

The Effects of Vitamin D Supplementation in Newly Diagnosed Type 1 Diabetes Patients: Systematic Review of Randomized Controlled Trials

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■ Abstract

AIM: The aim of this study was to examine the effects of vitamin D supplementation in patients newly diagnosed with type 1 diabetes (T1D) assessed by insulin needs and changes in glycemic indices, as evidenced by randomized controlled trials (RCTs). **METHODS:** A total of 7 RCTs were retrieved from PubMed/Medline and EBSCO databases by MeSH term search, and were reviewed systematically. The RCTs included examined the effects of alphacalcidole (n = 2), cholecalciferol (n = 2), and calcitriol (n = 3) supplementation on changes in daily insulin dose (DID), fasting C-peptide (FCP), stimulated C-peptide (SCP), and HbA1c. In

total, 287 individuals, diagnosed with T1D within a period of 4 weeks to 1 year and aged between 5 to 38 years, were examined. **RESULTS:** Significant positive effects on DID, FCP, and SCP levels were observed after supplementation with alphacalcidole and cholecalciferol, whereas supplementation with calcitriol showed no effect. **CONCLUSIONS:** Vitamin D supplementation in the form of alphacalcidole and cholecalciferol appears to be beneficial in the treatment of T1D patients by attenuating the natural history of the disease.

Keywords: type 1 diabetes · new-onset diabetes · vitamin D · randomized control trial · insulin · HbA1c · pancreatic beta-cell · stimulated C-peptide · fasting C-peptide

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease leading to β -cell destruction in the pancreas and concurrent insulin deficiency [1, 2]. Data from large epidemiologic studies indicate that the incidence of T1D has been increasing by 2-5% worldwide, and that the prevalence of T1D is approximately 1 in 300 US citizens over the age of 18 [3]. This alarming trend has triggered extensive research to detect the mechanisms involved in T1D pathophysiology and develop new agents. This re-

search has led to the discovery of associations with multiple endocrine, paracrine, and immunological pathways, including those related to vitamin D [4].

Vitamin D, also known as calciferol, exists in two major forms, namely vitamin D₂ or ergocalciferol and vitamin D₃ or cholecalciferol, which are mainly found in plant and animal products, respectively [4, 5]. Cholecalciferol can also be synthesized in the skin through ultraviolet B radiation [4]. The inactive forms of vitamin D are transported to the liver where they are hydroxylated and converted into 25-hydroxyvitamin D

(25(OH)D) or calcidiol. Thereafter, calcidiol is converted to the biologically active form of the vitamin, 1,25-dihydroxyvitamin D (1,25(OH)₂D) or calcitriol [6].

Alphacalcidole is another form of vitamin D₃, which is used extensively in the treatment of renal osteopathy as it allows the ingestion of higher doses of vitamin D with a reduced risk of hypercalcemia, and it can be produced at relatively low costs compared to calcitriol [7]. Previous studies have demonstrated that the daily use of alphacalcidole is well tolerated with few observed adverse effects [8, 9]. Nevertheless, the recommended dietary allowance (RDA) published by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (formerly National Academy of Sciences) for people between 1 and 70 years, is no higher than 600 IU/day, while for the elderly (>70 years) it is 800 IU/day [10].

In vitro studies in human cell lines and animal studies indicate that vitamin D exhibits anti-inflammatory and immunomodulatory properties [11-13]. Based on the findings of preclinical studies, vitamin D seems to play a regulatory role in insulin secretion, β -cell survival, and calcium flux within pancreatic β -cells [6]. Furthermore, numerous studies have shown that vitamin D supplementation may restore glucose-stimulated insulin [4, 14].

The potential biological mechanisms by which the insufficient levels of vitamin D might be associated with the development of T1D remain unclear. Primary evidence from *in vitro* studies has shown that pancreatic tissue, specifically pancreatic islets, express vitamin D receptors (VDRs) and 25-hydroxyvitamin D₃-1 α -hydroxylase (1 α -OHase) [15], an enzyme that catalyzes the hydroxylation of 25(OH)D (calcifediol) to 1,25(OH)₂D₃ (calcitriol). Furthermore, the pancreas responds to circulating levels of 1,25(OH)₂D₃ [13]. Thus, the expression and activity of 1 α -OHase in pancreatic islets and the timely response of insulin-secreting cells to 1,25(OH)₂D₃ suggest that locally produced 1,25(OH)₂D₃ is vital for physiological islet function [15].

There is evidence supporting the hypothesis of a 1,25(OH)₂D₃-induced activation of insulin biosynthesis. However, results remain divergent. While an *in vitro* effect was found, including the activation of pre-proinsulin messenger RNA (mRNA) in 48-h cultured islets from fed rats, no effect of 1,25(OH)₂D₃ on insulin biosynthesis was observed *in vivo* [16]. Furthermore, supplementation of vitamin D-deficient animals with vitamin D restored insulin secretion [16].

Abbreviations:

1,25(OH) ₂ D	1,25-dihydroxyvitamin D
1,25(OH) ₂ D ₃	1,25-dihydroxyvitamin D ₃
1 α -OHase	25-hydroxyvitamin D ₃ -1 α -hydroxylase
25(OH)D	25-hydroxyvitamin D
CCBRG	Cochrane Collaboration Back Review Group
DID	daily insulin dose
FCP	fasting C-peptide
FNB	Food and Nutrition Board
HbA1c	hemoglobin A1c
HLA	human leucocyte antigen
LADA	latent autoimmune diabetes of the adult
mRNA	messenger RNA
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines
PICOS	Participants, Interventions, Comparisons, Outcomes, and Study design approaches
RCT	randomized controlled trial
RDA	recommended dietary allowance
SCP	stimulated C-peptide
SMBG	self-monitored blood glucose
T1D	type 1 diabetes
T2D	type 2 diabetes
VDR	vitamin D receptor

Vitamin D may act synergistically or additively with other nutrients on insulin secretion, e.g. with calcium [15]. However, our understanding of the exact mechanism by which vitamin D and calcium or other nutrient-to-nutrient interactions may enhance β -cell function or improve insulin resistance remains limited.

Despite a large amount of evidence from experimental and observational studies supporting the promising outcomes of the effects of vitamin D on glucose metabolism and the immune system, results from clinical studies remain inconsistent, which makes it impossible to recommend vitamin D supplementation for the treatment of T1D [1]. Thus, the aim of this systematic review was to examine the effects of vitamin D supplementation on insulin deficiency in newly diagnosed T1D patients, as reported by randomized controlled trials (RCTs). A secondary aim was to review information on the most effective, safe, and appropriate type of vitamin D, as well as its dosage and duration of supplementation required for the potential treatment of T1D.

2. Methodology

2.1 Search strategy

A systematic review was carried out using PubMed/Medline and EBSCO databases. The search strategy included medical subject heading

Table 1. Search strings and keywords used to select the studies

No.	Search string / keywords	EBSCO	PubMed
1	(((((Vitamin D) OR 1-alpha-hydroxyvitamin D3) OR ergocalciferol) OR cholecalciferol) OR calcitriol) OR alfalcidol) OR alphacalcidole) OR 1alpha,25-dihydroxyvitamin D3)	93,285	51,195
2	(((((Type 1 diabetes) OR pancreatic beta-cell) OR diabetes treatment) OR T1D) OR new-onset T1D) OR recent-onset T1D) OR T1D) OR beta-cell residual function)	101,237	31,819
3	(((((Stimulated C-peptide) OR AUC C-peptide) OR fasting C-peptide) OR FCP) OR HbA1c) OR A1c) OR insulin requirement) OR daily insulin dose) OR DID)	3,025,635	29,651
4	((Randomized control trial) OR RCT) OR randomized)	713,856	385,667
5	1-4 combined	34	11

Legend: AUC - area under the curve, DID - daily insulin dose, FCP - fasting C-peptide, HbA1c - glycated hemoglobin, RCT - randomized controlled trial, T1D - type 1 diabetes

(MeSH) terms, as shown in **Table 1**. Chronologically limited RCTs were considered only. A secondary scan of the lists of retrieved papers was performed to identify any additional RCTs that met the inclusion criteria, as outlined below in subsection 2.2 “study selection”. When searching PubMed “title/abstract” was used as a filter, “AB Abstract” was used in the EBSCO database.

2.2 Study selection

This review was set up based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). PRISMA is an evidence-based set of criteria applicable to the preparation of systematic reviews and meta-analyses; it can be used as a guideline for preparing systematic reviews of research interventions [17]. A structured approach was used to set up the research question for this review, using five components commonly known as the Participants, Interventions, Comparisons, Outcomes, and Study design approach (PICOS) [18]:

1. Participants: newly diagnosed T1D patients with standard insulin treatment; no restrictions were placed on gender, age, race, and geographical distribution of the individuals enrolled in the study.
2. Interventions: vitamin D oral supplementation; the supplements used were vitamin D, 1- α -hydroxyvitamin D3, ergocalciferol, cholecalciferol, calcitriol, alphacalcidole or 1 α ,25-dihydroxyvitamin D3.
3. Comparisons: placebo and other non-vitamin D interventions.
4. Outcome: changes in daily insulin doses (DID, IU/d); changes in glycemic indexes:

hemoglobin A1c (HbA1c, %), fasting C-peptide (FCP, nmol/l), and stimulated C-peptide (SCP, (pmol/l), (ng/ml), (nmol/l \times 120 min)).

5. Study design: RCTs.

Studies excluded from the selection were:

- Clinical studies in patients with type 2 diabetes (T2D)
- Animal studies
- Clinical studies in healthy individuals
- Clinical studies in which supplementation was combined with calcium and/or other vitamins

A p-value of <0.05 was considered statistically significant for all included studies.

2.3 Assessment of methodological quality and data extraction

Two authors (G.E. and C.S) extracted independently the detailed information from the selected trials. Qualitative and quantitative information from each study was extracted, including author names, year of study, geographic study location, study size, age of participants, type of exposure (i.e. formulation), duration of study, and dosage of vitamin D supplementation.

The methodological quality of the included RCTs was assessed by means of 11 predefined criteria based on the updated Cochrane Collaboration Back Review Group (CCBRG) method (**Table 2**) [19]. The internal validity criteria that refer to the characteristics of the study are related to:

- Selection bias (criteria 1 and 2)

Table 2. Quality assessment of seven randomized controlled trials using the 11 criteria proposed by van Tulder [19]

RCT	R adequate	Concealed treatment allocation	Similarity of groups at baseline	Patient blinded to intervention	Care provider blinded to intervention	Outcome assessor blinded to intervention	Cointerventions avoided or similar	Acceptable compliance	Acceptable drop-out rate	Similar timing of outcome assessment	Intention-to-treat analysis	Overall score
Pitocco, 2006 [20]	U	N	Y	N	N	N	Y	Y	Y	Y	Y	6/11
Li, 2009 [21]	U	N	Y	N	N	N	Y	Y	Y	Y	Y	6/11
Bizzarri, 2010 [22]	U	Y	U	Y	Y	N	U	Y	Y	Y	Y	7/11
Walter, 2010 [23]	Y	Y	Y	Y	Y	N	Y	U	Y	Y	Y	9/11
Gabbay, 2012 [24]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	8/11
Ataie-Jafari, 2013 [25]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	8/11
Treiber, 2015 [26]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	8/11

Legend: High quality: ≥ 8 out of 11 validity criteria. Low quality: < 8 out of 11 validity criteria [19]. *Abbreviations:* Y - yes, N - no, U - unknown.

- Performance bias (criteria 4-8)
- Attrition bias (criteria 9 and 11)
- Detection bias (criteria 6 and 10) (**Table 2**)

The above criteria were characterized as: “yes”, “no” or “unknown”. Two authors (G.E. and C.S.) used the assessment instrument independently to evaluate the quality of each study. Whenever there was a disagreement between the two investigators, a third author (M.I.) provided an additional evaluation. Accordingly, each study was assessed as high quality if the total score of positive responses was ≥ 8 out of 11; it was regarded as low quality if the total score of positive responses was ≤ 7 out of 11.

3. Results

3.1 Search strategy and study selection

The search strategy and study selection processes were performed according to the "PRISMA" method, as described above. The flow chart for included studies is presented in **Figure 1** [14]. Overall, 7 studies were deemed eligible for inclusion in the current analysis [20-26].

The quality assessment of the studies included revealed 4 studies [23-26] of high methodological quality ($\geq 8/11$ validity criteria) and 3 studies [20-22] of low quality ($\leq 7/11$) [19]. **Table 2** shows the result of the quality assessment of the included studies.

3.2 Description of study characteristics

The study characteristics are summarized in **Table 3**. The studies were conducted in different geographic locations. Alphacalcidole, cholecalciferol, and calcitriol were the main forms of vitamin D supplementation used in the studies. The time between diagnosis of T1D and initiation of vitamin D intervention varied, ranging between 4 weeks and 1 year. Similarly, the duration of vitamin D supplementation varied between 6 and 24 months.

3.3 Effect on DID during and after treatment

The study by Pitocco *et al.* (2006) showed that DID was significantly lower in the treatment than in the control group at month 3 and 6 of treatment ($p = 0.03$), but no effect was seen at 12 months [20]. In the study by Ataie-Jafari *et al.* (2013), the DID was significantly different between the two groups ($p = 0.008$) in the between-subject comparison, with lower values for DID in the treatment than in the control group [25]. Furthermore, in the study by Treiber *et al.* (2015), DID was significantly increased in the control group after 12 months of treatment ($p < 0.001$), while no change was observed in the treatment group [26]. The results of vitamin D supplementation effects on DID are shown in **Table 4**.

3.4 Effects on glycemc indices

There was no significant effect on HbA1c levels during or after treatment, but there was an effect

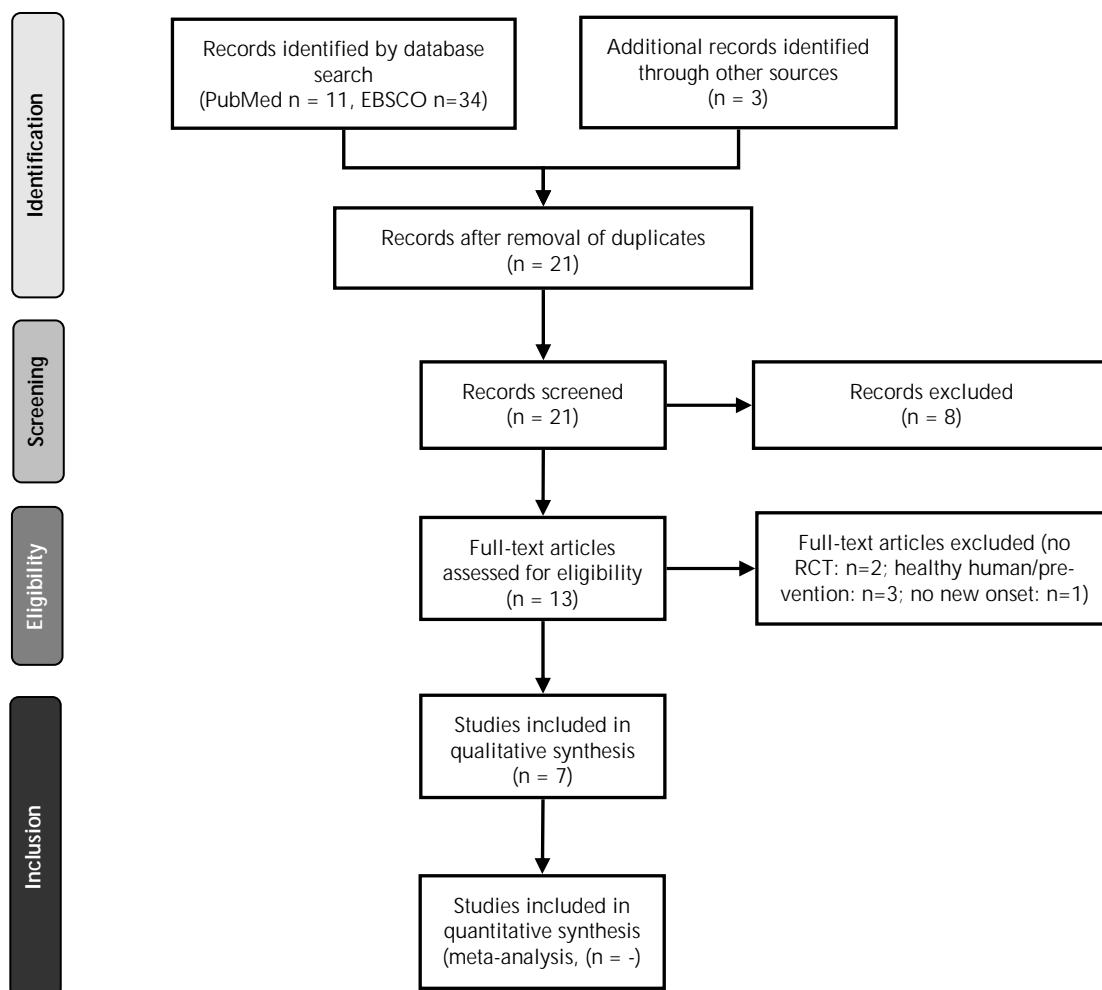


Figure 1. PRISMA flow diagram for the selection of studies of this systematic review. The search strategy was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

on FCP. In the study by Gabbay *et al.* (2012), the cumulative incidence of progression to undetectable levels of FCP (≤ 0.1 ng/ml) during the 18 months of monitoring was lower in the treatment than in the control group ($p = 0.01$) [24]. In the study by Ataie-Jafari *et al.* (2013), within-subject comparisons showed that the differences in FCP between the treatment group and the control group were highest at 3 and 6 months of treatment ($p = 0.049$) [25]. FCP levels were reduced in the treatment group compared to those of the control group.

In the study by Li *et al.* (2009), FCP levels decreased significantly in the control group between baseline and months 6 and 12 of therapy ($p = 0.006$), but no changes were observed in the treat-

ment group [21]. Also, FCP levels were maintained or increased in vitamin D-treated patients compared to control subjects ($p < 0.01$). The results of the effect of vitamin D supplementation on the FCP are shown in **Table 4**.

A positive effect on SCP was found by Gabbay *et al.* (2012). In this study, SCP increased in the first 12 months ($p = 0.01$), and showed reduced decline after 18 months in the treatment group compared to the control group ($p = 0.03$) [24]. The cumulative incidence of progression to undetectable SCP (≤ 0.1 ng/ml) was observed in 6.2% of the patients in the treatment group and in 37.5% of subjects in the placebo group ($p = 0.047$). The results of vitamin D supplementation on SCP are shown in **Table 4**.

Table 3. Basic characteristics of the studies included

Study	Subjects (n)	Age (yr)	Insulin treatment	Diabetes duration (wk, yr)	Outcome
Pitocco, 2006, Italy [20]	TG (n = 34) CG (n = 33)	>5	Regular insulin at meals and NPH insulin at bedtime	< 4wk	DID, HbA1c, FCP, SCP
Li, 2009, China [21]	TG (n = 17) CG (n = 18)	38.5 ± 12.5 42.8 ± 12.9	Premixed human insulin (Novolin 30 R or Humulin 70/30, Novo Nordisk or Eli-Lilly) twice daily	1.0 (0.1–4.0) yr 0.5 (0.1–4.0) yr	FCP, SCP
Bizzarri, 2010, Italy [22]	TG (n = 15) CG (n = 12)	11-35 (mean: 18)	Regular insulin at meals and NPH insulin at bedtime	< 12 wk	DID, HbA1c, FCP, SCP
Walter, 2010, Germany [23]	TG (n = 22) CG (n = 18)	31.4 ± 6.8 24.0 ± 6.0	Normal insulin regimen as intensive insulin therapy, unless changes were clinically indicated.	< 8 wk	DID, HbA1c, FCP, SCP
Gabbay, 2012, Brazil [24]	TG (n = 17) CG (n = 18)	7-30 (mean: 13.5) 7-30 (mean: 12.5)	Intensive insulin therapy (multiple (>3) daily injections) with SMBG	< 24 wk	DID, HbA1c, FCP, SCP
Ataie-Jafari, 2013, Iran [25]	TG (n = 29) CG (n = 25)	10.2±2.5 11.1±1.6	Short- and intermediate-acting (NPH) insulin as 2 to 3 injections daily depending on the SMBG	< 8 wk	DID, HbA1c, FCP
Treiber, 2015, Austria [26]	TG (n = 14) CG (n = 15)	11.0-17.5 (mean:12) 9.5-15.5 (mean:13)	No relevant information	< 12 wk	DID, HbA1c, FCP, SCP

Legend: CG - control group, DID - daily insulin dose, HbA1c - glycated hemoglobin, FCP - fasting C-peptide, SCP - stimulated C-peptide, SMBG - self-monitored blood glucose, TG - treatment group.

4. Discussion

The current review shows that alphacalcidole, cholecalciferol, and calcitriol are the main forms of vitamin D supplementation examined in patients with newly diagnosed T1D. This is a systematic review including studies of different population characteristics, from different countries (namely Italy, China, Germany, Brazil, Iran, and Austria), and with patients of different ages (children and adults). Moreover, the duration of supplementation varied between 6 to 24 months, and the doses of vitamin D differed between the studies. Although all different types of supplementation were found to be safe, there was a considerable variation in their effectiveness. Another factor that may have led to inconsistencies between the study results is the different quality of the studies included, with some studies below the cutoff for high quality [20-22] and some above [23-26] (**Table 2**).

4.1 Positive effect on T1D progression after alphacalcidole supplementation

Alphacalcidole supplementation resulted in considerable differences in FCP and DID levels, which was possibly due to the effect of dosage and duration of supplementation [18, 25]. The current findings indicate that alphacalcidole appears to be the ideal form of supplementation in patients with newly diagnosed T1D. It is noteworthy that these

are the only existing studies using alphacalcidole supplementation in patients with diabetes. Therefore, more research is required to confirm the effectiveness of this particular treatment through well-designed, high-quality, randomized controlled trials.

4.2 Positive effect on T1D progression after cholecalciferol supplementation

Our review identified considerable differences in the effects of cholecalciferol supplementation on FCP [24], SCP [24], and DID levels [24, 26] in newly diagnosed T1D patients. These differences may be affected by the dosage and duration of cholecalciferol supplementation. For example, the positive effect shown in the study by Gabbay *et al.* (2012) may be explained by the relatively long period of 18 months (with daily supplementation of 2000 IU) [24], while in the study by Treiber *et al.* (2015) cholecalciferol was administered at a higher dose (70 IU/kg/day), but for a shorter period of time (12 months) [26].

After 12 months of treatment, cholecalciferol supplementation showed an indirect positive and potentially protective effect on DID, which was due to a negative effect in the control group (increase in DID). Although both studies [24, 26] are of high methodological quality, the positive effects were most pronounced in the first study [24]. These findings agree with previous studies showing that

Table 4. Assessment of study outcomes (DID, HbA1c, FCP, and SCP) during follow-up, before and after vitamin D supplementation

Study	Design	Population	Vitamin D dose in intervention group	Comparator group treatment	Outcome	Conclusions
Pitocco, 2006 [20]	Open-labeled RCT	70 T1D subjects, <4 wk since diagnosis, age >5 yr	Calcitriol 0.25 µg on alternate days plus insulin for 1 yr	Nicotinamide 25 mg/kg daily plus insulin	Increase in FCP of 0.13 nM from diagnosis to 1 yr. No difference among groups. DID lower in the treatment group (p<0.03).	Minor effect at 3 and 6 mo, no effect at 12 mo (DID)
Li, 2009 [21]	RCT (parallel)	35 LADA subjects	Alphacalcidole 0.5 µg daily plus insulin for 1 yr	Insulin only	FCP decreased in insulin-alone group (p = 0.006). 70% of patients treated with 1-α(OH)D ₃ maintained or increased FCP concentrations after 1 yr of treatment, while only 22% of patients treated with insulin alone maintained stable FCP levels (p < 0.01)	Major effect (FCP)
Bizzarri, 2010 [22]	RCT (double-blinded)	34 T1D subjects, <12 wk since diagnosis, age 11-35 yr	Calcitriol 0.25 µg per day plus insulin for 2 yr	Insulin only	No differences in HbA1c, FCP, and DID between treatment and placebo group at 6, 12, and 24 mo	No effect
Walter, 2010 [23]	RCT (double-blinded)	40 T1D subjects, <2 mo on insulin therapy, age 18-39 yr	Calcitriol 0.25 µg per day plus insulin for 9 mo	Insulin only (placebo)	Mean FCP and DID comparable in both groups	No effect
Gabbay, 2012 [24]	RCT (double-blinded)	38 T1D subjects, <6 mo, age 7-30 yr	Cholecalciferol 2000 IU per day plus insulin for 18 mo	Insulin only (placebo)	Cumulative incidence of progression to undetectable FCP (≤0.1 ng/ml) 18.7% in treatment group and 62.5% in control group (p = 0.01). SCP enhanced in the first 12 mo (12% vs. -35%; p = 0.01), and less decay until 18 mo (-14% vs. -46%) in treatment compared with placebo group (p = 0.03)	Major effect (FCP, SCP)
Ataie-Jafari, 2013 [25]	RCT (placebo-controlled, single-blinded, parallel)	61 T1D subjects, <8 wk, age 8-15 yr	Alphacalcidole 0.25 µg once or twice daily (based on serum Ca) plus insulin for 6 mo	Insulin only (placebo)	Lower DID in the treatment group in mo 0-3 (p = 0.05), but not overall (p = 0.285); lower DID preceded higher FCP in treatment group in mo 3-6 (p = 0.049)	Major effect (DID, FCP)
Treiber, 2015 [26]	RCT (placebo-controlled, double-blinded)	29 T1D subjects, <12 wk, age >6 yr	Cholecalciferol 70 IU/kg body weight/day plus insulin for 12 mo	Insulin only (placebo)	DID significantly increased in the placebo group (p < 0.001); no significant difference in FCP and SCP	Major effect (DID)

Legend: Significance at p < 0.05. *Abbreviations:* DID - daily insulin dose, FCP - fasting C-peptide, HbA1c - glycated hemoglobin, LADA - latent autoimmune diabetes of the adult, SCP - stimulated C-peptide, T1D - type 1 diabetes.

dosages of 2000 IU/day given early in life may have a protective effect, and reduce the risk of T1D [8, 27, 28]. The results indicate that further investigation is required to evaluate whether a daily standardized dose of cholecalciferol equal to 2000 IU for about 6 to 18 months is effective in improving pancreatic β-cell function in newly diagnosed T1D patients.

4.3 Inconsistent effects on T1D progression after calcitriol supplementation

Our review identified that short-term calcitriol supplementation in doses of 0.25 µg/day has no ef-

fect on glycemic indices at the end of the treatment [20, 22, 23]. Moreover, only one of the above-mentioned studies was of high methodological quality [23], thus weakening the evidence of the potentially positive effect of calcitriol supplementation in these patients. The dose of supplementation seems to be too small to induce a significant effect. A review by Antico *et al.* (2012) indicated that the dose of vitamin administered in human studies is insufficient to attenuate the progression of the autoimmune disease [29]. Therefore, more studies are necessary to determine the most effective and safe dose of calcitriol in newly diagnosed T1D patients.

5. Methodological considerations

The key strength of the current review is the sole inclusion of RCTs, a study design which is less likely to be biased and affected by confounding variables. More than half of the studies included were assessed as high quality (4/7), which reinforces reliability of the study outcomes.

The limitations of the current study concern the diversity in ethnicity of the study populations included, in length of treatment, and in type of supplementation used. The studies included supplementations ranging from 6 to 24 months. Long-term follow-up studies of >24 months simply did not exist. Furthermore, factors such as history of diabetes control and baseline vitamin D levels prior to commencement of therapy were not examined in the studies, but could have affected outcomes.

The diversity in study populations regarding comorbidity, medical history, and medications, as well as the differing criteria for patient inclusion and exclusion in the studies are limitations that need to be eliminated in future clinical trials. Future studies should also consider the genetic diversity of the disease as this could be another factor impacting outcome. The human leukocyte antigen (HLA) region has numerous polymorphisms that are among the greatest contributors to the genetic susceptibility to T1D. Although many studies to date include data regarding genes associated with T1D, more research is necessary to reveal the exact mechanisms by which HLA and other associated loci confer T1D susceptibility, and lead to altered disease severity and progression [30].

Beside variations in the study population, the differences in outcomes may also be attributed to factors such as biomarker accuracy and efficiency in diagnosing and predicting T1D [31]. Furthermore, interaction with other medications may also blur the effect of vitamin D in T1D [32, 33], while iron status may further affect the level of HbA1c independent of glycemia [34]. Comorbidities and racial differences may further account for the observed diversity in biomarker levels. Since all cur-

rently available glycemic biomarkers have advantages and limitations, a more careful examination of the variables measured may yield better results, better decisions, and better claims for future therapeutic regimens.

Finally, the lack of basic research regarding the biological mechanisms of action required to justify the observed correlation between vitamin D and T1D increases the need for experimental studies. These studies may elucidate the key mechanisms and provide reproducible results that lead to translational medicine and clinical practices in the future.

6. Conclusions

The current analysis showed that vitamin D supplementation has a short-term positive effect on newly diagnosed T1D patients. This has been found in most of the studies irrespective of the heterogeneity of the study characteristics (e.g. differences in type, duration, and dosage of supplementation) and differences in study populations (e.g. regarding age and ethnicity).

In particular, alphacalcidole is a promising form for supplementation therapy as it has positive effects on pancreatic β -cell function. Cholecalciferol is another safe and effective form of supplementation. The effectiveness of calcitriol remains controversial; it is assumed that it is less effective and safe than the other two forms of vitamin D supplements.

Finally, studies have shown evidence that vitamin D intake early in life reduces the risk of T1D, although there is not enough evidence for an association between maternal intake of vitamin D and risk of T1D in the offspring [29, 30]. These results highlight the need for further research in this field. High-quality and long-term RCTs are required to elucidate further the role of vitamin D in pancreatic β -cell function and T1D in both pediatric and adult populations.

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References

1. **Harinarayan CV.** Vitamin D and diabetes mellitus. *Hormones (Athens)* 2014. 13(2):163-181.
2. **van Belle TL, Coppieters KT, von Herrath MG.** Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev* 2011. 91(1):79-118.
3. **Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ.** Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am* 2010. 39(3):481-497.
4. **Busta A, Alfonso B, Poretsky L.** Role of Vitamin D in the Pathogenesis and Therapy of Type 1 Diabetes Mellitus, Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments, InTech 2011, Chapter 19, pp 403-422.
5. **Griz LH, Bandeira F, Gabbay MA, Dib SA, Carvalho EF.** Vitamin D and diabetes mellitus: an update 2013. *Arq Bras Endocrinol Metabol* 2014. 58(1):1-8.
6. **Mitri J, Pittas AG.** Vitamin D and diabetes. *Endocrinol Metab Clin North Am* 2014. 43(1):205-232.
7. **Ritzerfeld M, Klasser M, Mann H.** Alfacalcidol in the

- therapy of renal bone disease. *Int J Clin Pharmacol Ther* 2001. 39(12):546-550.
8. **Harris SS.** Vitamin D in type 1 diabetes prevention. *J Nutr* 2005. 135(2):323-325.
 9. **Vieth R.** Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999. 69(5):842-856.
 10. **National Institute of Health.** Vitamin D - Fact Sheet for Health Professionals. <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>.
 11. **Jolliffe DA, Griffiths CJ, Martineau AR.** Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. *J Steroid Biochem Mol Biol* 2013. 136:321-329.
 12. **Kongsbak M, Levring TB, Geisler C, von Essen MR.** The vitamin D receptor and T cell function. *Front Immunol* 2013. 4:148.
 13. **Olliver M, Spelmink L, Hiew J, Meyer-Hoffert U, Henriques-Normark B, Bergman P.** Immunomodulatory effects of vitamin D on innate and adaptive immune responses to streptococcus pneumoniae. *J Infect Dis* 2013. 208:1474-1481.
 14. **George PS, Pearson ER, Witham MD.** Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med* 2012. 29(8):e142-e150.
 15. **Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M.** Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol* 2004. 89-90(1-5):121-125.
 16. **Bourlon PM, Billaudel B, Faure-Dussert A.** Influence of vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. *J Endocrinol* 1999. 160(1):87-95.
 17. **Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Plos Med* 2009. 6(7):e1000097.
 18. **O'Connor D, Green S, Higgins JP.** Defining the review question and developing criteria for including studies. *John Wiley and Sons*, 2008, pp. 81-94.
 19. **van Tulder M, Furlan A, Bombardier C, Bouter L, Editorial Board of the Cochrane Collaboration Back Review Group.** Updated method guidelines for systematic reviews in the cochrane collaboration back review group. *Spine (Phila Pa 1976)* 2003. 28(12):1290-1299.
 20. **Pitocco D, Crino A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, Anguissola GB, Visalli N, Suraci C, Matteoli MC, et al.** The effects of calcitriol and nicotinamide on residual pancreatic beta-cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI). *Diabet Med* 2006. 23(8):920-923.
 21. **Li X, Liao L, Yan X, Huang G, Lin J, Lei M, Wang X, Zhou Z.** Protective effects of 1-alpha-hydroxyvitamin D3 on residual beta-cell function in patients with adult-onset latent autoimmune diabetes (LADA). *Diabetes Metab Res Rev* 2009. 25(5):411-416.
 22. **Bizzarri C, Pitocco D, Napoli N, Di Stasio E, Maggi D, Manfrini S, Suraci C, Cavallo MG, Cappa M, Ghirlanda G, et al.** No protective effect of calcitriol on beta-cell function in recent-onset type 1 diabetes: the IMDIAB XIII trial. *Diabetes Care* 2010. 33(9):1962-1963.
 23. **Walter M, Kaupper T, Adler K, Foersch J, Bonifacio E, Ziegler AG.** No effect of the 1alpha,25-dihydroxyvitamin D3 on beta-cell residual function and insulin requirement in adults with new-onset type 1 diabetes. *Diabetes Care* 2010. 33(7):1443-1448.
 24. **Gabbay MA, Sato MN, Finazzo C, Duarte AJ, Dib SA.** Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual beta-cell function in new-onset type 1 diabetes mellitus. *Arch Pediatr Adolesc Med* 2012. 166(7):601-607.
 25. **Ataie-Jafari A, Loke SC, Rahmat AB, Larijani B, Abbasi F, Leow MK, Yassin Z.** A randomized placebo-controlled trial of alphacalcidol on the preservation of beta cell function in children with recent onset type 1 diabetes. *Clin Nutr* 2013. 32(6):911-917.
 26. **Treiber G, Prietl B, Frohlich-Reiterer E, Lechner E, Ribitsch A, Fritsch M, Rami-Merhar B, Steigleder-Schweiger C, Graninger W, Borkenstein M, Pieber TR.** Cholecalciferol supplementation improves suppressive capacity of regulatory T-cells in young patients with new-onset type 1 diabetes mellitus - A randomized clinical trial. *Clin Immunol* 2015. 161(2):217-224.
 27. **Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM.** Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001. 358:1500-1503.
 28. **Zipitis CS, Akobeng AK.** Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008. 93(6):512-517.
 29. **Antico A, Tampoia M, Tozzoli R, Bizzaro N.** Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmun Rev* 2012. 12(2):127-136.
 30. **Noble JA, Erlich HA.** Genetics of type 1 diabetes. *Cold Spring Harb Perspect Med* 2012. 2(1):a007732.
 31. **Wright LA, Hirsch IB.** The challenge of the use of glycaemic biomarkers in diabetes: reflecting on hemoglobin A1c, 1,5-anhydroglucitol, and the glycated proteins fructosamine and glycated albumin. *Diabetes Spectr* 2012. 25:141-148.
 32. **Albright ES, Ovalle F, Bell DS.** Artificially low hemoglobin A1c caused by use of dapson. *Endocr Pract* 2002. 8(5):370-372.
 33. **Uzu T, Hatta T, Deji N, Izumiya T, Ueda H, Miyazawa I, Kanasaki M, Isshiki K, Nishio T, Arimura T.** Target for glycemic control in type 2 diabetic patients on hemodialysis: effects of anemia and erythropoietin injection on hemoglobin A(1c). *Ther Apher Dial* 2009. 13(2):89-94.
 34. **El-Agouza I, Abu Shahla A, Sirdah M.** The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis. *Clin Lab Haematol* 2002. 24(5):285-289.