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journal homepage: www.elsevier.com/locate/jsbmbVitamin D and diabetes[☆]Anastassios G. Pittas^{a,*}, Bess Dawson-Hughes^{a,b}^a Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, MA, United States^b Bone Metabolism Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, United States

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ABSTRACT

On the basis of evidence from animal and human studies, vitamin D has emerged as a potential risk modifier for type 1 and type 2 diabetes (type 1 diabetes and type 2 diabetes). Vitamin D is thought to have both direct (through activation of the vitamin D receptor) and indirect (via regulation of calcium homeostasis) effects on various mechanisms related to the pathophysiology of both types of diabetes, including pancreatic beta-cell dysfunction, impaired insulin action and systemic inflammation. Observational case-control studies have shown that vitamin D supplementation in pregnancy or early childhood is associated with reduced risk of incident type 1 diabetes. There are no trials on the effect of vitamin D (ergocalciferol or cholecalciferol) on type 1 diabetes. An association between vitamin D insufficiency and incident type 2 diabetes has been reported in longitudinal observational studies, but the association is not consistent. Results from small underpowered trials and post-hoc analyses of data from larger trials designed for bone-specific outcomes show no effect of vitamin D supplementation on glycemia in healthy adults but vitamin D may retard the progression to diabetes in adults with glucose intolerance. Because vitamin D is an excellent marker of general health status, the positive results reported in some observational studies might reflect unmeasured and unaccounted confounding. Therefore, the hypothesis that vitamin D may modify diabetes risk needs to be confirmed in trials specifically designed for that purpose.

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1. Introduction

Diabetes, a chronic condition associated with serious morbidity, increased mortality and accelerated health care costs, is rapidly becoming a global epidemic. The total number of people with diabetes worldwide is expected to rise from 171 million in 2000 to 366 million by 2030 [1]. Although the majority of new cases are due to type 2 diabetes, the incidence of type 1 diabetes has been increasing as well. The growing incidence and prevalence of diabetes highlights the need for innovative approaches for the management and prevention of the disease. Epidemiologic data suggest that 9 out of 10 cases of type 2 diabetes could be attributed to modifiable habits and lifestyle [2]; however, lifestyle changes are difficult to achieve and maintain long term. Much less is known about modifiable risk factors for type 1 diabetes. Therefore, identification of modifiable risk factors for prevention of both types of diabetes is needed. Recently, there has been increasing evidence from animal

and human studies, to suggest that vitamin D may play a role in modifying risk of diabetes [3].

2. Potential mechanisms of action of vitamin D on glucose metabolism

Type 1 diabetes is due to autoimmune destruction of pancreatic beta cells leading to absolute insulin deficiency. For type 2 diabetes to develop, impaired pancreatic beta-cell function, insulin resistance and systemic inflammation are often present. There are several lines of evidence to support that vitamin D influences all these pathways [3].

A role for vitamin D in pancreatic beta-cell function might be mediated by the binding of circulating 1,25-dihydroxyvitamin D to the beta-cell vitamin D receptor. Alternatively, vitamin D could function through activation of 25-hydroxyvitamin D (25OHD) by 1-alpha-hydroxylase, which is expressed in beta cells. Vitamin D may directly enhance insulin sensitivity by stimulating the expression of insulin receptors and/or by activating peroxisome proliferator-activated receptor (PPAR- δ), a transcription factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue. Vitamin D may also affect insulin secretion and sensitivity indirectly via its role in regulating extracellular calcium concentration and flux through cell membranes in the beta cell and peripheral

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insulin-target tissues. Finally, the well-recognized immunomodulatory properties of vitamin D in relation to T-cell activity [4] would influence a number of steps in the autoimmune process leading to type 1 diabetes.

3. Evidence from human studies linking vitamin D and type 1 diabetes

3.1. Observational studies for type 1 diabetes

Vitamin D insufficiency has long been suspected to be a risk factor for type 1 diabetes. Indirect evidence comes from studies that have reported higher incidence and prevalence of type 1 diabetes in countries at higher latitude compared to counties at lower latitude [5]. There is also seasonal variation in the birth date of patients who subsequently develop type 1 diabetes, with risk increasing with births in the spring-summer months, which suggest an effect of lower sunshine in utero [6]. Type 1 diabetes is also more commonly diagnosed in the winter [7,8]. These ecological studies use latitude and season as proxies for limited sunshine, which is associated with lower vitamin D status; however, this is only a hypothesis as other factors may be responsible for the association (e.g. virus infections or sedentary behaviors, which are more common in the winter).

There are four case-control studies (retrospective) and one longitudinal (prospective, Table 1) cohort study (all from Europe) reporting an association between vitamin D status in the pregnant mother or the infant and incident type 1 diabetes [9]. These studies have reported an inverse association between intake of vitamin D supplements during lactation [10] or infancy [11], or intake of cod liver oil (a major source of vitamin D in certain countries) during pregnancy or infancy [12] and incident type 1 diabetes. A recent meta-analysis of these studies reported a lower risk for developing type 1 diabetes with self-reported vitamin D supplementation in early childhood (odds ratio 0.71, 95% confidence interval [CI] 0.60–0.84) [9]. Other studies have found that increased vitamin D intake during pregnancy [13] or during infancy [14] is associated with reduced diabetes-related autoimmunity, providing indirect evidence for a beneficial role of vitamin D on the pathophysiology of type 1 diabetes. However, the association between vitamin D intake during pregnancy or in early life and type 1 diabetes risk is not consistent [12,14].

3.2. Randomized controlled trials in relation to type 1 diabetes

There are no trials that have reported the effect of vitamin D₂ (ergocalciferol) or D₃ (cholecalciferol) supplementation on prevention or treatment of type 1 diabetes. In a pilot, open-label trial in 70 children, mean age of 14 years, with recent-onset type 1 diabetes, calcitriol had a modest favorable effect on residual pancreatic beta-cell function; however, the reduction in hemoglobin A1c concentration after 1 year was not statistically significant [15].

4. Evidence from human studies linking vitamin D and type 2 diabetes

4.1. Observational studies for type 2 diabetes

Several cross-sectional studies have examined the association between vitamin D status and prevalence of glucose intolerance or type 2 diabetes. Although most have reported an inverse association between vitamin D status and glucose intolerance, others failed to show such an association (studies reviewed by Pittas et al. [3]).

Two longitudinal cohort studies from the US and one study from Finland (which analyzed two separate cohorts) have reported an

Table 1 Prospective (longitudinal) observational cohort studies of vitamin D status and diabetes.

Study, year (reference) cohort [country]	Gender, mean baseline age (range), y	Vitamin D measure; comparison ^a	Mean follow-up, y	Results, adjusted RR, OR, or HR (95% CI)	Ascertainment method of diabetes	Adjustments
Type 1 diabetes Hypponen et al., 2001 [11] [Finland]		Vitamin D supplementation during infancy; "regular" vs. "none"	14	0.12 (0.03, 0.51)	Central drug national registry	Neonatal, anthropometric and social
Type 2 diabetes Liu et al., 2005 [16] Women's Health Study [US]	Women, 52 (45–75)	Vitamin D intake (total); ≥ 511 IU/d vs. ≤ 159 IU/d	9	0.73 (0.54, 0.99)	Validated self-report	Age
Pittas et al., 2006 [17] Nurses Health Study [US]	Women, 46 (30–55)	Vitamin D intake (total); >800 IU/d vs. ≤ 200 IU/d	20	0.87 (0.69, 1.09)	Validated self-report	Age, BMI, exercise, residence, family history of diabetes, hypertension, calcium intake, smoking, alcohol, coffee, other dietary factors
Knekt et al., 2008 [18] Finnish Mobile Clinic Health Examination Survey [Finland]	Men, ND (40–74)	25(OH)D; 75 nmol/L vs. 25 nmol/L	9	0.49 (0.15, 1.64)	Medication-treated, registry-based	Age, BMI, exercise, season, residence, smoking, education, medications
Knekt et al., 2008 [18] Mini-Finland Health Survey [Finland]	Women, ND (40–74) Men, 53 (40–69)	25(OH)D; 61 nmol/L vs. 22 nmol/L 25(OH)D; 75 nmol/L vs. 22 nmol/L	9	0.91 (0.37, 2.23) 0.17 (0.05, 0.52)	Medication-treated, registry-based	Age, BMI, exercise, season, residence, smoking, education, medications
	Women, 53 (40–69)	25(OH)D; 61 nmol/L vs. 20 nmol/L		1.45 (0.58, 3.62)		

Only studies where the predictor (vitamin D status) was assessed prior to the outcome (type 1 or type 2 diabetes) are included. 25(OH)D, serum or plasma 25-hydroxyvitamin D; BMI, body mass index; HR, hazard ratio; IU, international units; ND, no data; OR, odds ratio; RR, relative risk. To convert 25(OH)D concentration from nmol/L to ng/mL divide by 2.459.
^a Highest/lowest risk category vs. reference category.

Table 2
Summary of randomized controlled trials of vitamin D supplementation (ergocalciferol [D₂] or cholecalciferol [D₃]) on diabetes outcomes.

Study, year (reference) [country]	Mean baseline age (range), y	Participants	Baseline, mean 25(OH)D, nmol/L	Interventions (n)	Study duration	Outcome (units) [vitamin D vs. placebo, change or incidence] [reported P value]
Type 1 diabetes						
No studies						
Type 2 diabetes						
Nielsen et al., 1984 [19] [Denmark]	ND (45–54)	Postmenopausal, healthy	ND	D ₃ 2000 IU/d (n = 25) vs. placebo (n = 103), All received calcium 500 mg/d	2 y	FPG (mmol/L) [0.12 vs. 0.13] [NS]
Pittas et al., 2007 [21] [US]	71 (ND)	Normal fasting glucose	75	D ₃ 700 IU/d + calcium citrate 500 mg/d (n = 108) vs. placebo (n = 114)	3 y	FPG (mmol/L) [0.15 vs. 0.12] [P = 0.55]
De Boer et al., 2008 [22] [US]	71 (ND)	Impaired fasting glucose	75	D ₃ 700 IU/d + calcium citrate 500 mg/d (n = 45) vs. placebo (n = 47)	3 y	FPG (mmol/L) [0.02 vs. 0.34] [P = 0.042]
Sugden et al., 2008 [20] [UK]	ND (50–79)	Postmenopausal without diabetes	<79	D ₃ 400 IU/d + calcium carbonate 1000 mg/d (n = 16,999) vs. placebo (n = 16,952)	7 y	Diabetes ^a (% cohort) [96 vs. 95] HR 1.01 (0.94, 1.10) [P = 0.95]
von Hurst et al., 2009 [25] [New Zealand]	64 (ND)	Stable type 2 diabetes	37	D ₂ 100,000 IU orally once (equivalent to 1785 IU/d) (n = 17) vs. placebo (n = 17)	8 wk	Hemoglobin A1c (%) [0.01 vs. -0.05] [P = 0.74]
Zittermann et al., 2009 [24] [Germany]	42 (23–68)	Insulin resistance without diabetes and 25(OH)D <50 nmol/L	Median ~20	D ₃ 4000 IU/d (n = 42) vs. placebo (n = 39)	26 wk	FPG (mmol/L) [0.1 vs. 0.1] [P = 0.82]
Jorde et al., 2009 [23] [Norway]	48 (18–70)	Healthy, BMI >27 kg/m ²	30	D3 3332 IU/d (n = 100) vs. placebo (n = 100), All received weight reduction advice for 24 wk	1 y	Hemoglobin A1c (%) [-0.25 vs. -0.25] [P = 0.96]
	56 (21–75)	Stable type 2 diabetes	59	D3 40,000 IU weekly (equivalent to 5714 IU/d) (n = 16) vs. placebo (n = 16)	26 wk	FPG (mmol/L) [-0.21 vs. -0.27] [P = 0.39] Hemoglobin A1c (%) [-0.2 vs. -0.2] [P = 0.90] FPG (mmol/L) [-0.2 vs. 0.4] [P = 0.43]

25(OH)D, serum or plasma 25-hydroxyvitamin D; FPG, fasting plasma glucose; ND, no data. To convert FPG from mmol/L to mg/dL, divide by 0.0555. HR, hazard ratio; RR, relative risk.

^a Incident diabetes, self-reported by study participants.

association between vitamin D status and risk of incident type 2 diabetes [16–18] (Table 1). In the Women's Health Study, an intake of 511 IU/day or more of vitamin D was associated with lower risk of incident type 2 diabetes compared with an intake of 159 IU/day or less (2.7% vs. 5.6% of the cohort developed type 2 diabetes, respectively) [16]. However, this analysis did not adjust for any covariates other than age. In a subgroup analysis from the Nurses Health Study, there was a statistically significant association with lower risk of type 2 diabetes among women who reported the highest intake of both vitamin D and calcium (RR 0.67; 95% CI 0.49, 0.90 for intake of 800 IU/day vitamin D and 1200 mg/day calcium vs. 400 IU/day vitamin D and 600 mg/day calcium) [17]. A statistically significant association between higher vitamin D status and lower risk of incident type 2 diabetes was also reported among men in the Mini-Finland Health Survey cohort (RR 0.17; 95% CI 0.05, 0.52; comparing 25[OH]D concentration of 75 nmol/L vs. 22 nmol/L) [18]. Three analyses (two in women [17,18] and one in men [18]) suggested a lower, but statistically non-significant, risk of type 2 diabetes among participants in the highest vs. the lowest vitamin D status category, while one analysis in men reported a non-statistically significant increase in risk with higher vitamin D status.

4.2. Randomized controlled trials in relation to type 2 diabetes

There are seven controlled trials that have examined the effect of supplementation with a variety of formulations of vitamin D on type 2 diabetes-related parameters (fasting plasma glucose, hemoglobin A1c or incident type 2 diabetes) (Table 2) [19–25]. Study duration varied from 2 months to 7 years and doses ranged from 400 IU/day to a single dose of 100,000 IU of vitamin D. In five studies that provided vitamin D supplementation without concomitant calcium, there was no effect on glycemic measures [19,20,23–25]. There are two trials that have reported the effect of combined vitamin D₃ and calcium supplementation on type 2 diabetes, in post-hoc analyses. In one of these trials designed to assess bone related outcomes, combined vitamin D₃ (700 IU/day) and calcium (500 mg/day) supplementation attenuated the increase in fasting glycemia in the subgroup of participants with impaired fasting glucose at baseline, but had no effect on fasting glycemia among those with normal glucose tolerance at baseline [21]. In contrast, combined vitamin D₃ (400 IU/day) and calcium supplementation (1000 mg/day) in the Women's Health Initiative (WHI) trial did not reduce the risk of incident diabetes over a 7-year period [22]. In the WHI, there was also no significant effect of treatment on fasting glycemia or simple indices of insulin resistance. This null result in the WHI study may be due to the small dose of vitamin D (400 IU/day) given to the active treatment group and "cross contamination" as the trial design allowed all participants to take vitamin D supplements on their own during the trial.

5. Summary of evidence from the human studies on type 1 and 2 diabetes

Although cross-sectional studies have reported relatively consistent associations between low vitamin D status and prevalent type 1 or type 2 diabetes [3,26], the evidence from longitudinal observational studies is sparse and inconclusive and, therefore, definite conclusions cannot be drawn for a variety of reasons: recall bias in the case-control studies in type 1 diabetes when the predictor (vitamin D status) was ascertained by recall years after the diagnosis of diabetes, considerable variability among the various cohorts, lack of adjustment for important confounders and, importantly, residual confounding given that vitamin D status is an excellent marker of overall health. It is also difficult to draw

definitive conclusions from trials, because there is only a small underpowered trial in relation to type 1 diabetes that used the active form of vitamin D while trials in relation to type 2 diabetes were post-hoc analyses.

6. Optimal intake of vitamin D in relation to diabetes

The optimal vitamin D intake and 25OHD concentration is currently hotly debated and there is growing consensus that vitamin D intakes above the current recommendations may be associated with better health outcomes. In the US, currently recommended intakes for vitamin D are 400 IU/day for those aged 51–70 years and 600 IU/day for those aged >70 years [27] but these intakes are currently under review by the US Institute of Medicine. Based on the available studies reviewed here, it is difficult to draw definitive conclusion for the optimal 25OHD level in relation to diabetes.

7. Conclusions and future directions

An inverse association between vitamin D status and both types of diabetes is suggested by observational studies. However, the lack of large prospective observational studies that have measured 25(OH)D as the exposure variable prior to ascertainment of the outcome and the lack of randomized trials specifically designed to test the effects of vitamin D on diabetes limits drawing any definitive conclusions. To better define the clinical role of vitamin D as a potential intervention for prevention and management of diabetes, high quality observational studies that measure 25(OH)D as the exposure variable and randomized controlled trials specifically designed to test such an hypothesis are needed.

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