerostin is acutely regulated by mechanical loading [57] and by a variety of physiologic conditions, some leading to decreased sclerostin levels (i.e., mechanical loading, high PTH [58, 59], high estrogen [60, 61]) and some leading to increased sclerostin levels (i.e., mechanical unloading [61, 62], advancing age [60, 61, 63], skeletally detrimental drugs [64]). In T1D, as expected for a disease characterized by lower bone formation and Wnt-signaling inhibition, [10] increases in sclerostin gene expression [10, 65] have been reported, *in vivo*, in STZ-induced diabetic rats [65]. Moreover, *in vitro*, osteocytes treated with high glucose (22 mM [66] or 30 mM [67]) or with advanced glycation end-products (AGEs) [66] exhibit increased expression of sclerostin protein and mRNA, along with osteocyte apoptosis [66]. In contrast, treatment with sclerostin-neutralizing antibodies has been shown to reverse the deficits in bone mass, bone strength and fracture healing that are evident in rodent models of both T1D [68] and T2D [69] confirming the link between the “ high-sclerostin” state of diabetes and reduced bone formation in this disease.

Increased sclerostin levels have also been reported in some [70, 71] but not all [72] clinical studies of adults with longstanding T1D, but not in children [73], possibly indicative of an exaggerated age-related increase in sclerostin levels in T1D [70]. Interestingly, this is similar to studies in adult patients with T2D, and with prediabetes, which also demonstrate increased serum sclerostin levels [72] [74-77]; in T2D, specifically, sclerostin levels correlate positively with glycated hemoglobin levels and with measures of insulin resistance [74, 76, 77], but negatively with bone-specific alkaline phosphatase (BSAP) [74]. However, in contrast to several studies in postmenopausal non-diabetic women which also show an increased fracture risk in women with the highest sclerostin levels [78, 79], one recent study of T1D patients in Denmark found the opposite; specifically, T1D patients with the “highest tertile of sclerostin had an 81% decreased risk of a fracture compared with the lowest tertile” [80].

DMP1, MEPE, FGF23 and T1D

Currently, very little is known about the effect of T1D on other osteocyte-expressed proteins, such as dentin matrix protein-1 (DMP1), fibroblast growth factor 23 (FGF23) or matrix extracellular phosphoglycoprotein (MEPE). While acute hyperinsulinemia via euglycemic clamp technique has been shown to increase serum FGF23 levels in patients with T2D, serum levels of FGF23 in patients with T1D do not appear to differ from normal range values [81]. Pro-inflammatory stimuli, *in vitro*, have also been shown to increase osteocyte secretion of FGF23 [82], but a direct effect of pro-inflammatory cytokines on osteocyte function in T1D has, to our knowledge, not been reported.

Osteocyte number and survival and T1D

The topology of the lacunar-canalicular network appears to be largely genetically pre-programmed and stable, so as to provide the necessary requirements for osteocyte cell survival [83]. However, a significant reduction in lacunar density has been reported in both Akita mice (a model of spontaneous T1D) [83], and in STZ-treated rats [84], possibly reflecting the decrease in osteoblast differentiation that is expected in T1D. A decrease in sclerostin-positive osteocyte number, identified by immunostaining, has also been demonstrated in the tibiae of STZ-induced diabetic mice, accompanied by a reduction in osteocyte viability [85]; others have reported a decrease in maxillary alveolar bone osteocyte number in a rat model of diabetic periodontitis [86]. Similarly, using a rat model of partial insulin deficiency (nicotinamide/streptozotocin), a reduction in osteocyte density was identified in hyperglycemic animals, and osteocyte density was restored by co-therapy with an insulin-sensitizer (metformin) [87]. Overall, a reduction in osteocyte density appears to be a consistent finding in animal models of insulinopenia.

Mechanical Loading and T1D

Mechanical loading, as a stimulus for bone accrual, is a potent adaptive response orchestrated by osteocytes. The impact of T1D on bone response to mechanical loading had been investigated, both *in vivo* and *in vitro* [88]. Male Akita mice, a model of severe insulin-deficiency diabetes, demonstrate impaired bone formation in response to repetitive mechanical loading of the ulna, when compared to wild-type mice or to female Akita mice (a model of milder blood glucose elevation) [88]. Consistent with these findings, exposure of MLO-Y4 osteocytes to hyperglycemic culture conditions has been shown to: 1) impair the osteocyte mechanosignaling response to oscillatory fluid shear stress [88, 89]; and to 2) attenuate the expected activation of anti-apoptotic pathways [88].

Summary

While comparatively little is known about the effects of T1D on osteocytes, T1D or animal models of insulin deficiency are characterized by a reduction in osteocyte density, yet an increase in expression or concentration of the osteocyte biomarker, sclerostin. The association between increased secreted or circulating sclerostin levels in diabetes with the findings of reduced osteocyte/lacunar density and/or osteocyte survival might suggest that in T1D, similar to other low bone formation conditions (i.e., glucocorticoid-induced

osteoporosis [90]), osteocyte apoptosis paired with increased sclerostin, may contribute to the uncoupling of bone remodeling to favor bone resorption.

Effects of T1D on osteoclasts

Bone resorption, mediated by osteoclasts, plays a key role in bone (re)modeling and osteogenesis in T1D. In humans, T1D with poor glycemic control is associated with increased bone resorption and bone loss over time [91]. These early data suggested increased osteoclastic activity in T1D as a possible causative factor for diabetic bone disease.

Modulation of RANK/RANKL/OPG system by Type 1 diabetes

Receptor activator of nuclear factor-kappa B ligand (RANKL) binds receptor activator of nuclear factor-kappa B (RANK) in pre-osteoclasts and promotes osteoclast differentiation, survival and activation [92]. The interaction of RANKL with OPG, a decoy receptor of RANKL, and subsequently their ratio plays a key role in the downstream osteoclast maturation pathways. In this mechanism, OPG appears to act as a negative regulator of osteoclastogenesis. Recent data suggest that increased bone turnover may be associated with increased soluble RANKL (s-RANKL) activity, as seen in children and adolescents with T1D, which would promote increased osteoclast activity and bone resorption [93]. In support of this theory, it has been shown that peripheral blood derived osteoclasts from humans with T1D are less sensitive to OPG than osteoclasts from control subjects, indicating a heightened sensitivity in RANKL/RANK signaling [94]. Genes coding for the RANKL/RANK/OPG system and the corresponding markers were found to be altered in humans with T1D and insulinopenic animal models. Some studies found increased OPG gene expression in young patients with T1D [2] and in chronic hyperglycemic conditions *in vivo* [11] and *in vitro* [37], which suggests a decreased osteoclast differentiation and a possible adaptive protection against excessive bone resorption in diabetes. Others found downregulation of OPG expression in STZ-induced diabetes in mice [46]. In addition, bone RANKL mRNA levels are increased in studies of STZ-induced diabetes [11] and in an osteoblast cell line under hyperglycemic conditions [37], but to a lesser extent than OPG, whereas other studies show RANKL induced osteoclastogenesis to be reduced *in vitro* by high glucose concentrations, insulin deficiency [95] and AGEs [96]. These findings suggest that RANKL/RANK induced osteoclast activation might not be the predominant mechanism throughout the course of T1D that drives bone resorption, and that other factors may interfere with osteoclast activity.

Other markers of increased osteoclast activity in Type 1 diabetes

Long term insulinopenic rodent models demonstrate that osteoclastic activity is upregulated, as indicated by studies showing increased cathepsin K (a lysosomal protease active in osteoclast bone resorption), and tartrate-resistant acid phosphatase (TRAP) expression in bones of STZ-induced diabetic rats [97] and increased markers of bone turnover such as C-terminal telopeptide [98]. In addition, osteoclast cultures from NOD mice contain smaller osteoclasts, yet they resorb more bone than control osteoclasts and express more cathepsin K, MMP-9 and pro-osteoclastogenic mediators [99]. In other studies, cathepsin K was significantly increased in mice with severe diabetes (high-dose STZ) but not with low-dose

STZ-induced diabetes or a short duration of diabetes [12, 9, 97, 100]. Contrary to these finding, a recent study in STZ-induced diabetic mice (late onset) shows significantly lower mRNA levels of both cathepsin K and TRAP compared to control mice, in addition to lower osteoclast number and suppressed angiogenesis [25].

The variability in reports regarding osteoclastic activity in T1D has led some to hypothesize that the timing of onset of T1D on osteoclast gene regulation may provide a possible explanation as to why some genes are differentially regulated at certain intervals [100] while others suggest that osteoclasts may be more responsive to resorptive stimuli in T1D as the disease progresses. The duration of diabetes and the disease-associated inflammatory environment might also contribute, as reduced bone resorption and turnover during diabetes advancement, could be explained by changes in pro- and anti-inflammatory cytokines in bone [46, 101]. Unfortunately, the role of cytokines on osteoclast function in Type 1 diabetes is not well documented. In a single study, osteoclasts from NOD mice have been characterized in the presence and absence of inflammatory stimuli [99] and were found to not only lack a response to LPS-mediated deactivation, but also to be more active compared to control osteoclasts in the presence of LPS, as evidenced by increased cathepsin K and MMP-9 secretion.

Summary

Overall, osteoclast activity appears to be enhanced in T1D, although the mechanisms underlying this finding are not well understood. The fine tuning of osteoclast gene regulation in T1D and insulinopenic animal models seems to be dependent on the severity and the duration of the disease as well as on concurrent inflammatory mediators, all of which appear to contribute to the variability seen in gene expression and levels of markers of osteoclast activity. Treatments targeted to diminish osteoclast activity may have a role in the prevention of diabetic bone disease in T1D. For example, anti-resorptives, such as bisphosphonates, have been shown to have a positive effect in preventing bone loss in a mouse model of T1D [102].

Conclusions

Type 1 diabetes is associated with insulin deficiency and impaired bone homeostasis. Osteoblasts, osteocytes and osteoclasts are all affected by T1D, in terms of differentiation, survival and activity (Table 1). Although STZ-induced diabetes may mimic the hyperglycemic environment of Type 1 diabetes, when interpreting results from *in vitro* studies, the fact that such studies may be conducted under different conditions (such as higher glucose concentrations) compared to those observed in diabetic patients should be taken into consideration. A breadth of studies have addressed the effects of an insulinopenic and hyperglycemic environment on osteoblasts, with the majority demonstrating a decrease in bone formation, bone mineralization and poor osteoblast activity under these conditions; however, the effects of T1D are not very well characterized in osteocytes and osteoclasts, with the limited studies available reporting either no changes or increases in bone resorption and remodeling. Further studies focused on the impact of T1D on osteocytes and osteoclasts are needed to validate these findings and delineate the underlying mechanisms.

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••Of major importance

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Table 1

Effects of Type 1 diabetes on osteoblasts, osteocytes and osteoclasts.

Cell type	Markers of activity	Differentiation and survival	Other factors
Osteoblast	↓ Osteocalcin [1, 30-33] ↓ Collagen [36] ↓/↔ Alk Phosphatase [10, 8, 27, 32, 33]	↓/ ↔ Runx-2 [4, 5, 8, 9] ↓ Wnt/ β-catenin pathway [10] ↑ PPAR-γ [8] ↓ Number [18, 25] ↓ Survival/↑ apoptosis [26, 42]	↓ IGF-1/ IGF-1 R [14, 15] ↓ Insulin/ IR [14, 15] ↓ PTH [28] ↑ TNF-α, IL-1, IL-6 [47-50] ↑ AGEs [40-42]
Osteocyte	↑ Sclerostin [10, 66] ↔ FGF23 [81]	↓ Viability, ↓ number [85] ↓ Density [87]	Response to mechanical loading [88, 89]
Osteoclast	↓/↑ RANKL* [11, 37, 93, 95, 96] ↑/↓ OPG* [2, 11, 37, 46] ↓/↑OPG/RANKL* [11, 37, 94] ↑/ ?↓ Cathepsin K* [12, 9, 25, 97, 100] ↑/↓ TRAP* [25, 97] ↑ CTX [98]	No response to LPS deactivation [99]	?Inflammation* (Interleukins, TNF-α)

With * are shown controversial or not well studied findings. Increased (↑), decreased (↓) and unchanged (↔) effects are indicated.