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Skeletal growth and bone mineral acquisition in type 1 diabetic children; abnormalities of the GH/IGF-1 axis

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Abstract

Type 1 Diabetes Mellitus (T1DM) is one of the most common chronic diseases diagnosed in childhood. Childhood and adolescent years are also the most important period for growth in height and acquisition of skeletal bone mineral density (BMD). The growth hormone (GH)/insulin like growth factor -1 (IGF-1) axis which regulates growth, is affected by T1DM, with studies showing increased GH and decreased IGF-1 levels in children with T1DM. There is conflicting data as to whether adolescents with T1DM are able to achieve their genetically-determined adult height. Furthermore, data support that adolescents with T1DM have decreased peak BMD, although the pathophysiology of which has not been completely defined. Various mechanisms have been proposed for the decrease in BMD including low osteocalcin levels, reflecting decreased bone formation; increased sclerostin, an inhibitor of bone anabolic pathways; and increased leptin, an adipocytokine which affects bone metabolism via central and peripheral mechanisms. Other factors implicated in the increased bone resorption in T1DM include upregulation of the osteoprotegerin/ receptor-activator of the nuclear factor- κ B ligand pathway, elevated parathyroid hormone levels, and activation of other cytokines involved in chronic systemic inflammation. In this review, we summarize the clinical studies that address the alterations in the GH/IGF-I axis, linear growth velocity, and BMD in children and adolescents with T1DM; and we review the possible molecular mechanisms that may contribute to an attenuation of linear growth and to the reduction in the acquisition of peak bone mass in the child and adolescent with T1DM.

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Keywords

Type 1 diabetes Mellitus (T1DM); bone mineral density (BMD); growth velocity; growth hormone (GH); insulin-like growth factor-1 (IGF-1)

INTRODUCTION

TYPE 1-DIABETES Mellitus (T1DM) results from an immune-mediated destruction of the beta-cells of the pancreas leading to insulin deficiency, elevated blood glucose, and ketosis when not treated. Previously designated as juvenile or insulin-dependent diabetes mellitus (IDDM), T1DM has its onset in patients most frequently from infancy through the third decade of life. T1DM is one of the most common chronic pediatric diseases and it has a major impact on public health. According to “The SEARCH for Diabetes in Youth Study” (a multicenter study aimed at understanding the epidemiology in children and youth), reported in 2014, (1) about 200,000 youth (less than 20 years old) and over a million adults (20 years old and older) live with T1DM in the USA. The incidence of T1DM has been globally rising during the past decades (2). By the year 2050, it is expected that 600,000 youth and about four million people over the age of twenty will live with T1DM—a vast increase in the number of patients.

Patients with T1DM frequently have alterations in their growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis. They may fail to achieve normal peak bone mass, increasing the likelihood of developing osteoporosis and associated fractures later in life. This review will summarize our current knowledge of abnormalities in the GH/IGF-1 axis in T1DM and their potential relationship to metabolic bone disease. Although renal insufficiency may develop as a long-term complication of T1DM and contribute to altered bone mineral density (3), this review will be limited to pathology and mechanisms that occur in the context of normal renal function.

THE GROWTH HORMONE (GH)/INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) AXIS IN PATIENTS WITH T1DM

One of the most important axes that contribute to bone growth is the GH/IGF-1 axis. Pituitary-secreted GH regulates hepatic production of IGF-1 and its serum levels and regulates bone acquisition via its direct effects on osteoblasts and osteocytes. Linear and radial bone growth as well as gains of bone mineral density (BMD), are greatly affected by GH, the endocrine (serum) IGF-1, and bone-tissue derived IGF-1 (autocrine/paracrine IGF-1). Together with insulin, GH and IGF-1 also regulate carbohydrate and lipid metabolism to facilitate body growth, puberty, and maturation.

Several studies have reported abnormalities in the GH/IGF-1 axis in patients with T1DM. Specifically, patients typically display hypersecretion of GH (4–7) and low serum IGF-1 levels (8–11). Hypersecretion of GH in T1DM children is typically seen during puberty, a period when insulin requirement increases, due to the effects of physiological pubertal insulin resistance (12). Hypersecretion of GH likely results from the low IGF-1 levels (13) eventually leading to hepatic GH resistance. Low levels of IGF-1 quite possibly relate to

both portal insulinopenia and GH resistance in the liver (14). In a study with a small T1DM cohort (12 subjects), glargine treatment increased hepatic insulin action and was associated with increases in serum IGF-1 levels (15). Decreases in serum IGF-1 levels in 36 patients with T1DM (average age 13–18 years) were linked to increases in the inflammatory cytokines IL6 and IL8, which are known to inhibit IGF-1 transcription (16, 17).

A study of 92 Spanish children with IDDM showed that their IGF-1 levels were significantly lower at every developmental stage when compared with matched control subjects (11). Their IGF-1 levels were also negatively correlated with glycemic control, particularly during puberty, as was previously described in an earlier study (18). Another study of 137 newly diagnosed subjects (age 17 years and younger) has also shown that poor glycemic control (higher HbA1c) was associated with low levels of IGF-1, but this was independent of age or pubertal status (19). In a group of 86 T1DM patients (average age ~12 years) it was found that IGF-1 and IGF-1 receptor levels were significantly lower in mononuclear cells from peripheral blood of these patients as compared to controls (17).

Abnormalities in the GH/IGF-1 axis in T1DM included changes in levels of the IGF-1 binding proteins (IGFBPs) that modulate IGF-1 bioactivity in serum and tissues (20). Several studies have reported increased levels of IGFBP-1 in T1DM patients, which are negatively regulated by insulin and believed to contribute to growth impairments seen in affected children via sequestration of IGF-1 (10, 11, 21, 22). IGFBP-2 seemed to increase in T1DM patients and may relate to their increased body adiposity (10). In most studies IGFBP-3, the main carrier of IGF-1 in serum [as part of the ternary complex (IGFBP-3, acid labile subunit and IGF-1)], was not altered in T1DM (10, 11, 21).

Abnormalities in the GH/IGF-1 axis in T1DM children contribute to stunted pubertal growth and reductions in acquisition of peak bone mass (23–26). In 1930, Mauriac described a girl with T1DM who had poorly controlled diabetes and showed hepatomegaly and short stature (27). Nowadays, Mauriac syndrome is rare. However, reductions in final height and low BMD in children with T1DM are reported (23, 26, 28–30) in some but not all studies.

HEIGHT AND HEIGHT VELOCITY IN ADOLESCENTS WITH T1DM

Linear growth (height gain) is determined by the height of the growth plates at the end of long bones. Cells of the growth plate (chondrocytes) are found in three stages: rest, proliferation, and hypertrophy. GH and IGF-1 play major roles in chondrocyte proliferation, differentiation, and hypertrophy, which control linear growth, especially during puberty. Absence of GH/IGF-1 action leads to short stature in both human and animal models (31). The reductions in serum IGF-1 levels found in T1DM were therefore thought to be the cause for growth abnormalities in these subjects. However, this was not obvious in all studies (summarized in table 1) as some reports indicated improved and others impaired growth velocity.

Large retrospective studies have shown that children with T1DM gained more weight during infancy and showed a higher linear growth when compared to controls at the time of diagnosis (32–36). Songer et al have compared 200 newly diagnosed T1DM subjects with their non-diabetic siblings and found that T1DM children (aged 5–9 years) at the diagnosis

were taller than expected (37). However, during pubertal growth T1DM children showed attenuation of height gain (37), which was subsequently shown to be sex-dependent (38, 39), and attributed to reductions in serum IGF-1 levels. Several years later, a study from the Oxford district of 184 children with T1DM also found that children aged 5–10 ($n=73$) years at diagnosis were taller than controls at the same age, while those diagnosed under the age of 5 years ($n=37$) were shorter, and those diagnosed at 10 years or older ($n=74$) were similar in size to controls (40). In this study, the pubertal growth spurt was blunted in all groups but was more profound in females (30).

There are conflicting reports showing normal or slightly reduced final height in T1DM subjects. In the Oxford study, (40) final heights were not significantly different from the mid-parental height SDS despite a reduced growth spurt during puberty. Bonfig et al collected final adult height data on 1685 patients in Germany with T1D diagnosed before the age of 10 years (41): the mean height-SDS (H-SDS) at the time of diagnosis in the patients was 0.25 ± 0.95 SDS. The final adult height in girls was 167.1 ± 6.2 (-0.16 ± 0.97 SDS) cm and in boys 179.6 ± 7.1 cm (-0.17 ± 1 SDS). When the subjects were divided into different groups based on glycemic control, it was noted that the group with $HbA1c < 7$ had final adult height $+0.030$ SDS. The groups with $HbA1c$ between 7–8 % and > 8 % had final adult SDS of -0.122 and -0.308 respectively, suggesting that poor glycemic control is associated with slightly decreased final adult height. Similarly, Parathasarathy et al measured height velocities in 160 children with a mean age of 9.4 years and found that height velocity at the end of 2 years was 5.5 ± 2 cm (-0.3 ± 1.5 SDS) (42). Children on a basal bolus regimen had a better $HbA1c$ of 8.4 ± 1.7 % in comparison to those on split mix insulin, who exhibited $HbA1c$ of 9 ± 1.8 %. Children on the basal bolus regimen also had a higher growth velocity of 0.5 ± 1.6 vs children on split mix insulin -0.3 ± 1.4 . This study showed again that poor glycemic control was associated with decreased growth velocity.

When reconciling the data, we should review the ages reported in each study, consider heterogeneity between populations, and pay attention to the control groups selected for the studies. We should also remember that genetic variations contribute to adult height, and these variations differ between populations. In summary, data so far suggest that children with T1DM, who are well-controlled (for blood glucose, i.e. $HbA1c$), will achieve normal final height (41).

BONE MINERAL DENSITY (BMD) IN CHILDREN AND ADOLESCENTS WITH T1DM

Unlike the minor reductions detected in longitudinal bone growth (height) in T1DM subjects, reductions in BMD (43–48) are more profound and may have implications on adult bone health. Possible complications include osteoporosis, risk of fracture (49), issues with bone healing (50), and issues with bone regeneration.

In the 1970s, before widespread use of dual-energy X-ray absorptiometry (DEXA), peripheral quantitative computed tomography (pQCT), and broadband ultrasound attenuation (BUA), studies of T1DM children and adolescents reported loss of skeletal tissue that occurred early and was unrelated to the severity or duration of the disease (51). Later on, using photon absorptiometry and radiogrammetry on 78 T1DM patients (mean age 15.2 yr, mean duration of diabetes 6.7 yr), the authors found reduced bone mass without evidence

of impaired overall growth or delayed maturation (52). Reduced bone mass did not vary with serum glucose control in this study. Using the same method of photon absorption, mineral density of the forearm bone in 196 T1DM patients (age 6–26 years) was significantly lower than that in 124 controls (53). Further, in a study of 45 diabetic patients (aged 5.2–19.4 years) and 246 healthy non-diabetic children (aged 2.8–20.8 years), BMDs measured by DEXA in the lumbar spine (L1-L4) and at the distal third forearm were significantly lower in diabetic patients than in controls, most notably during the pubertal spurt (46). The greatest differences were found in males and in the trabecular bone. Here again, HbA1c and duration of diabetes did not correlate with BMD. These data are in line with data from comparisons of BMC by DEXA of 127 T1DM patients and 319 controls (aged 6 to 20 years) (38). T1DM patients have shown significantly lower bone mineral content (BMC)/lean body mass than controls. Low serum IGF-I levels correlated independently with BMC in patients of all ages and both sexes, whereas disease duration and HbA1c levels did not.

However, there are several studies that established correlations between low BMD, low IGF-1 and glycemic control (namely HbA1c levels). Data from 55 T1DM adolescents and 95 controls whose tibiae were analyzed by pQCT (44) show that subjects with T1DM had lower tibia trabecular and femoral neck density, as well as lower whole body mineral content and density (by DEXA). Here, the mean HbA1c was inversely related to tibia trabecular bone density and whole body bone mineral content (BMC). Similarly, analyses of BMD by DEXA in 86 T1DM children and adolescents and 90 controls revealed that patients with T1DM had low BMD, which worsened with poor glycemic control (54). These data correlated with reduced IGF1, IGF1R and TGF β 1 gene expressions in peripheral blood mononuclear cells in the T1DM patients. Negative correlation between lumbar BMD z-score and HbA1c was also found in data from 27 T1DM adolescents (age 13.1 $\pm$ 1.7 years) by DEXA, as compared to controls (55). Measurements of bone quality by BUA at the calcaneal site of 26 pre-pubertal T1DM children (age 4.1–13.1 years) and 45 age-, sex- and body-size-matched control children showed significant reductions in BUA z-score in T1DM as compared to controls (43) and a significant negative correlation with HbA1c ($r = -0.59$; $P = 0.007$). Comparable findings were reported in a study of 42 T1DM (ages 12–18) and 199 controls showing reduced bone mass and bone size in T1DM patients (despite normal growth and maturation) that negatively correlated with HbA1c (56).

Notwithstanding the aforementioned studies, the controversy over the impact of T1DM on bone health still exists, as several studies reported normal BMD in T1DM patients (57–59) or only site specific low BMD (60). Lastly, we mention that skeletal evaluations in patients with T1DM were done using different methodologies, each with considerable limitations. When assessing skeletal health, one should evaluate tissue mineral content, tissue geometry, microarchitecture, and quality. The duration of the disease and the complications at the time of BMD measurements should also be accounted for, as T1DM-associated microvascular disease associates with deficits in cortical and trabecular BMD (61). Reconciling the data reported herein, we conclude that patients with T1DM show reductions in serum IGF-1, which are associated with low BMD. Osteopenia in young patients with T1DM is a common complication that may/may not relate to the duration and/or severity of the disease. A meta-analysis of 23 studies (in adults and children) from 16 countries included analyses of 2716 females of which 965 with T1DM and 1230 males of which 537 with T1DM, evaluated

BMD at 5 bone sites (whole body, spine, femur, hip, forearm), and found low BMD at all sites in T1DM patients, which was sex and age dependent (2).

POSSIBLE MOLECULAR MECHANISMS INVOLVED IN INHIBITION OF ACHIEVING PEAK BONE MASS IN T1DM SUBJECTS

The pathophysiological mechanisms underlying the reduced BMD in T1DM children are unknown. Numerous studies have used primary osteoblast and osteoclast cultures from human and rodent models of T1DM, as well as osteoblast-like and osteoclast-like cell lines, to understand how hyperglycemia affects cellular differentiation, function, apoptosis and eventually bone mass in T1DM subjects. These studies have advanced our understanding of bone cell function under conditions of hyperglycemia in vitro. However, in the current review, we will focus primarily on clinical evidence from children (pre-pubertal and pubertal age, and not adult T1DM) that shed light on the possible molecular mechanisms of reduced BMD in T1DM patients.

Impaired BMD and bone metabolism in children diagnosed with T1DM is attributed to several factors. Humans and animal models show that bone resorption is minimally affected in T1DM, while bone formation is severely compromised. Reduced bone-forming osteoblast activity during bone modeling results from multiple local factors in the bone marrow as well as systemic factors, all affecting osteoblast cell differentiation and function.

Insulin, IGF-1 and GH—Insulin, GH, and IGF-1 are all anabolic hormones, which all directly influence bone cells and potentially contribute to low BMD in T1DM. Diminished insulin signaling in the bones of T1DM subjects may contribute to decreased osteoblast differentiation. However, in vitro studies exhibit osteoblast differentiation without addition of insulin. Furthermore, in vivo studies with global insulin (IR) receptor knockout mice that were rescued by over-expression of human IR in the pancreas, liver, and brain suggested that reduced insulin receptor signaling in bone is not a major factor contributing to bone loss in T1DM (62). We have discussed throughout the importance of the GH/IGF-1 axis in bone acquisition in patients with T1DM. In fact, human data support the notion that lack of IGF-1 has negative effects on bone and associate with osteopenia in T1DM patients (but not necessarily decrease in linear growth) (Figure 1). The roles of GH and IGF-1 in bone acquisition have been documented in numerous studies using animal models (reviewed in (31)), both of which play critical roles in osteoblast differentiation, collagen deposition, and bone mineralization.

Osteocalcin is an osteoblast-derived hormone that has been shown to regulate bone formation as well as beta-cell function, body adiposity, and overall glucose metabolism (63, 64). The possible contribution of osteocalcin to reduced BMD in T1DM was tested in several studies, mostly using adult patients. In a study of 78 patients aged 11.5 ± 4.3 years with T1DM and 11 controls, serum osteocalcin negatively correlated with HbA1c levels (65). In that study osteocalcin also negatively correlated with leptin, which reflects body adiposity. A study with adult T1DM patients confirmed that long duration of T1DM associates with low osteocalcin and inversely correlates with HbA1c and BMI (66). Reduced

serum osteocalcin indicates reduced number or function of osteoblasts contributing to reduced bone formation in T1DM.

Osteoprotegerin/RANKL—Osteoprotegerin (OPG), a member of the tumor necrosis factor receptor (TNFR) family, is a circulating glycoprotein which serves as a decoy receptor for the receptor-activator of the nuclear factor- κ B ligand (RANKL). The OPG/RANKL system regulates osteoclast activity, namely bone resorption. Note that OPG/RANKL have multiple other functions and are also implicated in cardiovascular diseases associated with diabetes. Several studies in T1DM children have demonstrated increases in serum soluble RANKL (sRANKL). In a study with 40 T1DM children and adolescents (age 13.04 ± 3.53 yr) and 40 controls, it was found that patients had higher levels of sRANKL and OPG and significantly lower BMD (67). Similarly, plasma OPG levels in 26 pre-pubertal T1DM children (4.1–13.1 years) were higher and significantly correlated with HbA1c when compared to controls (43). In 56 children with T1DM (aged 12.1 ± 3.4 yr) and in 46 controls serum OPG levels significantly increased, but RANKL did not change. OPG was positively associated with HbA1c and negatively associated with BMI (68). Lastly, in a cross-sectional study with 75 children and adolescents with T1DM and 100 control subjects aged 6–20 years old, T1DM patients showed low BMD and significantly increased OPG gene expression in peripheral blood lymphocytes (28). Together, most studies suggest that OPG is elevated in T1DM and may serve as a new marker of reduced BMD in children with T1DM. Nonetheless, with regard to bone resorption, the studies are inconsistent and thus we cannot conclude that low BMD is due to elevated bone resorption.

Sclerostin—Osteocytes, the bone resident cells, are the main producers of sclerostin, which is an endogenous inhibitor of the Wnt/beta-catenin bone anabolic pathway. In a cross-sectional study of 106 T1DM subjects (12.2 ± 4 years), along with 80 controls, serum sclerostin and dickkopf-1 (DKK-1; another inhibitor of the Wnt/beta-catenin pathway) significantly increased (69). However, these findings were not confirmed in another cross-sectional study of 40 T1DM children (age 13.04 ± 3.53 yr) and 40 controls (70). In that study, T1DM patients had similar levels of sclerostin with controls. In adult T1DM patients (128 men and premenopausal women mean age 43.4 ± 8.8 years) with long duration of the disease (22.4 ± 9.5 years), higher levels of serum sclerostin were found in T1DM compared with controls, irrespective of gender (71). This data indicate that sclerostin levels may be dependent on disease duration, however more studies are needed to prove that. Overall, the elevated sclerostin levels could explain the compromised bone formation in T1DM children.

Vitamin D—Epidemiological studies suggest a link between vitamin D deficiency in early life and T1DM. A study of 170 T1DM patients and 170 age, gender and ethnicity matched controls (age >16 years) revealed that vitamin D deficiency was considerably higher in T1DM children (90.6%) compared to controls (85.3%) (72). Similarly, 53 Iranian T1DM patients age 8–18 years and disease duration of less than 8 weeks were all vitamin D deficient (77%) or insufficient (23%) (73). A cross-sectional study of 100 Saudi children with T1DM and 100 healthy controls showed that the mean levels of 25(OH)-Vitamin D (25OHD) were significantly lower in the T1DM children compared to controls (36.7 ± 14.3 nmol/l versus 44.8 ± 14.1 nmol/l). Overall, 84% of the T1DM children, and 59% of

the healthy children were vitamin D deficient. There was no correlation between HbA1c and 25OHD level (74). Likewise, a case-control study including 56 children with T1DM (14 newly diagnosed) and 46 unrelated control children revealed that serum 25OHD was lower in children with T1DM than in controls even after covariate adjustment. Children newly diagnosed with T1DM had lower 1,25(OH)(2) D than controls or children with established diabetes (75). Interestingly, decreased serum 25OHD levels in 100 patients with T1DM (aged 4.7–19.9 years) significantly correlated with higher insulin requirement (76). However, not all studies show low 25OHD in T1DM patients. In a case-control study including 80 T1DM Egyptian children (aged 6 to 16 years) and 40 controls, serum vitamin D did not differ between groups (77). However, while none of the control children showed secondary hyperparathyroidism, 32.5% of T1DM showed increased serum levels of PTH (77). In summary, whether low vitamin D is a risk factor or consequence of T1DM is unknown, the aforementioned studies should be revisited, especially since now 30 nmol/l is considered adequate for vitamin D levels in children with T1DM.

Parathyroid hormone (PTH)—Considering the possible abnormalities in urinary calcium excretion (increased) and possibly duodenal calcium absorption (decreased) in T1DM patients, it is expected that PTH levels will increase and may exert deleterious effects on bone. However, few studies have tested the possible contribution of PTH to the low BMD in T1DM children. Two studies reported no differences in PTH levels in serum between T1DM and controls children (43, 52), while one study showed elevated PTH serum levels in patients (78). Studies in pubertal children and in the growing mice suggest that PTH increases during bone modeling and may play a role in bone formation during growth (79–81). Clearly, the relationship between PTH and low IGF-1/low BMD described herein calls for further investigation.

Marrow adiposity—T1DM-associated bone loss correlates with increased bone marrow adiposity in mice (82). Bone marrow stromal cells can differentiate to form osteoblasts or adipocytes (82). In vitro studies demonstrated that promoting adipocyte maturation reduced the number of osteoblasts in cultures (83). Negative associations between the number of osteoblasts and adipocytes in marrow was also seen in iliac crest biopsies from patients with osteoporosis, supporting the notion that stromal cells switch from osteoblastic to the adipocytic fate in osteoporosis (84). A study of 30 young women (age of 22) with childhood-onset of T1D and low trabecular BMD showed that although median visceral adipose tissue in patients was higher than controls, there was no difference in vertebral bone marrow adiposity (85). So far there are no reports on marrow adiposity in children with T1DM. Thus, the contribution of marrow adiposity to bone loss/low BMD in T1DM patients is unknown. Based on in vitro studies it is plausible to hypothesize that the elevated glucose levels and metabolic stress seen in T1DM drive marrow progenitors towards adipocytes, while suppressing osteoblast differentiation, eventually leading to decreased BMD.

Leptin—In-vitro studies demonstrate that leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes (86). Thus, several studies have measured serum leptin levels in T1DM children. The results are conflicting as few studies have shown diminished serum leptin in newly diagnosed T1DM

patients (87–89), while other studies showed normal (90) or elevated serum leptin in T1DM children (91, 92). Studies that evaluated the relationship between leptin and BMI in T1DM children are inconclusive, showing positive (87) or no relationship between serum leptin and body adiposity (93). Despite these inconsistencies, it is widely accepted that insulin treatment in T1DM results in increased serum leptin levels (88, 89, 94–99). In a longitudinal study conducted over 9 years, in 46 T1DM children and 40 controls, both boys and girls with T1DM had higher leptin levels adjusted for percent body fat than controls (96). In girls, but not boys, leptin levels related to insulin dose and greater gains in fat mass. It is yet to be explored whether elevations in serum leptin following insulin treatment contribute to lowering BMD in T1DM children.

Inflammation—Several studies have shown that T1DM patients show increased systemic inflammation as evident by elevated levels of C-reactive protein (100–102), interleukin-6 (IL-6) (103), and fibrinogen (104). Serum IL-8 in T1D adolescents (age 13–18) with poor or favorable glucose control was increased in T1DM patients and inversely correlated with serum IGF-1 levels and positively correlated with HbA1c (16). In a study of 60 T1DM patients (age 14.67 ± 1.53 years) and 40 controls, IL-6 and IL-8 were higher in T1DM patients and positively correlated with HbA1c (105). Increases in IL-6 and TNF α were seen also in a study of 30 T1DM children, but were limited to the newly diagnosed cases (106). These findings are in line with a study of 27 children with T1DM who showed elevated serum IL-1 β , TNF- α only in the newly diagnosed T1DM children (107). A high-throughput real-time RT-PCR study was set to examine differences in gene expression profiles in peripheral blood mononuclear cells from 928 adult T1DM patients and 922 control subjects. High expression of genes implicated in immune function, such as inflammation (S100A8, S100A9, MND4, and IL12-A), immune regulation/promotion (TGFB1 and SELL), and antigen processing and presentation (CD74 and PSMB3) were found in T1DM patients (108). None of the studies tested the relationship between elevations in serum cytokines to the low BMD observed in T1DM patients. Thus, despite compelling data, it is yet to be determined whether bone loss in T1DM has an inflammatory basis, or whether inflammation is part of the complications of the disease that appears in late stages.

Hyperglycemia—Hyperglycemia, as seen in uncontrolled T1DM subjects, can drive several mechanisms that may contribute to osteoblast malfunction. These include increases in oxidative stress that may cause osteoblast cell death (79); increased glycation of enzymes (80) and growth factors such as IGF-1 (81) that are important in osteoblast differentiation and function; and increased glycation of collagen (109), which inhibits osteoblast maturation and matrix mineralization (110, 111). Hyperglycemia can also cause hyperosmotic extracellular conditions, which affect osteoblast function (112, 113) and osteocalcin secretion (112). This leads to a shift in substrate utilization resulting in an increased extracellular pH, and consequently impaired mineralization (114).

In summary, bone loss in T1DM subjects likely results from defects in bone formation and reduced peak bone acquisition. Impaired bone accrual during pubertal growth is attributed to reduced osteoblast cell numbers, as well as impaired osteoblast differentiation and function, all regulated by the GH/IGF-1 axis.

Concluding remarks

- **The GH/IGF-1 axis** is impaired in T1DM subjects, specifically during puberty. Portal insulinopenia in T1DM patients is associated with decreased hepatic output of IGF-1 and pituitary hypersecretion of GH.
- **Growth velocity and final adult height** in children with well-controlled T1DM are not affected. A few studies show that poor-controlled T1DM is associated with decreased final height.
- **BMD** is reduced in children with T1DM and these reductions are sustained through adulthood, leading to osteopenia and eventually osteoporosis with high risk for fracture. Loss of BMD occurs in both the axial and appendicular skeleton and can be seen in both cortical and trabecular bone compartments.
- **The influence of sex** on T1DM-associated bone loss is unknown.
- **Reduced BMD** is attributed mostly to decreases in IGF-1.
- **Glycemic control and duration of the disease are not always related to BMD.** Osteopenia does not always relate to the duration and/or severity of the disease as measured by HbA1c.
- **Systemic markers** including osteocalcin or RANKL do not show a clear relationship with BMD in children with T1DM. Similarly, associations between leptin, PTH, sclerostin, vitamin D, and BMD have not been established thus far, although they are still being investigated. Systemic cytokine levels have been evaluated in a few studies, but relationships with BMD were not established.
- **Bone modeling is reduced in T1DM patients**, likely due to their reduced osteoblast number or function. Evidence regarding bone resorption is inconsistent in human subjects. There are indications of increased bone marrow adiposity in T1DM patients, suggesting a shift of bone cell fate from osteoblast to adipocyte. However, this was not tested directly in T1DM patients and the relationship between marrow adiposity and BMD is unknown.

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Gaps in knowledge

Despite an advanced understanding of T1DM etiology and progression, it remains unclear whether the autoimmunity leading to beta cell loss and the development of T1DM has a direct role in causing bone tissue abnormalities, or whether the bone changes are entirely secondary to the metabolic abnormalities in T1DM. The exact mechanism of bone loss in T1DM is not fully understood. Further studies are needed to understand the interplay between osteoblast, osteoclast, and osteocyte cell function and their contribution to bone modeling (during growth) and bone remodeling (during adulthood) in T1DM patients. Furthermore, although there are several modalities for the treatment of bone loss in adult patients, treatment to induce bone gains in children with T1DM has not yet been established. Lastly, with improved modalities of treatment, T1DM patients will have an almost normal life expectancy. It remains to be seen if future therapies targeting bone accrual in adolescence will aid in long term bone health.

Highlights

- **The GH/IGF-1 axis** is impaired in T1DM.
- **Growth velocity and final adult height** is normal in children with well-controlled T1DM.
- **Bone mineral density (BMD)** is reduced in children and adults with T1DM.
- **Glycemic control and duration of the disease are not always related to BMD.**
- **Systemic markers** including osteocalcin, RANKL, leptin, PTH, sclerostin, or vitamin D, do not show clear relationship with BMD in T1DM children.
- **Bone modeling is reduced in T1DM**, likely due to reduced osteoblast number or function. Evidence regarding bone resorption is inconsistent.

Possible mechanisms leading to low BMD in T1DM. Beta-cell dysfunction in T1DM results in low/undetectable levels of insulin that reach the liver through the portal vein, leading to low secretion of IGF-1 to serum. The low levels of IGF-1 result in increased secretion of GH (due to a negative feedback loop between these hormone peptides). Elevations in GH result in liver GH resistance. Studies have established that the low levels of IGF-1 in T1DM correlate with decreased BMD (not decreased height). However, other factors may contribute to the low BMD in T1DM, such as osteocalcin, OPG, RANKL, PTH, leptin, sclerostin, vitamin D (VD), marrow adiposity, and inflammation.

Table 1

Review of literature summarizing heights at diagnosis, final adult heights, growth velocities and biochemical parameters evaluating the GH/IGF-1 axis in T1DM children.

Author	Number and age of subjects	Height (H) at Diagnosis	Height (H) at final assessment	Other assessments
Jivani SK (115)	60 F, 56 M Ages 1–13 yr	Height percentile F- Dx < 6 yrs - 55 F- Dx > 9 yrs - 41.5 M- Dx < 6 yrs - 42.16 M- Dx > 10 yrs - 25.42	Height Percentile F- Dx < 6 yrs - 33.68 F- Dx > 9 yrs - 41.9 M- Dx < 6 yrs - 21.33 M- Dx > 10 yrs - 21.2	
Songer TJ (37)	200 subjects Ages 0–17 yr	0–4 yr - 47 5–9 yr - 64 10–13 yr - 50 14–17 yr - 38		
Thon A (116)	39 F, 50 M Ages 11.6 ± 2.4 yr	H-SDS +0.04 ± 0.10	H-SDS -0.51 ± 1.01 (after 3yr)	
Vanelli M (25)	117 F, 87 M Ages 1.5–21 yr.			T1DM M have normal pubertal growth velocity. F with onset of T1DM before puberty show decreased growth velocity and final adult height. HbA1c 10.1 ± 1.8% -Peak growth velocity 6.9 ± 1.0 cm/yr HbA1c 8.9 ± 2.4% - Peak growth velocity 8.5 ± 0.9 cm/yr
Brown M (30)	184 subjects. Ages 0–18 yr	H-SDS <5 yrs 0.12 ± 0.93 5–10 yrs 0.58 ± 1.14 >10 yrs 0.22 ± 0.98	H-SDS < 5 yrs -0.74 ± 0.96 5–10 yrs 0 ± 1.26 >10 yrs 0.09 ± 1.10	
Du Caju MV (24)	24 F, 22 M Age 7.5 ± 3 yr.	H-SDS F 0.41 ± 0.99 M 0.56 ± 0.68	H-SDS F 0.27 ± 0.97 M 0.48 ± 0.89	
Gunczler P (117)	45 F, 34 M. Age 8.4 ± 3 yr.	H percentile HbA1c < 9 %, 48 ± 28 HbA1c > 9 %, 55 ± 23	H percentile after 5 yrs HbA1c < 9 %, 48 ± 27 HbA1c > 9 %, 42 ± 26	
Salerno M (29)	30 F, 32 M Ages 0.8–12.7 yr	H-SDS F 0.4 ± 1 M 0.5 ± 1	H-SDS F -0.4 ± 0.9 M -0.4 ± 1.1	
Danne T (118)	82 F, 115 M Ages 1–15 yr.	H-SDS 0.2	H-SDS -0.3	
Ahmed ML (39)	23 F, 23 M F Median age 10.36 M Median age 11.27	H-SDS F 0.814 M 0.235	H-SDS F -0.037 M -0.043	IGF-1 SDS at peak height velocity: F -0.623 ± 0.971, M 1.526 ± 0.88.
Holl RW (119)	232 F, 204 M Age 8.2 ± 0.2 yr.	H-SDS F 0.49 ± 0.12 M 0.35 ± 0.14	H-SDS F 0.28 ± 0.17 M 0.27 ± 0.11	
Cianfarani S (9)	25 F, 35 M Age 6.4 ± 3.9 yr.	H-SDS < 6 year 0.79 ± 1.2 >6 year 0.43 ± 1.6		IGF1 SDS <6yr -0.05 ± 1.6, IGFBP3 SDS <6yr 0.3 ± 1.05 IGF1 SDS >6yr -1.44 ± 2.2,IGFBP3 SDS >6yr -0.56 ± 1.18
Elamin A (120)	35 F, 37 M Ages 7–13 yr	H-SDS F -0.15 ± 0.40 M 0.04 ± 0.96	H-SDS F -1.72 ± 0.79 M -1.63 ± 0.44	Poor diabetes control with mean HbA1c 9.8 %.
Bonfig W (41)	846 F, 839 M Ages < 10 yr.	H-SDS 0.22 ± 1	H-SDS F -0.16 ± 0.97 M -0.17 ± 1 H-SDS with HbA1c > 8% was -0.308.	
Tattersall RB (121)	35 Twins			Twin diagnosed before puberty is 1.8 inches shorter vs unaffected twin. Twin diagnosed before puberty is 2.9 inches shorter vs

Author	Number and age of subjects	Height (H) at Diagnosis	Height (H) at final assessment	Other assessments
				diagnosed after puberty. No difference in height between twins diagnosed after puberty vs unaffected.
Leslie RD (122)	12 twins. Age < 14 years.			T1DM subjects showed reduced growth velocity. 6/7 co-twins who developed diabetes had reduced growth velocity before the onset of diabetes.
Chiarelli F (123)	30 M. Ages pre-pubertal 10.3 ± 2 yrs, pubertal 13.8 ± 1.1 yrs, post-pubertal 18.5 ± 1.3 yrs.		H – SDS Pre-pubertal 0.68 ± 0.9 Pubertal 0.15 ± 1.6 Post-pubertal 0.19 ± 0.8	IGF1; Pre-pubertal: T1D 180 ± 120 Control 177 ± 43 Pubertal: T1D 380 ± 146 Control 471 ± 166 Post-pubertal: T1D 364 ± 144 Control 353 ± 53 Diabetes duration ~ 6 years.
Kanumakala S (124)	F 49, M 43 Age ~ 8 years	H – SDS F -0.29 ± 1.19 M -0.17 ± 0.99	H – SDS F -0.13 ± 1.07 M -0.39 ± 0.99	
Demir K (125)	F 46, M 55 Age 8.9 ± 3.5 years.	H – SDS F 0.1 ± 0.9 ; M 0.3 ± 1.1	H – SDS (After 5 years) F -0.3 ± 0.9 ; M 0.1 ± 1	
Radetti G (10)	54 subjects. Ages 8.3 ± 2.4 years.			Pre-pubertal IGF1 SDS -2.2 ± 0.7 IGFBP3 SDS -0.07 ± 2 . Pubertal IGF1 SDS -2.3 ± 0.6 IGFBP3 SDS 0.08 ± 0.8 .
Leb J (126)	270 F, 317 M. Ages 0.3–20.3 years	H - SDS F 0.74 ± 1.46 M 0.15 ± 1.1	Height F 167 cm (Target 165.6) M 176.5 cm (Target 176.8)	
Huang C (127)	31 F, 13 M Ages 10.43 ± 2.95	H – SDS F 0.44 ± 0.91 M -0.03 ± 0.67	H – SDS F -0.05 ± 0.86 M -0.13 ± 0.66	Poor diabetes control with mean HbA1c 10.33 %.

F – Female, M – Male, H-Height, GH – Growth Hormone, IGF1 – Insulin like growth factor – 1, IGFBP3 – Insulin like growth factor binding protein 3, Dx-diagnosis, yr-year, SDS – Standard deviation score, %-height percentile.