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Type 1 Diabetes Mellitus and its Effects on Bone

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Abstract:

Background: Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by destruction of pancreatic β-cells leading to absolute insulin deficiency. Beyond its metabolic complications, T1DM has significant adverse effects on skeletal health, particularly during childhood and adolescence, which are critical periods for bone mineral accrual. Children with T1DM are at increased risk of reduced bone mineral density (BMD), impaired bone quality, and future fractures due to multiple interconnected mechanisms including insulin deficiency, disruption of the insulin-like growth factor-1 (IGF-1) axis, chronic hyperglycemia, advanced glycation end-product accumulation, inflammatory cytokine activation, and osteocyte dysfunction. Disease duration, poor glycemic control, pubertal status, and alterations in calcium-phosphorus metabolism further contribute to skeletal impairment. Early identification of bone abnormalities in pediatric patients with T1DM is therefore essential to minimize long-term skeletal complications and improve quality of life.

Keywords: Type 1 diabetes mellitus; Bone mineral density; Osteoporosis; Osteoblast dysfunction; Advanced glycation end-products; Children; Fracture risk; Insulin deficiency.

Introduction:

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by immune-mediated destruction of pancreatic β-cells, resulting in absolute insulin deficiency and lifelong dependence on exogenous insulin therapy. It is one of the most common endocrine disorders affecting children and adolescents worldwide, with a steadily increasing global incidence over the past decades. According to the International Diabetes Federation, approximately 1.2 million children and adolescents are currently living with T1DM globally. Although advances in insulin therapy and glucose monitoring technologies have improved disease management, T1DM remains associated with multiple acute and chronic complications affecting different organ systems, including the skeletal system **(1).**

Bone health has emerged as an important yet underrecognized aspect of T1DM, particularly during childhood and adolescence, which represent critical periods for bone mineral accrual and skeletal maturation. Several studies have demonstrated that children with T1DM exhibit lower bone mineral density (BMD), impaired bone microarchitecture, and increased susceptibility to fractures compared with healthy peers. The mechanisms underlying diabetic bone disease are multifactorial and include insulin deficiency, disruption of the insulin-like growth factor-1 (IGF-1) axis, chronic hyperglycemia, oxidative stress, and accumulation of advanced glycation end-products (AGEs), all of which negatively affect osteoblast differentiation and bone matrix quality **(2).**

In addition to impaired bone formation, T1DM is associated with enhanced osteoclast activity and altered bone remodeling. Hyperglycemia-induced inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α stimulate osteoclastogenesis through activation of the RANKL/OPG signaling pathway, leading to increased bone resorption. Furthermore, osteocyte dysfunction and elevated sclerostin levels contribute to suppression of Wnt/β-catenin signaling, thereby reducing osteoblastic activity and impairing bone regeneration. These pathophysiological alterations collectively result in deterioration of both bone quantity and quality, explaining the elevated fracture risk observed even in patients with relatively preserved BMD values **(3).**

Several clinical factors influence the severity of skeletal impairment in children with T1DM, including disease duration, glycemic control, pubertal status, sex differences, nutritional deficiencies, and disturbances in calcium-

phosphorus metabolism. Longer disease duration and poor glycemic control have been associated with progressive reductions in BMD and impaired bone mineral accrual. Female patients appear particularly vulnerable because of the critical role of estrogen in skeletal development during puberty. Therefore, early recognition of bone abnormalities and implementation of preventive strategies such as optimal glycemic control, adequate calcium and vitamin D intake, and regular physical activity are essential to minimize long-term skeletal complications in pediatric patients with T1DM **(4).**

5.1 Overview of Type 1 Diabetes Mellitus:

5.1.1 Definition and Epidemiology:

Type 1 diabetes mellitus (T1DM) is a chronic, organ-specific autoimmune disease resulting from the selective destruction of insulin-producing pancreatic beta cells by self-reactive T lymphocytes, ultimately culminating in absolute insulin deficiency and lifelong dependence on exogenous insulin replacement. The principal beta cell autoantigens include insulin, glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8). T1DM constitutes approximately 85–90% of all diabetes cases diagnosed in children and adolescents below 15 years of age. The global incidence of T1DM in children has been rising at an estimated rate of 2–3% per year over recent decades, with the International Diabetes Federation estimating that approximately 1.2 million children and adolescents currently live with T1DM worldwide **(1).**

5.1.2 Pathogenesis and Risk Factors:

The genetic basis of T1DM susceptibility is complex and polygenic, with HLA class II genes encoding HLA-DR and HLA-DQ molecules contributing approximately 40–50% of familial clustering. The highest-risk HLA genotype is the compound heterozygote HLA-DR3/DQ2 + DR4/DQ8, present in approximately 30–40% of T1DM patients in European populations. Beyond the HLA region, over 50 additional susceptibility loci have been identified, including variants in PTPN22, IL2RA, and CTLA-4. Despite strong genetic predisposition, the incomplete concordance rate (30–50%) in monozygotic twins underscores the critical role of environmental factors as disease triggers in genetically susceptible individuals, including enteroviral infections, gut microbiome composition, and insufficient vitamin D signaling **(5).**

5.1.3 Clinical Presentation and Diagnosis:

The symptomatic presentation of T1DM typically occurs acutely over days to weeks, following a prolonged subclinical phase of progressive beta cell destruction. The classical symptoms - polyuria, polydipsia, polyphagia, and unexplained weight loss - reflect the metabolic consequences of severe insulin deficiency. Diabetic ketoacidosis (DKA) - characterized by hyperglycemia, ketonemia, and high anion gap metabolic acidosis - is the presenting manifestation in 15–40% of newly diagnosed children in high-income countries. Diagnosis is established according to standard criteria: fasting plasma glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL with symptoms, 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, or HbA1c ≥6.5% **(5).**

5.1.4 Management of T1DM in Children:

The management of T1DM in children is predicated on insulin replacement to replicate physiological insulin secretion. The standard regimen combines a long-acting basal insulin analogue with rapid-acting analogues for mealtime and correction dosing, with the general glycemic target of HbA1c below 7.0% (53 mmol/mol) without significant hypoglycemia. Continuous glucose monitoring (CGM) with Time in Range (TIR) as the primary efficacy metric has transformed pediatric T1DM management. Hybrid closed-loop systems represent the current standard of care in high-resource settings. Teplizumab - an anti-CD3 monoclonal antibody approved in 2022 - represents the first disease-modifying therapy for T1DM, delaying clinical onset in at-risk individuals and preserving residual beta cell function in newly diagnosed patients **(6).**

5.2 Pathophysiology of Bone Disease in T1DM:

Bone disease is a well-established but often underrecognized complication of T1DM extending to both children and adults. Meta-analyses have documented a substantially elevated fracture risk in T1DM, with pooled

relative risks for hip fracture ranging from 3.2 to 7.3 in adult studies - a magnitude substantially exceeding what would be predicted from BMD measurements alone, implying that bone quality impairment contributes independently to skeletal fragility. In children, the long-term skeletal consequences begin accumulating from the time of diagnosis, with evidence of reduced bone mineral accrual and lower BMD demonstrable even in the prepubertal period **(7).**

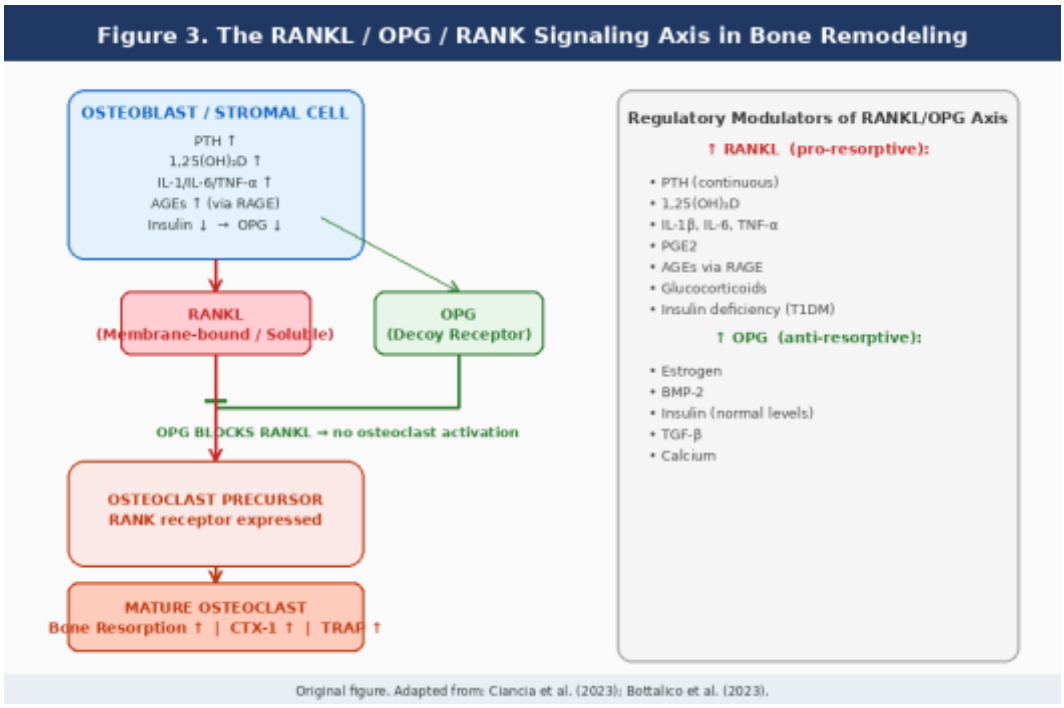

Figure (1): The RANKL/OPG/RANK signaling axis in bone remodeling, illustrating the pro-resorptive and anti-resorptive regulatory signals and their perturbation in type 1 diabetes mellitus. Original figure adapted from **Ciancia et al. (3) and Bottalico et al. (2).**

5.2.1 Insulin Deficiency and IGF-1 Axis Disruption:

Insulin exerts direct anabolic effects on osteoblasts through the PI3K/Akt pathway (promoting survival and protein synthesis), the MAPK/ERK pathway (promoting proliferation), and Wnt/β-catenin signaling (promoting differentiation). In T1DM, absolute insulin deficiency removes these direct trophic signals from osteoblasts, resulting in reduced proliferation, impaired differentiation (Runx2↓), decreased collagen synthesis, and increased apoptosis of mature osteoblasts. The consequence is a measurable reduction in bone formation rate reflected by low serum osteocalcin and P1NP levels in children with T1DM. Compounding these effects, insulin deficiency reduces hepatic IGF-1 synthesis, with low IGF-1 independently associated with reduced BMD, impaired linear growth, and delayed skeletal maturation **(8).**

5.2.2 Advanced Glycation End-Products and Bone Quality:

Chronic hyperglycemia drives the non-enzymatic condensation of reducing sugars with free amino groups on proteins, generating irreversible advanced glycation end-products (AGEs) - particularly pentosidine and carboxymethyllysine - that accumulate within the bone matrix in proportion to cumulative glycemic exposure. AGE accumulation in collagen forms aberrant intermolecular cross-links that stiffen the matrix and reduce its energy-absorbing capacity, while competing with and displacing the normal enzymatic pyridinoline cross-links that confer toughness. The resulting changes substantially elevate fracture risk independently of BMD. AGEs also impair bone cell biology through engagement of the receptor for AGEs (RAGE) on osteoblasts, osteoclasts, and osteocytes, activating NF-κB signaling and promoting RANKL expression, osteoblast apoptosis, and canalicular obstruction **(2).**

5.2.3 Enhanced Osteoclastogenesis and Inflammatory Cytokines:

While osteoblastic bone formation is suppressed in T1DM, osteoclast-mediated bone resorption is relatively enhanced in poorly controlled disease, creating a net catabolic imbalance. AGE-mediated RAGE activation on osteoblasts upregulates RANKL expression; insulin deficiency reduces OPG secretion; and elevated proinflammatory cytokines - particularly IL-1β, IL-6, and TNF-α - potently stimulate RANKL expression and directly promote osteoclast differentiation. Serum markers of bone resorption including CTX-1 and urinary deoxypyridinoline are elevated in children with T1DM relative to healthy controls, providing direct biochemical evidence of this pro-resorptive state **(3).**

5.2.4 Osteocyte Dysfunction and Sclerostin Elevation:

Osteocytes in the diabetic skeleton are subject to a hostile microenvironment comprising oxidative stress, elevated AGE concentrations, impaired nutrient delivery due to microangiopathy, and direct toxic effects of hyperglycemia on cell viability. These stressors promote premature osteocyte apoptosis and elevated sclerostin secretion. Sclerostin - by antagonizing Wnt ligand-induced β-catenin stabilization - potently suppresses transcription of pro-osteoblastic target genes, representing a targetable mechanism of bone formation suppression in T1DM **(2).**

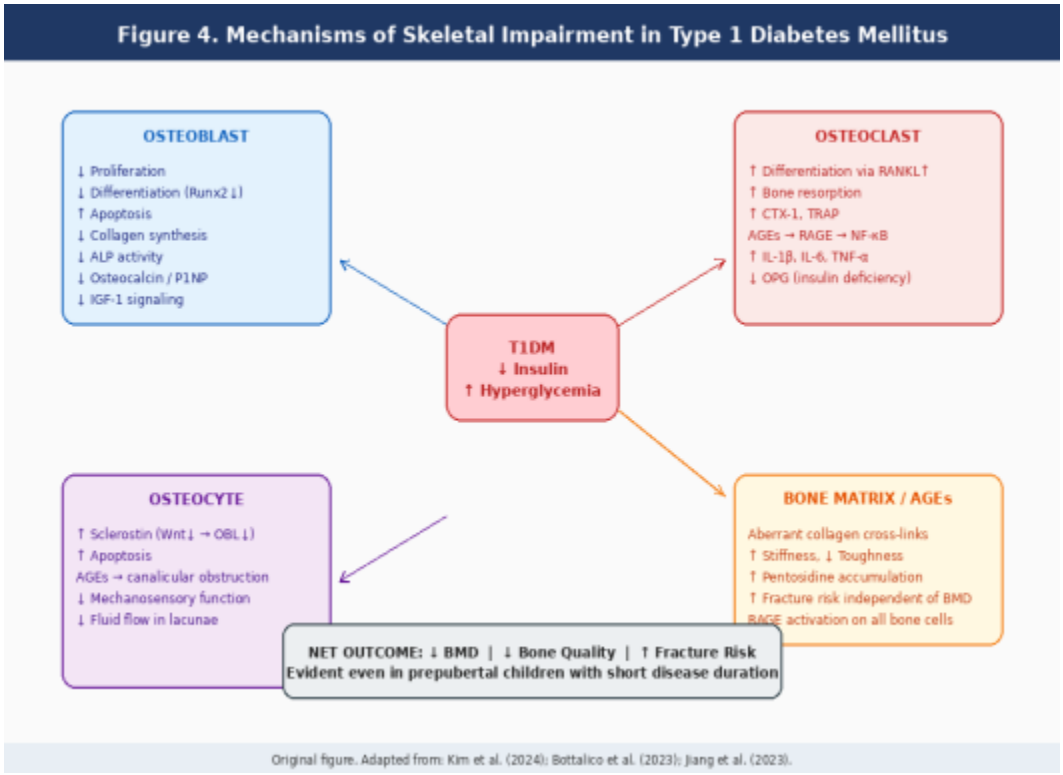

Figure (2): Summary of the mechanisms by which type 1 diabetes mellitus impairs the function of osteoblasts, osteoclasts, and osteocytes, and adversely affects bone matrix quality through advanced glycation end-product accumulation. The net outcome is reduced BMD, impaired bone quality, and elevated fracture risk. Original figure adapted from **Kim et al. (7); Bottalico et al. (2); Jiang et al. (9).**

5.3 Effect of Disease Duration on BMD:

The skeletal consequences of T1DM are cumulative and progressive, with longer disease duration consistently associated with lower BMD. In children, longitudinal studies have demonstrated that the deficit in whole-body and lumbar spine BMD Z-scores - already measurable at time of diagnosis - widens progressively with increasing years of disease. Subgroup analyses comparing children with shorter versus longer T1DM duration have documented significantly lower whole-body BMD and BMD Z-scores in the longer-duration group, with differences becoming statistically robust when disease duration exceeds three years - the approximate

threshold at which cumulative skeletal effects become sufficiently large to generate measurable cross-sectional differences **(7).**

5.4 Glycemic Control, HbA1c, and Bone Mineral Density:

The relationship between glycemic control - as indexed by HbA1c - and bone mineral density in children with T1DM is one of the most clinically pertinent yet most inconsistently reported associations in the pediatric diabetes-bone literature. Some studies have identified significant negative correlations between HbA1c and BMD Z-scores, consistent with the hypothesis that greater cumulative exposure to hyperglycemia drives proportionally greater AGE accumulation and more severe suppression of osteoblast function. However, a substantial number of studies - including the meta-analysis by **Zhu et al. (10)** pooling data from nine cross-sectional studies - have failed to demonstrate a significant independent association.

These observations suggest that targeting HbA1c improvement alone may be insufficient for bone protection in T1DM, and that attention to vitamin D, calcium, phosphate homeostasis, and physical activity is equally important **(7).**

5.5 Sex Differences and Pubertal Influences:

Female children with T1DM appear to be at substantially greater risk of impaired BMD - particularly at the lumbar spine and total body - compared to their male counterparts. Estrogen plays a particularly critical role in bone mineral accrual during the female pubertal growth spurt, and its suppression associated with impaired hypothalamic-pituitary-gonadal axis function in girls with poorly controlled T1DM disproportionately affects the female skeleton. Prepubertal children with T1DM represent a unique study population in which the skeletal effects of insulin deficiency and chronic hyperglycemia can be evaluated in relative isolation from the confounding influence of pubertal sex hormones - a consideration that motivated the specific focus of the present study on the prepubertal age group **(4).**

5.6 Calcium, Phosphorus, Alkaline Phosphatase, and Renal-Hepatic Contributions:

Disturbances in calcium and phosphorus homeostasis are well documented in children with T1DM and contribute importantly to impaired bone mineralization. Hypercalciuria - resulting from osmotic diuresis overwhelming tubular calcium reabsorption capacity - creates negative calcium balance that depletes skeletal calcium stores and, when compensated by secondary hyperparathyroidism, accelerates cortical bone resorption. Serum alkaline phosphatase (ALP) is frequently reduced in children with T1DM, reflecting the overall suppression of bone-forming osteoblastic activity **(9).**

Early renal tubular dysfunction - detectable as subclinical elevations of serum creatinine and blood urea nitrogen - may represent an important and underappreciated contributor to skeletal deterioration in children with T1DM even in the absence of clinical diabetic nephropathy. Hepatic involvement - from subclinical glycogenic hepatopathy to elevated transaminases - may impair hepatic 25-hydroxylation of vitamin D, reducing the availability of the precursor form required for renal activation. The combined renal and hepatic perturbations in T1DM represent an important secondary pathway through which the primary metabolic defect of insulin deficiency propagates to impair skeletal health **(2).**

5.7 Effect of Insulin Dose and Type on Bone:

Emerging evidence suggests that the type and dose of insulin regimen in T1DM management may exert independent influences on bone metabolism beyond effects on glycemic control. High doses of long-acting basal insulin analogues administered subcutaneously may paradoxically promote adipogenesis rather than osteoblastogenesis among mesenchymal stem cell populations through IRS-1-mediated pathway dysregulation. Several studies in pediatric T1DM cohorts have identified significant negative correlations between total daily basal insulin dose and whole-body BMD, suggesting that higher insulin requirements - as a proxy for worse metabolic control - are associated with lower BMD. These associations emphasize the importance of achieving efficient glycemic control with the minimum necessary insulin dose through strategies including lifestyle optimization and emerging technologies such as closed-loop insulin delivery **(9).**

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