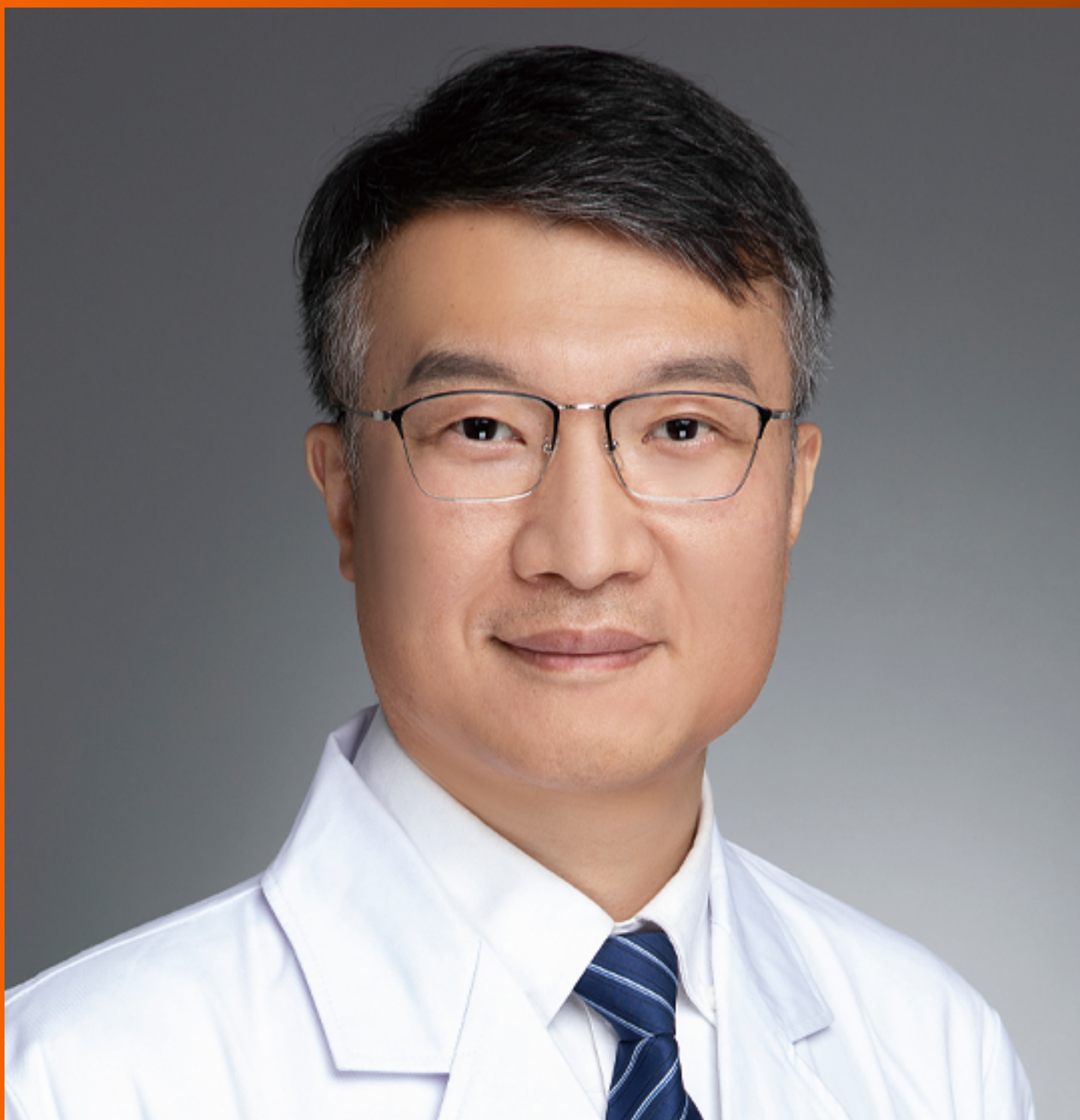


# World Journal of *Diabetes*

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**ABOUT COVER**

Editorial Board Member of *World Journal of Diabetes*, Gong Su, MD, PhD, Chief Physician, Deputy Director, Center of Cardiology, Hangtian Central Hospital, Peking University, Beijing 100049, China. su\_gong@yahoo.com

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## Mechanisms of altered bone remodeling in children with type 1 diabetes

Giacomina Brunetti, Gabriele D'Amato, Stefania De Santis, Maria Grano, Maria Felicia Faienza

**ORCID number:** Giacomina Brunetti 0000-0002-0681-1432; Gabriele D'Amato 0000-0001-5160-9340; Stefania De Santis 0000-0001-6877-2208; Maria Grano 0000-0002-7121-5899; Maria Felicia Faienza 0000-0002-1899-8337.

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**Giacomina Brunetti**, Department of Biosciences, Biotechnologies and Biopharmaceutics, University "A. Moro" of Bari, Bari 70125, Italy

**Gabriele D'Amato**, Department of Women's and Children's Health, ASL Bari, Neonatal Intensive Care Unit, Di Venere Hospital, Bari 70124, Italy

**Stefania De Santis**, Department of Pharmacy-Drug Science, University of Bari Aldo Moro, Bari 70126, Italy

**Maria Grano**, Department of Emergency and Organ Transplantation, Univ Bari, Bari 70124, Italy

**Maria Felicia Faienza**, Department of Biomedical Sciences and Human Oncology, Pediatric Unit, University "A.Moro", Bari 70124, Italy

**Corresponding author:** Giacomina Brunetti, PhD, Academic Research, Department of Biosciences, Biotechnologies and Biopharmaceutics, University "A. Moro" of Bari, Via Orabona 4, Bari 70125, Italy. [giacomina.brunetti@uniba.it](mailto:giacomina.brunetti@uniba.it)

### Abstract

Bone loss associated with type 1 diabetes mellitus (T1DM) begins at the onset of the disease, already in childhood, determining a lower bone mass peak and hence a greater risk of osteoporosis and fractures later in life. The mechanisms underlying diabetic bone fragility are not yet completely understood. Hyperglycemia and insulin deficiency can affect the bone cells functions, as well as the bone marrow fat, thus impairing the bone strength, geometry, and microarchitecture. Several factors, like insulin and growth hormone/insulin-like growth factor 1, can control bone marrow mesenchymal stem cell commitment, and the receptor activator of nuclear factor- $\kappa$ B ligand/osteoprotegerin and Wnt- $\beta$  catenin pathways can impair bone turnover. Some myokines may have a key role in regulating metabolic control and improving bone mass in T1DM subjects. The aim of this review is to provide an overview of the current knowledge of the mechanisms underlying altered bone remodeling in children affected by T1DM.

**Key Words:** Type 1 diabetes; Children; Bone remodeling; Osteoclasts; Osteoblasts

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**Core Tip:** Bone fragility is a well-known complication related to type 1 diabetes mellitus, and it can manifest from the disease onset, already in childhood. The mechanisms underlying this relationship, and the precise role of metabolic control in preventing bone impairment, are not yet fully understood. Future studies are needed to clarify better the factors responsible for bone damage in diabetic subjects, and to identify strategies for avoiding and managing osteopenia/osteoporosis in these subjects.

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## INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a common endocrine disease that affects approximately 500000 children and adolescents worldwide. Moreover, in the last decade the incidence has been rising and the age at onset dropping[1]. Micro and macrovascular T1DM-related complications may already have developed a few years after disease onset[2] and are correlated with the age at onset, diabetes duration, body mass index, and pubertal development[3-5]. Hyperglycemia is the main systemic risk factor for diabetic complications, although multiple biochemical pathways, such as the formation of advanced glycation end products, oxidative stress, endoplasmic reticulum stress, inflammatory cytokines, and kallikrein-bradykinin activation, link the adverse effects of hyperglycemia with the microvascular dysfunction[6]. Consequently, long-term glycemic control is considered the most important modifiable factor to delay the onset, as well as the progression of microvascular complications, as clearly demonstrated by The Diabetes Control and Complications Trial[7]. In addition, beyond the effect of glycemic control, the impairment of some protective factors, such as insulin and insulin-like growth factor-1 (IGF1), may contribute to the vascular damage over time[8].

Recently, it was recognized that autoimmune diabetic disease also affects the skeleton[9-11]. In T1DM, a reduced bone mass may be present at an early stage after diagnosis[11], but it is unclear whether it is the duration of diabetes or degree of glycemic control that may induce a lifelong increased risk of fractures[12]. The association between glucose metabolism and bone-fat tissue interactions[13,14], as well as muscle-bone crosstalk, has been clearly demonstrated[15]. In particular, the skeleton acts as an endocrine organ, by modulating glucose tolerance through the secretion of bone-specific proteins, in particular osteocalcin (OCN). Furthermore, proteins involved in bone remodeling, like osteoprotegerin (OPG), are associated with an impaired insulin function[16].

The aim of this review is to provide an overview of current knowledge of the mechanisms underlying altered bone remodeling in children affected by T1DM.

## FACTORS INFLUENCING BONE MASS ACCRUAL IN T1DM CHILDREN AND ADOLESCENTS

Childhood and adolescence are the critical ages for linear growth, bone mineral accrual, and the attainment of the peak bone mass, which is a key determinant of the lifelong risk of osteoporosis[17,18]. Therefore, osteoporosis prevention begins by improving bone mineral gains during an individual's years of growth[19]. During peripuberty, the bone mineral content and bone mineral density (BMD) in the lumbar spine and proximal femur increase by four-fold to six-fold. Furthermore, puberty is also the time when the main gender differences in bone growth emerge, particularly in terms of bone size and bone mass content. At the same time, the peak T1DM onset time ranges between the ages of 9 and 14 years[20], so children and adolescents affected by T1DM may be particularly predisposed to bone impairment.

Among the risk factors for osteoporosis, some factors are modifiable, such as a balanced diet and exercise, which have an important role already in childhood,



whereas obvious non-modifiable factors include gender, age, genetic factors, diseases, and drugs[21,22].

Impaired bone mass accrual (density and quality) in T1DM children has been attributed to multiple local factors in the bone marrow, as well as to systemic factors, which affect osteoblast (OB) differentiation and function (Figure 1).

### Local factors in the bone marrow

Several studies have suggested that hyperglycemia impairs the biology and function of multipotent bone marrow-derived mesenchymal stem cells (BMSCs), which generate mesodermal tissues including cartilage, bone, muscle, tendon, ligament, and fat[23]. In particular, hyperglycemia both reduces the proliferation and increases the senescence of BMSCs *in vitro*[24,25] and also inhibits OB activities[26] (Figure 1). In addition, runt-related transcription factor 2 (*RUNX2*) and *RUNX2*-related osteogenic genes are downregulated in T1DM[27], suggesting that diabetic conditions may affect the BMSC fate commitment. Chronic hyperglycemia increases the expression of peroxisome proliferator-activated receptors (*PPAR*) genes, which also stimulate BMSCs differentiation in bone marrow adipocytes[28] (Figure 1). In addition to this, thiazolidinediones, antidiabetic *PPAR $\gamma$*  agonists, promote marrow adipogenesis, thus increasing the fracture risk[29]. The bone marrow adipose tissue (BMAT) is considered to be a single anatomical entity with a different distribution in the various skeletal sites. In an animal T1DM model, BMAT was significantly augmented, and bone formation was inversely associated with the adipocytes in the bone marrow[30]. BMAT also directly regulates osteoclastogenesis by producing receptor activator of nuclear factor- $\kappa$ B ligand (*RANKL*)[31]. Bone morphogenetic protein-6 (*BMP6*) is known to induce bone formation (Figure 1), and adipose-derived BMSCs overexpressing *BMP6* have been shown to be capable of repairing bone defects in an animal model[32]. In addition, *BMP6* can probably mitigate T1DM-associated bone loss by directing BMSC differentiation towards the osteogenic lineage. Recently, *BMP6* supplementation in streptozotocin-induced diabetic mice has been demonstrated to directly restore BMD without influencing glucose levels[33], although a possible indirect role of *BMP6* exerted through the modulation of glucose concentrations was observed[34].

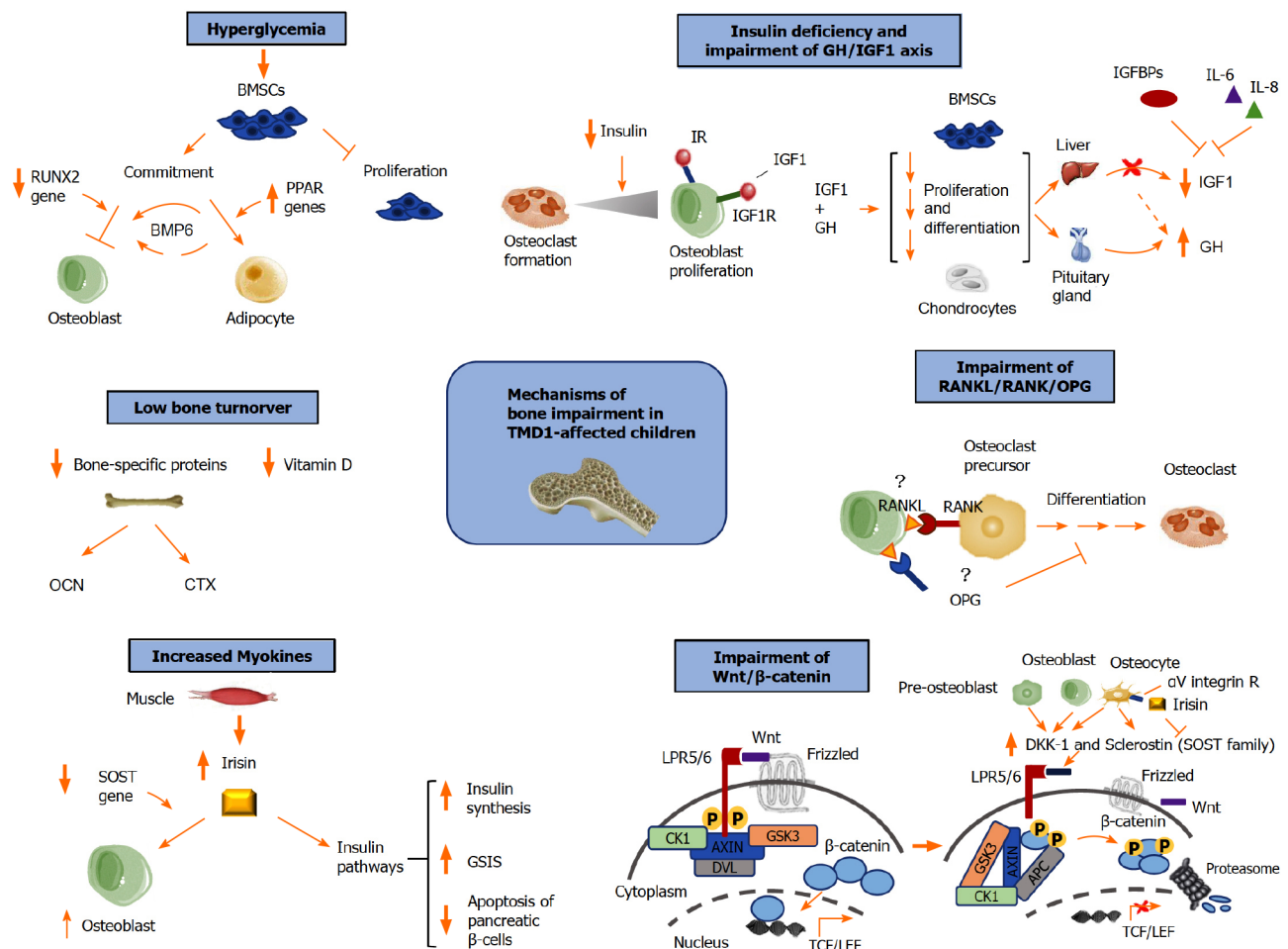
This finding suggests that hyperglycemia may not be the main determinant of bone loss in T1DM patients, since other factors, like insulin and the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis, could modulate BMSCs osteogenesis *via* *BMP6* or other pathways.

### Insulin and GH/IGF-1 axis

Insulin, GH, and IGF-1 are anabolic hormones that directly affect bone cells (Figure 1). Insulin stimulates both osteoclast (OC) formation and OB proliferation, achieving a steady state in favor of bone formation[35]. Insulin signaling is essential for normal bone acquisition, as demonstrated in insulin receptor (IR) knockout mice[36], likely due to the role of insulin in the regulation of bone energy metabolism. Moreover, IR activation in the growth plate of mice fed with a hypercaloric diet stimulates skeletal growth as well as growth plate chondrogenesis[37]. OBs also express the IGF-1 receptor (IGF1R), and IGF-1 binds both to IGF1R and, with a lower affinity, to IR, thus triggering the insulin signaling pathway and exerting osteoanabolic activities.

Linear growth as well as BMD are critically affected by the GH/IGF-1 axis. Moreover, GH and IGF-1 play a key role at the growth plate, acting on chondrocyte proliferation, differentiation, and hypertrophy. Abnormalities in this axis have been reported in T1DM subjects, especially during puberty because of the increased insulin requirements due to physiological insulin resistance. In particular, T1DM patients exhibit GH hypersecretion, resulting from portal insulinopenia associated with a decreased hepatic output of IGF-1 together with pituitary hypersecretion of GH. The low IGF-1 serum levels are also related to increased levels of the inflammatory cytokines interleukin-6 and interleukin-8, which inhibit IGF-1 transcription[38] (Figure 1).

Several studies have established correlations between a low BMD, low IGF-1, and glycemic control in T1DM children and adolescents, also providing evidence of low BMD in subjects with poor glycemic control[39-42]. These data are correlated with reduced IGF1, IGF1R and transforming growth factor  $\beta$ 1 gene expression in peripheral blood mononuclear cells in T1DM patients[43]. In addition, changes in the levels of the IGF-1 binding proteins that modulate IGF-1 bioactivity in serum and tissues have been observed in T1DM subjects[44].



**Figure 1 Mechanisms underlying altered bone remodeling in type-1-diabetes.** APC: Adenomatous polyposis coli; BMP6: Bone morphogenetic protein-6; BMSCs: Bone marrow-derived mesenchymal stem cells; CK1: Casein kinase I; CTX: C-terminal cross-link of collagen; DKK-1: Dickkopf-1; DVL: Disheveled; GH: Growth hormone; GSIS: Glucose-stimulated insulin secretion; GSK3: Glycogen synthase kinase 3 beta; IR: Insulin receptor; IGF1: Insulin-like growth factor-1; IGF1R: Insulin-like growth factor-1 receptor; IGF1BPs: IGF-1 binding proteins; IL-6: Interleukin-6; IL-8: Interleukin-8; LPR5/6: LDL receptor related protein 5; OCN: Osteocalcin; OPG: Osteoprotegerin; PPAR: Peroxisome proliferator-activated receptors; RANK: Receptor activator of nuclear factor-kappa B; RANKL: Receptor activator of nuclear factor-kappa B ligand; RUNX2: Related transcription factor 2; SOST: Sclerostin; TCF/LEF: T-cell factor/lymphoid enhancer factor.

### RANKL/RANK/OPG pathway

Bone health depends on the balance between OCs, the bone-reabsorbing cells, and OBs, the bone-forming cells. In several pediatric diseases, bone impairment is due to an imbalance of OBs and OCs activity accomplishing the remodeling process[45]. OBs produce positive and negative regulators of osteoclastogenesis, such as the RANKL and the natural decoy receptor for RANKL, OPG, respectively[46]. Although OBs are a major source of RANKL, this cytokine is also expressed by osteocytes, fibroblasts, and immune system cells, including T cells and mature dendritic cells[47]. OCs differentiate under the control of RANKL, which binds to its receptor, RANK. OPG is the RANKL decoy receptor, thus acting as a negative regulator of osteoclastogenesis (Figure 1). OPG is produced not only by OBs but also by B lymphocytes and dendritic cells, as well as several cytokines[47,48]. In the last years, the impaired OB differentiation and function mechanisms in diabetic bone have been further elucidated, demonstrated by low serum levels of OB markers in T1DM subjects[49], and a decreased osteoblastic activity in streptozotocin-induced T1DM mice[50]. However, OC activity and bone resorption in T1DM are still debated. In diabetic animal models, an increase in OC numbers[51], as well as messenger RNA (mRNA levels of tartrate resistant acid phosphatase (TRAP) and cathepsin K, bone resorption markers, has been demonstrated[52,53]. By contrast, bone resorption was unaffected or even decreased in T1DM rodents[54]. In a recent study by Yang *et al*[55] the OC activity of trabecular bone was increased in diabetic mice at the early stage, accompanied by an augmented protein expression of RANKL. Remarkably, the RANKL mRNA levels remained unchanged, suggesting that the increased bone resorption in early-stage diabetic mice is induced by RANKL derived from BMAT rather than from the bone tissue itself[55].



This finding indicates that BMAT could be a key factor in regulating bone homeostasis in pathological conditions such as diabetes.

Data about OPG and RANKL levels in T1DM children and adolescents are conflicting. Chrysis *et al*[56] found that serum OPG levels were significantly increased in patients with T1DM compared with controls, whereas RANKL levels did not change. The low RANKL levels in T1DM patients are probably due to blockade of the RANKL signal by an OPG increase on the OPG/RANKL/RANK axis[56]. Consistently, Galluzzi *et al*[57] observed significantly higher levels of OPG in children with long-lasting T1DM compared to the controls. In the study by Szymańska *et al*[58], OPG levels were higher in T1DM subjects at the onset as compared to the control group, and decreased thereafter, while on the contrary, RANKL levels were lower than in controls but increased during follow-up. The authors speculated that the decreased insulin secretion in patients at the onset of diabetes may result in decreased insulin binding to the OB receptor, leading to a transitory increase of OPG levels in the early stage of diabetes[58]. Loureiro *et al*[59] reported low OPG levels in T1DM children, which were correlated with the metabolic control level. In the recent study by Karalazou *et al*[60], T1DM patients showed higher RANKL levels and lower OPG levels than controls. Taking literature data into account, high OPG levels would seem to be positively associated with the progression of diabetes and the development of complications[61-63], while low OPG levels are not associated with microvascular alterations[64,65].

### **Wnt/ $\beta$ -catenin pathway**

The Wnt/ $\beta$ -catenin pathway is a signal transduction cascade that controls numerous processes during development. Thus, aberrant Wnt signaling underlies a broad range of diseases in humans.

The pathway is regulated at several levels, also by secreted Frizzled-related proteins and Wnt inhibitory protein, both of which inhibit interactions between Wnt and Wnt receptors[66] (Figure 1). Other Wnt inhibitors belong to the Dickkopf-1 (DKK-1) and the WISE/SOST families, which antagonize signaling by binding low-density lipoprotein-related receptor-5/6[67]. DKK-1 is expressed by preosteoblasts, OBs, and osteocytes, and acts as an antagonist of the canonical Wnt signaling by binding to low-density lipoprotein-related receptor-5/6 (Figure 1). Sclerostin is a secreted protein encoded by the *SOST* gene and produced by mature osteocytes, which antagonizes Wnt/ $\beta$ -catenin signaling by abrogating its bone anabolic actions[68,69] (Figure 1). DKK-1 and sclerostin are key regulators of bone mass, and high levels of these Wnt signaling inhibitors have been found in several bone diseases[70]. The important role of both molecules has also been demonstrated in a mouse model, showing that a bispecific antibody targeting sclerostin and DKK-1 supports bone mass accrual and fracture repair, exerting a greater effect compared to monotherapies[71]. In type 1 diabetic rats, an increased *SOST* mRNA and sclerostin expression has been observed [72]. Clinical studies and Homeostatic Model Assessment for Insulin Resistance have shown an inverse correlation between sclerostin and insulin levels, suggesting that sclerostin could modulate glucose homeostasis[73]. DKK-1 involvement has been demonstrated in a large cohort of T1DM children and adolescents affected by T1DM [74], in which DKK-1 levels were correlated with bone formation markers, the BMD-Z-score, sex, and pubertal stage[74]. Neumann *et al*[75] reported higher serum levels of sclerostin in T1DM subjects compared with controls but found no correlations between sclerostin levels and bone metabolism markers. On the contrary, Tsentidis *et al*[76] found comparable levels of sclerostin in T1DM children and controls. Recent data suggested that sclerostin levels are increased in pediatric T1DM patients and confirmed a relationship between sclerostin and the glucose metabolism[77]. In addition, in T1DM subjects' bone-derived OCN, as well as fat-derived leptin, appear to modulate sclerostin support in metabolic regulation[77]. Future studies are needed to clarify the role of sclerostin in bone impairment associated with T1DM.

### **Muscle-bone crosstalk**

Bone and muscles are integrated organs that exert a mutual control and are in turn controlled by several factors, such as the GH-IGF-1 axis, sex steroids, adipokines (*e.g.*, leptin, adiponectin, visfatin, resistin), and vitamin D[78,79]. In addition to mediating the muscle-bone crosstalk, muscles release myokines that affect other organs and tissues, including the liver, intestine, and adipose tissue, which in turn release cytokines and hormones responsible for regulating bone homeostasis. Among the myokines, irisin is a small peptide derived from the proteolytic cleavage of fibronectin III domain-containing protein 5, produced during physical exercise[80]. This myokine has been associated with the browning response and thermogenesis of white adipose

tissue[80]. In addition, it has an essential role in the bone-muscle unit, and exerts anabolic effects on bone, both *in vitro* and *in vivo*[81]. Irisin acts through the activation of osteoblastic bone formation, the induction of the pro-osteoblastic genes, and the decrease of osteoblastogenesis inhibitors[81]. The direct effect of irisin on OBs is exerted by means of a downregulation of *SOST* expression, which negatively regulates bone formation[81] (Figure 1). In agreement with this finding, Zhang *et al*[82] demonstrated *in vitro* that treatment with recombinant irisin on OB precursors causes the accumulation of  $\beta$ -catenin in the nucleus, suggesting that irisin restores *SOST*-mediated inhibition of the Wnt/ $\beta$ -catenin pathway by directly inhibiting *SOST*. In addition, irisin interacts with osteocytes by directly binding to  $\alpha$ V integrin receptors, thus protecting them from apoptosis, and inducing the secretion of *SOST in vivo*[83]. Regarding its metabolic effects, recombinant irisin has been shown to stimulate insulin biosynthesis and glucose-stimulated insulin secretion in a protein kinase A-dependent manner. It also prevents saturated fatty acid-induced apoptosis in human and rat pancreatic  $\beta$  cells, as well as in human and murine pancreatic islets, *via* the AKT/B-cell lymphoma 2 signaling pathway[84] (Figure 1). Studies in humans have elucidated the role of irisin both in healthy subjects and in patients affected by diseases related to bone metabolism, such as hyperparathyroidism and T1DM. In a recent study, irisin was demonstrated to be one of the main determinants of bone mineral status during childhood[85]. In addition, high irisin levels have been found in adult patients with long-lasting T1DM that were correlated with positivity for anti-glutamic acid decarboxylase antibodies, suggesting that autoimmunity can have a role in regulating the levels of this myokine[86,87].

In T1DM children and adolescents, elevated irisin levels have been found to be closely related to better metabolic control and an improved bone mass[88]. These findings are in agreement with the recent data showing that irisin can promote insulin synthesis as well as glucose-stimulated insulin secretion[84]. In addition, irisin overexpression enhanced insulin sensitivity in mice while reducing hyperlipidemia and hyperglycemia[89], suggesting that irisin could have a key role in diabetes management.

## BONE TURNOVER MARKERS IN T1DM CHILDREN

Bone is considered to be an endocrine “gland,” and its modulation of glucose tolerance by the secretion of bone-specific proteins, in particular OCN, has been clearly demonstrated[16]. OCN is the main non-collagen protein secreted by the OBs and stored in the bone extracellular matrix. The carboxylated form of OCN shows a high affinity to hydroxyapatite, the mineral present in bone. Instead, the uncarboxylated form is free in the circulation and regulates glucose metabolism and insulin resistance [90]. Several data have suggested that serum levels of uncarboxylated OCN are negatively correlated with insulin resistance, obesity, diabetes, and markers of the metabolic syndrome[91-93].

T1DM subjects show a low bone turnover, which is another mechanism underlying bone fragility in these subjects[94]. Previous studies demonstrated that both markers of bone resorption, such as the C-terminal cross-link of collagen (CTX), and markers of bone formation, such as OCN, were decreased in T1DM compared to healthy controls [94]. Furthermore, while levels of TRAP and procollagen type 1 amino terminal propeptide (P1NP) were comparable in patients with T1DM and healthy subjects, low vitamin D levels were found in T1DM patients[94]. Similarly, reduced OCN levels were observed in children and adolescents with T1DM, while P1NP levels would seem to be lower and CTX levels higher in T1DM than in healthy subjects[95]. Chen *et al*[96] showed low levels of bone alkaline phosphatase and CTX in T1DM children as compared to controls.

A recent report by Madsen *et al*[97] investigated bone turnover markers in relation to BMD and metabolic control in T1DM children and adolescents. The results of this study demonstrated that markers of bone formation and resorption were significantly decreased in both sexes, and HbA1c levels were negatively correlated to the resorption marker CTX but not to any of the bone formation markers[97]. Another important finding of this study was that the decreased levels of both markers of bone formation and bone resorption were independent of the T1DM duration and Tanner stage. Thus, the impairment of bone health in T1DM begins in early childhood, independently of age and pubertal stage.

A possible explanation for the low bone turnover in diabetic subjects may be an insulin deficiency, which contributes to a low bone formation, as demonstrated by low

bone turnover in a mouse model of insulinopenia and restoration following insulin treatment[98].

It is possible that the low bone turnover caused by insulin deficiency occurs over time and may not be detected in studies based on acute changes in insulin levels[99].

## FUTURE PROSPECTS IN THE MANAGEMENT OF BONE IMPAIRMENT IN T1DM SUBJECTS

T1DM is the most frequent chronic disease in the pediatric population. It is associated with an increased bone fragility from childhood onward, and hence the risk of fractures later in life. Although a low BMD is documented in diabetic individuals, the precise mechanisms underlying bone loss are not yet fully understood. Hyperglycemia seems not to be the main cause of bone impairment in T1DM patients, but other factors, like insulin deficiency, the GH/IGF-1 axis, and low bone turnover, could contribute to the bone impairment observed in these subjects. The use of diabetes technologies, like the use of insulin pumps and continuous glucose monitors, to achieve glycemia control appears to be correlated with an improved bone health, although further studies are needed to confirm this finding. In addition, prospective studies should clarify the causal relationships among metabolic control, bone turnover markers, the RANKL/OPG ratio, Wnt-signaling inhibitors, myokine activity, and bone mineralization in T1DM subjects.

To date, no specific biomarkers are available to predict accurately fracture outcomes in T1DM patients. Additional large-scale prospective studies are needed to identify high-risk patients. In addition to dual x-ray absorptiometry, a fracture risk assessment tool and trabecular bone score could, in the future, offer additional technologies to evaluate better the bone quality of T1DM patients[100].

There is no clear evidence in support of early intervention to avoid the risk of osteoporosis or of the use of anti-osteoporotic drugs in diabetic subjects[101].

Preclinical studies indicated that denosumab, a human monoclonal antibody to RANKL approved for the treatment of osteoporosis or for patients at high fracture risk [102], may stimulate  $\beta$ -cell proliferation in humans[103] and improve liver insulin sensitivity[104].

No data are currently available on romosozumab, an anti-sclerostin antibody indicated to reduce the risk of clinical and vertebral fractures in postmenopausal women with osteoporosis[105]. In addition, there are still few data on the effects of vitamin D, calcium intake, and physical activity on bone health in T1DM subjects [106]. Recently, toll-like receptor-4 (TLR4) has been correlated with diabetic bone disorders *via* the nuclear factor- $\kappa$ B pathway[107,108]. It has been demonstrated that TLR4 deletion improves streptozotocin-induced diabetic osteoporosis in mice, so TLR4 may be a possible therapeutic target for the treatment of diabetic osteoporosis[109].

## CONCLUSION

T1DM has a strong impact on bone health, and skeletal fragility is now recognized among the complications of diabetes. The fracture risk is greater in patients with T1DM and increases linearly with the disease duration. T1DM subjects show a decreased BMD already in childhood, possibly due to an absolute insulin deficiency and the inability of exogenous insulin to reflect endogenous insulin secretion. However, the reduction in BMD does not entirely explain the increase in bone fragility observed in these subjects. It is unclear whether reducing hypoglycemic events by means of continuous glucose monitoring and a closed-loop insulin delivery system can improve bone health in subjects with T1DM. Randomized clinical trials to evaluate the efficacy of anti-fracture drugs in diabetes are lacking, while some observational data have indicated an analogous efficacy in those with or without diabetes, so such drugs should be used according to existing indications.

Further studies are warranted to clarify better the factors responsible for bone damage in diabetic subjects and to identify efficacious strategies to prevent osteopenia/osteoporosis and the risk of fractures in these subjects.

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