

Vitamin D Deficiency in Newly Diagnosed Type 1 Diabetes Mellitus

Khatia Khvedelidze, MD¹;

Mariami Azirashvili, MD²;

Nato Tsiklauri, MD³;

Teona Nutsunidze, MD⁴.

¹ Department of Endocrinology, Caucasus Medical Center;

² Department of Endocrinology, Consilium Medulla Multiprofile Clinic;

³ Department of Endocrinology, Aversi Clinic;

⁴ Endocrinologist, National Institute of Endocrinology.

DOI: <https://doi.org/10.52340/spectri.2026.13.01.07>

Background: Type 1 diabetes mellitus (T1DM) is a multifactorial autoimmune disease in which environmental and nutritional factors interact with genetic susceptibility to drive β -cell destruction. Vitamin D has attracted growing interest for its immunomodulatory effects, mediated through vitamin D receptors expressed on immune cells and pancreatic β -cells.

Objective: This narrative review synthesizes current evidence on the role of vitamin D deficiency in the onset and progression of newly diagnosed T1DM, integrating mechanistic, epidemiological, and clinical data.

Methods: A narrative review of basic science, epidemiological, observational, and interventional studies addressing vitamin D metabolism, immunoregulation, and its relationship to T1DM.

Key Findings: Vitamin D modulates T-helper cell balance (suppressing Th1/Th17, promoting Th2/Treg), reduces pro-inflammatory cytokines, inhibits β -cell ferroptosis and apoptosis, and supports regulatory T-cell function. Vitamin D deficiency is highly prevalent at T1DM diagnosis (approximately 45–56% in pediatric cohorts) and shows seasonal and age-related variation. Birth-cohort studies suggest supplementation during infancy may reduce T1DM risk, while interventional trials in newly diagnosed patients show inconsistent results, with the strongest signals for short-term preservation of C-peptide/ β -cell function and enhanced Treg activity using cholecalciferol (vitamin D₃). No universally accepted dosing guidelines currently exist.

Conclusion: Vitamin D deficiency is common and mechanistically plausible as a contributor to T1DM pathogenesis, but current evidence supports correlation rather than proven causation. Routine screening in newly diagnosed pediatric T1DM patients is reasonable given the high deficiency prevalence, while large, standardized randomized controlled trials are needed to establish optimal dosing, timing, and clinical benefit.

Keywords: Vitamin D deficiency, Type 1 diabetes mellitus

D ვიტამინის დეფიციტი ახლად დიაგნოზირებული ტიპი 1 შაქრიანი დიაბეტის დროს

¹ხატია ხვედელიძე

²მარიამი აზირაშვილი

³ნატო წიკლაური

⁴თეონა ნუცუბიძე

¹კავკასიის მედიცინის ცენტრი; ² კონსილიუმ მედულა; ³ავერსის კლინიკა; ⁴

ენდოკრინოლოგიის ეროვნული ინსტიტუტი

შესავალი: ტიპი 1 დიაბეტი (T1DM) არის მრავალფაქტორული აუტოიმუნური დაავადება, რომლის დროსაც გარემო და კვებითი ფაქტორები ურთიერთქმედებენ გენეტიკურ მიდრეკილებასთან და იწვევენ β -უჯრედების დესტრუქციას. მზარდი ინტერესია ვიტამინ D-ის მიმართ მისი იმუნომოდულატორული ეფექტების გამო, რომლებიც განპირობებულია იმუნურ და პანკრეასის β -უჯრედებზე არსებული ვიტამინ D რეცეპტორებით.

მიზანი: მიმოხილვა აჯამებს არსებულ მონაცემებს ვიტამინ D-ის დეფიციტის როლის შესახებ ახლადდიაგნოზირებული T1DM-ის განვითარებასა და პროგრესირებაში, აერთიანებს მექანისტურ, ეპიდემიოლოგიურ და კლინიკურ მონაცემებს.

მეთოდები: ნარატიული მიმოხილვა ჩატარდა ბაზისური მეცნიერების, ეპიდემიოლოგიური, დაკვირვებითი და ინტერვენციული კვლევების საფუძველზე, რომლებიც ეხება ვიტამინ D-ის მეტაბოლიზმს, იმუნორეგულაციას და მის კავშირს T1DM-თან.

ძირითადი მიგნებები: ვიტამინ D არეგულირებს T-ჰელპერული უჯრედების ბალანსს

(თრგუნავს Th1/Th17-ს, ხელს უწყობს Th2/Treg-ს), ამცირებს პროანთებით ციტოკინებს, თრგუნავს β -უჯრედების ფეროპტოზსა და აპოპტოზს და მხარს უჭერს რეგულატორული T-უჯრედების ფუნქციას. ვიტამინ D-ის დეფიციტი ფართოდ არის გავრცელებული T1DM-ის დიაგნოზის დროს (დაახლოებით 45–56% პედიატრიულ კოჰორტებში) და ხასიათდება სეზონური და ასაკობრივი ცვალებადობით. დაბადებიდან მოყოლებული კოჰორტული კვლევები აჩვენებს, რომ ვიტამინ D-ის დამატებამ ჩვილობის პერიოდში შესაძლოა შეამციროს T1DM-ის რისკი, თუმცა ინტერვენციული კვლევების შედეგები ახლადდიაგნოსტირებულ პაციენტებში არაერთგვაროვანია. ყველაზე მკაფიო შედეგები, კოლეკალციფეროლის (ვიტამინ D_3) გამოყენებისას, უკავშირდება C-პეპტიდის/ β -უჯრედის ფუნქციის ხანმოკლე შენარჩუნებას და Treg-აქტივობის გაძლიერებას. ამჟამად არ არსებობს საყოველთაოდ მიღებული დოზირების რეკომენდაციები.

დასკვნა: ვიტამინ D-ის დეფიციტი ხშირია და მექანიზმის დონეზე სარწმუნო წვლილი შეაქვს T1DM-ის პათოგენეზში, თუმცა არსებული მონაცემები მხოლოდ კორელაციას ადასტურებს, არა მტკიცე მიზეზობრივ კავშირს. ვიტამინ D-ის სკრინინგი ახლადდიაგნოსტირებულ პედიატრიულ T1DM პაციენტებში გამართლებულია D ვიტამინის დეფიციტის მაღალი გავრცელების გამო, ხოლო ოპტიმალური დოზირების, დროისა და კლინიკური სარგებლის დასადგენად საჭიროა მასშტაბური, სტანდარტიზებული რანდომიზებული კონტროლირებადი კვლევები.

საკვანძო სიტყვები: D ვიტამინის დეფიციტი, ტიპი 1 შაქრიანი დიაბეტი.

Background: vitamin D deficiency is notable due to its immunomodulatory effects, prompting interest in vitamin D supplementation as a potential preventive or therapeutic strategy for autoimmune diseases, including T1DM.

The aim of the study is to assess vitamin D deficiency in newly diagnosed type 1 diabetes mellitus.

Introduction

1.1. Background on Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes (T1DM) is the most common form of diabetes seen in children and adolescents, although it can appear at any age. [1] It's a chronic autoimmune condition in which the body

gradually destroys its own pancreatic β -cells, leading to reduced insulin production over time and, eventually, the need for lifelong insulin therapy. [2][3] Common symptoms include polyuria, polydipsia, fatigue, and unintentional weight loss. [2]

1.2. Role of Environmental and Nutritional Factors in Autoimmunity

Type 1 diabetes (T1DM) is a multifactorial disease in which environmental exposures interact with genetic susceptibility to trigger autoimmunity against pancreatic β -cells. [2] [4] Epidemiological and experimental evidence links enterovirus infections, early growth patterns, and gut-microbiome alterations to the development of islet autoimmunity. [4] Among nutritional factors, vitamin D deficiency is notable due to its immunomodulatory effects, prompting interest in vitamin D supplementation as a potential preventive or therapeutic strategy for autoimmune diseases, including T1DM. [5]

1.3. Rising Interest in Vitamin D and Immune Function

Scientific interest in vitamin D has expanded beyond its role in bone metabolism, highlighting its strong immunomodulatory effects mediated through the vitamin D receptor (VDR) on immune cells and pancreatic β -cells. [6] As a result, vitamin D has become a major research focus, particularly regarding its influence on diabetes onset and its potential to mitigate disease progression and complications. [7]

1.4. Objective of This Narrative Review

This narrative review evaluates current evidence on vitamin D's role in the development and progression of Type 1 Diabetes Mellitus (T1DM). Given the controversial clinical trial results, it integrates basic science findings, epidemiological data, and clinical research to clarify the vitamin D–T1DM relationship, identify research gaps, and propose future directions for prevention and clinical practice.

Vitamin D: Overview and Immunological Role

2.1. Metabolism of Vitamin D: From Synthesis to Active Form

Vitamin D₃ can be produced in the skin under UV-B light or obtained as dietary vitamin D₂. [8] In all forms, it is inactive and must undergo two hydroxylation steps. [8] [6] In the liver, CYP2R1 converts it to 25(OH)D, the main indicator of vitamin D status. The kidneys then transform 25(OH)D into the active hormone 1,25(OH)₂D via CYP27B1. Extrarenal sites such as monocyte-macrophages can also produce the active form, supporting local immune regulation. [8]

2.2. Vitamin D Receptor (VDR) Expression in Immune Cells and Pancreatic β -Cells

Vitamin D acts broadly due to VDRs being present in many non-skeletal tissues. Immune cells express VDRs and can metabolize active vitamin D, enabling both autocrine and paracrine regulation of immune responses. [9] VDRs are also present in pancreatic β -cells, suggesting that vitamin D supports their function. [3]

2.3. Vitamin D as an Immunomodulator

2.3.1. Impact on T-Helper Cells (Th1/Th2 Balance)

Active vitamin D modulates T-helper cell differentiation by binding VDRs on activated T cells, reducing pro-inflammatory Th1 and Th17 cells while promoting Th2 and regulatory T cell (Treg) phenotypes. [7] This shift lowers Th1 cytokines (IFN- γ , IL-2) and increases anti-inflammatory mediators (IL-4, IL-5, IL-10). [7] In T1DM, vitamin D supplementation downregulates cathepsin G, reducing CD4⁺ T cell activation, limiting Th1 dominance, and enhancing Th2/Treg proportions. [9] This modulation helps dampen autoimmunity and preserves pancreatic β -cell function, potentially improving clinical outcomes. [9] [3]

2.3.2. Suppression of Pro-Inflammatory Cytokines (IL-1, IL-6, TNF- α)

Vitamin D reduces inflammation by downregulating key pro-inflammatory cytokines—IL-1 β , IL-6, and TNF- α —linked to β -cell damage and autoimmunity in T1DM. [3] It also inhibits NF- κ B phosphorylation and LPS-induced p38 activation, further limiting IL-6 and TNF- α production. [3] In human monocytes, vitamin D enhances anti-inflammatory pathways, including IL-10 secretion and antioxidant enzyme activity, promoting a tolerogenic immune environment. [7] This cytokine suppression can prolong the “honeymoon phase” in T1DM by reducing inflammatory stress on remaining β cells. [9]

2.3.3. Role in Regulatory T-Cell Function

Vitamin D supplementation increases the frequency and suppressive function of regulatory T cells (Tregs) in autoimmune diseases, including T1DM, systemic sclerosis, and multiple sclerosis. [9] Tregs are crucial for maintaining immune tolerance and preventing autoreactive T cell activity. [7] Vitamin D also supports Treg function indirectly by promoting tolerogenic dendritic cells with lower MHC-II and co-stimulatory molecule expression, limiting effector T cell activation, and fostering a regulatory immune environment. [3] Through these mechanisms, vitamin D helps restore immune balance and reduce autoimmune tissue damage. [9] [3] [7]

Epidemiology of Vitamin D Deficiency in T1DM

3.1. Global and Regional Prevalence in Newly Diagnosed Patients

T1DM will affect an estimated 9.5 million people worldwide in 2025, a 13% increase since 2021, largely due to better diagnosis, population growth, and reduced mortality. Most cases occur in individuals under 20, especially in low- and middle-income countries. Despite rising prevalence, data on vitamin D deficiency in newly diagnosed T1DM patients remain limited, particularly in under-resourced regions where malnutrition and diagnostic gaps may worsen deficiency. [1] This makes it challenging to clearly define the relationship between vitamin D deficiency and T1DM.

3.2. Age-Specific and Seasonal Variations in Vitamin D Levels at Diagnosis

Vitamin D deficiency at T1DM diagnosis shows clear seasonal variation, being more common in winter among children and adolescents. [10] Age is also a factor: a study in Bangladesh found vitamin D-deficient patients were significantly older than those with sufficient or insufficient levels at diagnosis ($p = 0.029$), indicating increased vulnerability with age. [11]

3.3. Geographic and Ethnic Differences

T1DM incidence, diagnosis, and outcomes vary geographically, with limited or outdated data from Africa, South America, and Asia. Ethnic differences add complexity, as non-European populations more often present with autoantibody-negative T1DM, increasing diagnostic uncertainty. [1] Although low vitamin D status is consistently associated with T1DM, the strength of this relationship differs by region, study design, and deficiency cutoff. Current evidence shows correlation, not causation—vitamin D deficiency is more common in T1DM, but whether it contributes to disease onset or results from it remains unclear. [10]

3.4. Prevalence in Children, Adolescents, and Adults

While T1DM is often seen as a childhood disease, most people with T1DM today were diagnosed as adults. The median global age of patients is 36, with over 1.1 million aged 60 or older. Diagnostic overlap with type 2 diabetes, particularly in older and non-European populations, complicates accurate epidemiology. Limited adult-focused data suggest that T1DM prevalence in older populations has historically been underestimated. [1]

Pathophysiological Links Between Vitamin D Deficiency and T1DM

4.1. Autoimmunity and Pancreatic Islet Cell Destruction

Low vitamin D levels are linked to autoimmune diseases, including T1DM, MS, IBD, RA, and SLE. Vitamin D helps maintain immune homeostasis by modulating T cells, B cells, monocytes/macrophages, dendritic cells, and other immune components, reducing autoimmune responses. [9] In T1DM, immune cell infiltration of pancreatic islets drives β -cell destruction. Vitamin D deficiency impairs T-cell regulation, increasing chemokine secretion and recruiting more immune cells to target β cells. [3]

4.2. Hypotheses on Vitamin D as a Protective Factor

Vitamin D promotes an anti-inflammatory, tolerogenic immune environment, regulating monocyte/macrophage function and reducing excessive immune responses. [9] It modulates T cells, limits $CD4^+$ activation, protects β cells, and reduces oxidative stress in T1DM. [3] Adequate vitamin D, especially early in life, may protect against T1D, while deficiency is common in patients. Vitamin D analogues like calcipotriol can protect islets from IL-1 β damage. [8]

4.2.1. Inhibition of Dendritic Cell Maturation

Vitamin D modulates dendritic cell (DC) function by inhibiting their maturation, creating tolerogenic DCs with low MHC expression that cannot present antigens. [9] [3] This leads to T cell unresponsiveness, suppressing B cell proliferation, plasma cell differentiation, memory β -cell formation, and autoantibody production. [3]

4.2.2. Reduction of β -Cell Stress, Apoptosis, and Ferroptosis:

Vitamin D protects β cells from immune-mediated damage, reduces oxidative stress, and regulates T cells in T1DM. [3] It inhibits β -cell ferroptosis via the $1,25(OH)_2D_3/VDR/FOXO1$ pathway, promotes autophagy, reduces apoptosis, enhances insulin secretion, and improves stress resistance. Vitamin D also protects retinal epithelial cells from high glucose-induced oxidative stress, inflammation, and ferroptosis, potentially preventing diabetic retinopathy. [7] Additionally, vitamin D lowers nitric oxide levels via upregulating the A20 protein, preserving β -cell function, and exerts antioxidant effects in monocytes and macrophages by boosting glutathione synthesis and recycling. [7] [9]

4.3. Vitamin D and Autoantibody Development (GAD65, IA-2, ZnT8)

T1DM progresses through four stages, with Stage 1 marked by persistent islet autoantibodies (ICAs, IAAs, GAD65, IA-2, and ZnT8) while individuals remain normoglycemic. [3] Vitamin D levels

show an inverse, though not statistically significant, association with ZnT8 autoantibodies. Observational studies suggest a link between vitamin D deficiency and T1D, but clinical trials remain inconclusive, indicating the need for larger randomized studies. [12]

4.4. Genetic susceptibility

4.4.1. VDR gene polymorphisms

The potential role of VDR gene polymorphisms in type 1 diabetes appears increasingly plausible. Four well-studied polymorphisms—ApaI, BsmI, TaqI, and FokI—have been investigated for their association with T1DM. Notably, the Environmental Determinants of Diabetes in the Young (TEDDY) study, a large prospective cohort of children at elevated T1DM risk based on HLA genotype or family history, is being conducted across centers in the USA and Europe [13]

A recent case-control study conducted at three major hospitals in Kuwait (Adan, Farwania, and Mubarak Al-Kabeese) analyzed four VDR gene polymorphisms in 253 children with newly diagnosed T1DM. The findings indicate that the FokI and TaqI polymorphisms are significantly associated with increased susceptibility to T1DM, contributing to genetic predisposition. [13]

Numerous studies have investigated the association between vitamin D receptor (VDR) polymorphisms and type 1 diabetes. Zhang et al. addressed this in a meta-analysis of 26 studies examining VDR gene variants in relation to T1D risk. [8]

In an Iranian study involving 101 children with T1D, several VDR polymorphisms were found to be associated with higher fasting and/or stimulated C-peptide levels, indicating better residual β -cell function. Additionally, serum vitamin D levels were positively correlated with C-peptide concentrations. [8]

4.4.2. HLA-DR/DQ interactions

Genetic predisposition to β -cell autoimmunity and subsequent type 1 diabetes is primarily associated with specific human leukocyte antigen (HLA) class II haplotypes involved in antigen presentation, particularly HLA-DR3-DQ2, HLA-DR4-DQ8, or both. [13]

HLA-DR genes are associated with progression from stages 1 and 2 to stage 3 type 1 diabetes, independent of the effects of linked HLA-DQ genes. [14]

Type 1 diabetes is associated with HLA-DR and -DQ loci, but pinpointing primary risk alleles is challenging due to limited recombination in the DR–DQ region. To investigate this, HLA genotype risks were analyzed in over 420 newly diagnosed children with type 1 diabetes and 340 matched controls from Sweden. [15]

The genetic risk for type 1 diabetes is largely attributed to allelic variants in the HLA class II locus, with the highest risk conferred by DRB104 (*DR4*), DRB103 (*DR3*), and DQB1*03:02 (*DQ8*) [16]

5. Clinical Evidence and Studies

5.1 - Observational studies linking vitamin D deficiency to T1DM onset

Several studies report a higher prevalence of vitamin D deficiency in children and adolescents with new-onset T1DM compared to healthy controls. [13]

The association between vitamin D and type 1 diabetes may be mediated through its immunomodulatory effects. The active form, 1,25-dihydroxyvitamin D, has been shown to reduce immune system activation [17]

The DISS (Diabetes Incidence Study in Sweden) study reported lower 25(OH)D levels in T1DM patients vs. controls at onset and after 8 years. [18]

Conversely, long-term follow-up studies in children suggest no association between pre-diagnostic vitamin D status and subsequent T1DM development. [13]

While vitamin D's roles in glucose metabolism and immune modulation have been extensively studied, the underlying mechanisms remain partially understood and are largely based on experimental or observational data rather than definitive causal evidence [19]

5.2 - Prospective studies and birth cohort findings

Studies assessing 25(OH)D levels or vitamin D-enriched food intake during pregnancy in relation to T1DM risk remain inconclusive. However, Sorensen et al. reported significantly lower 25(OH)D levels in Norwegian pregnant women whose children later developed T1DM, compared to those whose children did not. [2]

A landmark Finnish birth cohort study reported an approximately 80% reduction in type 1 diabetes risk among infants who received regular vitamin D supplementation. A subsequent systematic review and meta-analysis supported this finding, showing a 29% lower risk of type 1 diabetes in supplemented children [19].

In a birth cohort of 10,366 children, vitamin D supplementation was associated with a significantly reduced risk of type 1 diabetes (RR: 0.12; 95% CI: 0.03–0.51), suggesting a strong inverse association. [17]

In contrast, a case-control study of 383 Finnish women from the Finnish Maternity Cohort found no difference in first-trimester serum vitamin D levels between mothers of children who later developed T1DM and those of age-matched non-diabetic children (0–7 years) [13]

A report from the All Babies in Southeast Sweden (ABIS) study, using questionnaire data from 16,339 mothers, found no significant association between maternal vitamin D intake during pregnancy and the risk of T1DM in offspring aged 14–16 years [13]

5.3 - Interventional studies on vitamin D supplementation at or before diagnosis

Several interventional studies and randomized controlled trials have reported positive outcomes in patients with type 1 diabetes when vitamin D₃ supplementation is combined with insulin therapy, including improvements in β -cell function [2]

Numerous studies have investigated the impact of vitamin D supplementation during pregnancy, infancy, or early adulthood on the risk of developing T1DM later in life [18]

In a Finnish birth cohort study, Hyppönen et al. found that daily vitamin D supplementation (200 IU, via cod liver oil) in childhood was associated with a reduced incidence of T1DM over a 31-year follow-up [20]

In an observational birth cohort of 10,366 children, vitamin D supplementation was linked to a significantly reduced risk of type 1 diabetes (RR 0.12, 95% CI 0.03–0.51). The TEDDY study, involving 8,676 children, reported a modest inverse association between 25OHD levels and T1D risk (OR 0.93 per 5 nmol/L increase; 95% CI 0.89–0.97). [17]

Most studies using 1,25-dihydroxyvitamin D, the active form of vitamin D, have shown no significant benefit, with only one open-label study in 70 participants reporting a reduced insulin requirement at 3 and 6 months. [8]

5.4 - Contradictory findings and study limitations

Despite some positive findings, outcomes from human trials have been generally inconsistent and often disappointing. These variations may be attributed to several factors, including the form of vitamin D used (25(OH)D vs. 1,25(OH)₂D), intervention duration, dosage, and the stage of disease at the time of treatment [8]

Interestingly, all but one study investigating 25(OH)D alone reported beneficial effects; the one exception did not reach statistical significance but observed a trend toward benefit. Most studies using 1,25(OH)₂D, the active form of vitamin D has shown limited efficacy, with only one open-label study in 70 subjects reporting a reduced insulin dose at 3 and 6 months, but not beyond. [8]

One small study of 36 individuals with T1D and 27 controls found no differences in 25(OH)D levels or vitamin D-binding protein (DBP). Additionally, another study reported no association between vitamin D status and β -cell autoantibodies or FOXP3 expression in T cells. [8]

The variability in outcomes from human trials is generally disappointing, with, at best, only short-term benefits observed in newly diagnosed T1DM patients. Consequently, most researchers conclude that large-scale, prospective randomized controlled trials are urgently needed to definitively determine the role of vitamin D in T1DM [13]

6. Clinical Implications

6.1. Routine Vitamin D Screening in New T1DM Cases:

There is a high prevalence of vitamin D deficiency among children, adolescents, and youth with T1D, affecting approximately **45% to 46%** of this population [21]. Some studies report an even higher prevalence, with **56%** of participants having 25(OH)D levels less than 30 ng/mL in one study of new-onset T1D [22].

In Sudanese children and adolescents with T1D, the prevalence of vitamin D deficiency was found to be relatively high [23].

Given this significant burden, there is a recognized **need for increased clinical awareness and potentially routine screening** in pediatric T1D patients [21].

6.2. Potential Benefits of Early Supplementation:

- **Severity and Progression:** Low 25(OH)D levels at T1D onset have been associated with **more aggressive autoimmunity** and potentially **lower beta-cell mass** [22].

Fasting C-peptide levels were significantly lower in vitamin D-deficient subjects compared to those who were vitamin D-sufficient [22]. This suggests that **correcting vitamin D deficiency in early T1D stages may delay disease progression** to clinical onset (stage 3) and/or slow the decline of C-peptide [22].

- **Immune Modulation and Glycemic Control:** Vitamin D plays an immunomodulatory role [7]. Supplementation with cholecalciferol (vitamin D₃) has been shown to **increase the percentage and suppressive capacity of regulatory T-cells** in new-onset T1D [22].

In one study, vitamin D supplementation led to a **significant decrease in fasting blood glucose** and a significant increase in vitamin D levels, though the improvement in HbA1c was not statistically significant [23]. Other research indicates that vitamin D supplementation can reduce inflammation, promote insulin secretion, and reduce insulin resistance [7].

It may also **prolong the "honeymoon phase"** of T1D by reducing inflammatory responses [7].

- **Risk Reduction:** Some studies suggest that vitamin D supplementation during infancy is associated with a **reduced risk of T1D** [4].

For example, a Finnish birth-cohort study found that vitamin D intake of >2000 IU/day in the first year of life was associated with a significantly reduced risk of T1D [4].

6.3. Challenges: Optimal Dose, Timing, and Formulation (D2 vs. D3):

- **Variability:** There is **considerable heterogeneity** across studies in terms of design, methodology, study populations, dosage and duration of supplementation, timing of intervention,

and methods of measuring vitamin D status [5]. This variability complicates the ability to draw definitive conclusions [5].

- **Lack of Consensus:** The **ideal daily dosage** of vitamin D supplementation and the **optimal serum 25(OH)D levels** for maximum benefits in T1D-risk individuals and early-stage patients and for blood sugar control and complication management still **require further research** [7] [21].

Some studies investigating the link between specific dosages (e.g., 2000IU or varied quartiles of intake) and T1D risk found no significant effect [5].

- **Definition of Deficiency:** The absence of a **universally accepted definition or threshold for vitamin D deficiency** leads to inconsistencies in prevalence estimates across studies [21].

- **Confounding Factors:** Age, pubertal status, gender, and glycemic control may also influence the relationship between vitamin D and T1D outcomes, but adjusting for these factors is challenging due to small sample sizes in some studies [22]

6.4. Current Clinical Guidelines and Expert Recommendations:

As of the information available, there are **no specific recommendations** regarding vitamin D supplementation for T1D patients or those at risk of developing autoimmune diabetes [20] [5].

However, some sources suggest that intakes between 5 mcg daily and the 25 mcg daily tolerable upper intake level might be desirable [20]. It is broadly recommended that clinicians screen for vitamin D deficiency in children and adolescents with T1D to guide appropriate supplementation [10].

7. Research Gaps and Future Directions

7.1. Need for Longitudinal and Interventional Studies:

- **Causality and Effectiveness:** Well-designed, large-scale, long-term randomized controlled trials (RCTs) are crucial to establish causality, define optimal dosing strategies, and determine the long-term outcomes and true efficacy of vitamin D supplementation in preventing T1D progression or improving outcomes [21].

- **Standardization:** Future research should aim for standardized protocols for vitamin supplementation (including timing, dosage, and blood concentration) and consistent outcome assessment to address the current heterogeneity in findings [5].

7.2. Pediatric-focused vs. Adult-focused Evidence Gaps: While some studies include both youth and adults, or primarily focus on children, the varying effects of age on vitamin D metabolism and T1D progression mean that more targeted research is needed for specific age groups [2]. The initial study mentioned focused on youth and adults with recent-onset T1D, but its small sample size limited adjustments for age [22].

7.3. Potential for Vitamin D as a Modifiable Risk Factor or Therapeutic Target: Vitamin D is considered a substantial but modifiable public health risk factor for T1D [10].

Its role in immune regulation and its association with autoimmune disorders make it a potential therapeutic target [7]. Identifying and correcting vitamin D deficiency in at-risk individuals (stages 1 and 2 of T1D) or in newly diagnosed patients may prove important for preserving beta-cell function and slowing disease progression [22]. However, the multifactorial nature of T1D, involving genetic, epigenetic, environmental, and immunological factors, means that vitamin D's role is complex and may not be solely sufficient to prevent or significantly alter disease course [21]. Future research should also explore whether specific subgroups (e.g., those with severe deficiency) might benefit most from supplementation [21].

8. Conclusion

8.1. Summary of Key Findings

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune condition driven by the interaction of genetic susceptibility and environmental factors [3] [6] [7] [9]. Vitamin D has emerged as a critical nutritional factor due to its powerful immunomodulatory effects mediated through the vitamin D receptor (VDR) present on immune cells and pancreatic β -cells [1] [3] [6] [7] [8] [9]. Mechanistic studies demonstrate that active vitamin D modulates immune responses by reducing pro-inflammatory Th1 and Th17 cells while promoting Th2 and regulatory T cells (Tregs) [1] [3] [6] [8] [9]. Furthermore, vitamin D helps preserve β -cell function by reducing oxidative stress and inhibiting ferroptosis [1] [3] [7] [9]. Epidemiological data consistently reveal a high prevalence of deficiency in newly diagnosed pediatric patients, ranging from 45% to 56% [13] [21] [22]. While observational birth cohort studies have suggested that regular vitamin D supplementation during infancy may drastically reduce T1DM risk [17] [19] [20]. Interventional trial outcomes have been generally

inconsistent [8] [13] [21] [22]. Nevertheless, positive findings, particularly when using cholecalciferol (Vitamin D₃), include short-term improvements in β -cell function (C-peptide levels) and enhanced regulatory T-cell suppressive capacity in new-onset T1D [6] [7] [22] [23].

8.2. Clinical Takeaways for Endocrinologists and Pediatricians

Given the significant prevalence of vitamin D deficiency in T1D patients, there is a recognized need for increased clinical awareness and routine screening for vitamin D status in this population [2] [18] [21] [22] [23]. Low 25(OH)D levels at diagnosis are associated with more aggressive autoimmunity and potentially lower β -cell mass [21] [22] [23]. Consequently, correcting deficiency in the early stages of T1D is suggested to delay disease progression and the decline of C-peptide levels [21] [22] [23]. Supplementation may also prolong the "honeymoon phase" by reducing inflammatory stress and supporting immune balance through increased Treg function [1] [4] [5] [7] [22] [23]. However, clinicians must recognize that there are no specific, universally accepted clinical guidelines regarding the optimal dose, duration, or timing of supplementation for T1D management or prevention [3] [5] [7] [9] [10] [20] [21] [22]. Current recommendations generally support screening and appropriate correction of deficiency [5] [10] [20] [22].

8.3. Final Thoughts on Public Health Relevance

Vitamin D is a substantial but modifiable public health risk factor for T1D [2] [8] [9] [10] [22]. Its key role in immune regulation positions it as a potential therapeutic target [1] [7] [21] [22]. Public health efforts aimed at identifying and correcting vitamin D deficiency—especially in at-risk individuals (Stages 1 and 2) and newly diagnosed patients—could be important for preserving residual β -cell function [7] [21] [22]. However, as T1DM is a multifactorial disease, relying solely on vitamin D may not be sufficient to alter the disease course significantly [7] [21] [22]. To resolve the current heterogeneity in findings and establish definitive efficacy, well-designed, large-scale, long-term randomized controlled trials (RCTs) are critically needed to standardize protocols and define optimal dosing strategies [5] [13] [21] [22].

References:

1. Ogle GD, Wang F, Haynes A, Gregory GA, King TW, Deng K, et al. Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, 11th Edition, and the T1D Index Version 3.0. *Diabetes Research and Clinical Practice* [Internet]. 2025 May 22;225:112277. Available from: <https://doi.org/10.1016/j.diabres.2025.112277>
2. Daskalopoulou M, Pylli M, Giannakou K. Vitamin D deficiency as a possible cause of Type 1 diabetes in children and adolescents up to 15 years old: a systematic review. *The Review of Diabetic Studies* [Internet]. 2022 Jun 30;18(2):58–67. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10044049/>
3. He LP, Song YX, Zhu T, Gu W, Liu CW. Progress in the Relationship between Vitamin D Deficiency and the Incidence of Type 1 Diabetes Mellitus in Children. *Journal of Diabetes Research* [Internet]. 2022 Sep 2;2022:1–8. Available from: <https://doi.org/10.1155/2022/5953562>
4. Quinn LM, Wong FS, Narendran P. Environmental determinants of Type 1 diabetes: From association to proving causality. *Frontiers in Immunology* [Internet]. 2021 Oct 1;12:737964. Available from: <https://doi.org/10.3389/fimmu.2021.737964>
5. Low CE, Chew NSM, Rana S, Loke S, Chin RT, Kao SL, et al. Vitamin supplementation and its effect on incident type 1 diabetes mellitus and islet autoimmunity: a systematic review and meta-analysis. *Frontiers in Immunology* [Internet]. 2025 Apr 9;16:1505324. Available from: <https://doi.org/10.3389/fimmu.2025.1505324>
6. Artusa P, White JH, McGill University, McGill University. Vitamin D and its analogs in immune system regulation [Internet]. *Pharmacological Reviews*. 2025. Available from: <https://doi.org/10.1016/j.pharmr.2024.100032>
7. Li C, Fu J, Ye Y, Li J, He Y, Fang T. The impact of vitamin D on the etiopathogenesis and the progression of type 1 and type 2 diabetes in children and adults. *Frontiers in Endocrinology* [Internet]. 2024 Apr 8;15:1360525. Available from: <https://doi.org/10.3389/fendo.2024.1360525>
8. Yu J, Sharma P, Girgis CM, Gunton JE. Vitamin D and Beta cells in Type 1 diabetes: a systematic review. *International Journal of Molecular Sciences* [Internet]. 2022 Nov 20;23(22):14434. Available from: <https://doi.org/10.3390/ijms232214434>

9. Daryabor G, Gholijani N, Rezaei Kahmini F. A review of the critical role of vitamin D axis on the immune system [Internet]. Vols. 132–133, Experimental and Molecular Pathology. 2023 p. 104866. Available from: <https://doi.org/10.1016/j.yexmp.2023.104866>
10. Yang X, Chai M, Lin M. Proportion of vitamin D deficiency in children/adolescents with type 1 diabetes: a systematic review and meta-analysis. BMC Pediatrics [Internet]. 2024 Mar 16;24(1):192. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10943883/>
11. Zabeen B, Nahar J, Ahmed B, Tayyeb S, Islam N, Azad K. Vitamin D status in children and adolescents with type 1 diabetes in a specialized diabetes care centre in Bangladesh. Endocrinology Diabetes & Metabolism [Internet]. 2021 Nov 12;5(1):e00312. Available from: <https://pubmed.ncbi.nlm.nih.gov/34766458/>
12. Fuentes-Cantero S, González-Rodríguez C, Rodríguez-Chacón C, Galvan-Toribio R, Hermosín-Escudero J, Pérez-Pérez A, et al. Study of the diagnostic efficiency of anti-ZnT8 autoantibodies for type 1 diabetes in pediatric patients. Laboratory Medicine [Internet]. 2023 Sep 2;55(3):299–303. Available from: <https://doi.org/10.1093/labmed/lmad079>
13. Durá-Travé T, Gallinas-Victoriano F. Type 1 diabetes mellitus and vitamin D. Francesca Silvagno, Loredana Bergandi, editors. Int J Mol Sci [Internet]. 2025 May 11;4593. Available from: <https://doi.org/10.3390/ijms26104593>
14. Zhao LP, Papadopoulos GK, Skyler JS, Kwok WW, Bondinas GP, Moustakas AK, et al. Two DRB3 residues predictively associate with the progression to type 1 diabetes among DR3 carriers. JCI Insight [Internet]. 2025 Mar 4;10(7). Available from: <https://insight.jci.org/articles/view/184348>
15. Kockum I, Sanjeevi CB, Eastman S, Landin-Olsson M, Dahlquist G, Lernmark Å. Complex interaction between HLA DR and DQ in conferring risk for childhood type 1 diabetes. European Journal of Immunogenetics [Internet]. 1999 Oct 1;26(5):361–72. Available from: <https://pubmed.ncbi.nlm.nih.gov/10553503/>
16. The high-risk type 1 diabetes HLA-DR and HLA-DQ polymorphisms are differentially associated with growth and IGF-1 levels in infancy: the Cambridge Baby Growth Study. Supplementary Material. <https://pubmed.ncbi.nlm.nih.gov/34172490/>
17. Manousaki D, Harroud A, Mitchell RE, Ross S, Forgetta V, Timpson NJ, et al. Vitamin D levels and risk of type 1 diabetes: A Mendelian randomization study. PLoS Medicine [Internet]. 2021 Feb 25;18(2):e1003536. Available from: <https://doi.org/10.1371/journal.pmed.1003536>

18. Chakhtoura M, Azar ST. The role of vitamin D deficiency in the incidence, progression, and complications of Type 1 diabetes mellitus. *International Journal of Endocrinology* [Internet]. 2013 Jan 1;2013:1–10. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3610375/>
19. Nasser A, Papandreou D, Papadopoulou SK, Ismail LC. The role of vitamin D supplementation in Type 1, Type 2, and gestational Diabetes: A Comprehensive Updated Narrative review. *Clinics and Practice* [Internet]. 2025 Aug 7;15(8):148. Available from: <https://doi.org/10.3390/clinpract15080148>
20. Chakhtoura M, Azar ST. The role of vitamin D deficiency in the incidence, progression, and complications of Type 1 diabetes mellitus. *International Journal of Endocrinology* [Internet]. 2013 Jan 1;2013:1–10. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3610375/#B100>
21. Barot KS, Abbasi ZA, Mohan GVK, Abid SA, Hussain SA, Wei CR, et al. Prevalence of Vitamin D Deficiency in children and Adolescents with Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Cureus* [Internet]. 2025 May 10;17(5):e83843. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12147980/>
22. Baidal DA, Alvarez AM, Padilla N, Sanchez J, Lanzoni G, Alejandro R, et al. 25(OH) vitamin D levels and severity of Type 1 diabetes in youth and Adults with Recent-Onset Disease. *Journal of the Endocrine Society* [Internet]. 2025 Apr 10;9(6):bvaf061. Available from: <https://doi.org/10.1210/jendso/bvaf061>
23. Suliman HA, Elkhawad AO, Babiker OO, Alhaj YM, Eltom KH, Elnour AA. Does vitamin D supplementation benefit patients with type 1 diabetes mellitus who are vitamin D deficient? A study was performed at the Sudan Childhood Diabetes Center from 2019 to 2022. *SAGE Open Medicine* [Internet]. 2024 Jan 1;12:20503121241242931. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11072061/>