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Vitamin D and diabetes

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Synopsis

There has been increasing evidence suggesting that vitamin D may play an important role in modifying risk of diabetes. In this regard, Vitamin D has both direct and indirect effects, the latter via regulation of calcium effects on various mechanisms related to the pathophysiology of type 2 diabetes, including pancreatic beta cell dysfunction, impaired insulin action and systemic inflammation. The human evidence comes primarily from many cross-sectional and prospective observational studies, most of which showed an inverse association between vitamin D status and prevalence or incidence of type 2 diabetes. The effect of vitamin D supplementation on glycemia or incident type 2 diabetes has been reported in several trials with mixed results. The present article describes the biological plausibility behind the potential association between vitamin D and type 2 diabetes and summarizes the current evidence supporting a relation between vitamin D and type 2 diabetes and briefly reports on the potential association between vitamin D and type 1 diabetes.

Keywords

vitamin D; type 2 diabetes; insulin resistance; insulin sensitivity; 25-hydroxyvitamin D

Introduction

Type 2 diabetes mellitus is a significant global health care problem and pharmacotherapies to treat the disease continue to emerge. However, the increasing burden of type 2 diabetes calls for an urgent need for innovative approaches to prevent its development. Recently, vitamin D has risen as a potential diabetes risk modifier.

The potentially significant extra-skeletal role of vitamin D is highlighted in several recently published studies, including the demonstration of the expression of the vitamin D receptor in a large number of non-skeletal cells, including pancreatic beta cells. Additional evidence has strongly suggested that vitamin D plays an important role in modifying the risk of type 2 diabetes, an effect which is likely mediated by an effect of vitamin D on beta cell function, insulin sensitivity and systemic inflammation. The evidence comes primarily from cross-sectional and longitudinal observational studies reporting on the association between

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vitamin D status and risk of type 2 diabetes or glycemia among patients with established type 2 diabetes. More recently, short-term, small randomized trials have reported the effect of vitamin D supplementation with or without calcium on diabetes risk and glycemia with mixed results.

The aims of the review are to: (1) describe the biological plausibility behind the potential association between vitamin D and diabetes, with emphasis on type 2 diabetes where most of the evidence exists and (2) summarize and synthesize the evidence from observational studies that report on the association of vitamin D status and risk of diabetes and from randomized trials that report on the effect of vitamin D supplementation on glycemia in patients with diabetes or at risk for diabetes.

Review of vitamin D physiology

Vitamin D exists in 2 forms: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Vitamin D3 is synthesized in the skin upon exposure to solar ultraviolet B radiation. During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to pre-vitamin D3, which is immediately converted to vitamin D3 in a heat-dependent non-enzymatic process. Excessive exposure to sunlight degrades pre-vitamin D3 and vitamin D3 into inactive phyto-products (photo-degradation), avoiding vitamin D toxicity in the setting of excess sunlight. Vitamin D3 is also found is certain foods, such as fatty fish. Vitamin D2 is synthesized by plants and is found mostly in nutrients supplemented with vitamin D (e.g. milk) or dietary supplements. Whether endogenously synthesized or ingested through diet or supplements, vitamin D in the circulation is bound to the vitamin D-binding protein (DBP), which transports it to the liver, where vitamin D is converted by vitamin 25-hydroxylase to 25-hydroxyvitamin D [25OHD]. This form of vitamin D is biologically inactive and must be converted primarily in the kidneys by 25-hydroxyvitamin D-1alpha-hydroxylase to the biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. The presence of 1-alpha-hydroxylase in extra-renal tissues suggest that vitamin D may have important role beyond the musculo-skeletal system. 25-hydroxyvitamin D is the major circulating form of vitamin D and is an excellent biomarker of exposure, either from cutaneous synthesis or dietary intake. Blood concentration of 25OHD is used by clinicians as a biomarker to determine vitamin D status.

Classification of vitamin D status

Clinicians and researchers use blood concentration of 25OHD as a biomarker to determine vitamin D status. However, there is no consensus on the 25OHD thresholds for vitamin D deficiency or insufficiency. The main guidelines by the Institute of Medicine (IOM) and the Endocrine Society differ on classification of vitamin D status, as shown in Table 1.[1] [2] The differences are explained by what populations were targeted by the guidelines and how the evidence was synthesized. The IOM guidelines concentrated on the general healthy population and placed emphasis on intervention studies. The IOM found no convincing evidence to link vitamin D with benefits for non-skeletal outcomes, such as diabetes. The IOM concluded that blood concentration of 25OHD > 20 ng/mL is consistent with favourable skeletal outcomes while there are only sparse data to support a higher level. The IOM also concluded that a level above 50 ng/mL should be a cause of concern about potential adverse events. In contrast, the Endocrine Society clinical practice guidelines concentrate on people at high risk for vitamin D deficiency and placed more emphasis on observational (epidemiologic) studies. Endocrine Society guidelines concluded that blood concentration of 25OHD > 30 ng/mL is desirable for optimal skeletal outcomes without any upper limit that would be concerning for safety. However, the Endocrine Society guidelines have been criticized by incorrectly characterizing several large population subgroups as at

high risk and recommending widespread screening for vitamin D deficiency.[3] Both guidelines agreed that recommendations will require reconsideration in the future as additional data from ongoing randomized trials become available

Vitamin D intake requirements

The IOM report on dietary reference intakes for calcium and vitamin D recommends 600 international units per day of vitamin D for individuals 9–70 years and 800 international units for those older than 70 years as the recommended dietary allowance (RDA) (Table 2), [2] which is defined as the intake that meets the needs of 97.5% of the healthy population. The IOM report also concluded that the tolerable upper intake level (UL), above which the potential for adverse effects may increase with chronic use, is 4,000 IU/day. It is important to note that the UL amount is not intended as a target intake, rather, it is the upper limit for chronic intake of vitamin D above which toxicity may increase. In contrast, Endocrine Society clinical practice guidelines conclude that to raise the blood level of 25OHD consistently above 30 ng/mL, intakes of 1500 to 2000 IU/day may be required. The recommended intakes by the two guidelines differ for the same reasons as the recommendations for 25OHD levels. The IOM report clearly recognized the lack of long-term trials with vitamin D supplementation for non-skeletal outcomes as a major hurdle in establishing recommendation, while the Endocrine Society guidelines applied evidence from observational studies to develop its recommendations and considered 25OHD as a clinically important surrogate outcome that correlates with health and disease. The latter assumption should be approached with caution because although 25OHD is an excellent biomarker of exposure and correlates with outcomes, it is not a validated biomarker of effect that is causally related to health outcomes of interest. The evidence to support a causal association comes from long-term adequately powered randomized trials, which are lacking in relation to vitamin D and type 2 diabetes, as described below.

Biologic plausibility of an association between vitamin D and type 2 diabetes

Type 2 diabetes results from impaired beta cell function, increased insulin resistance and systems inflammation and there is evidence that vitamin D affects these pathways, as described next.

Vitamin D and insulin secretion

Based on pre-clinical studies, vitamin D seems to play a regulatory role in insulin secretion, beta-cell survival and calcium flux within beta-cells. A series of studies have shown that vitamin D deficiency impairs glucose-mediated insulin secretion in rat pancreatic beta cells [4–8], while vitamin D supplementation seems to restore such glucose-stimulated insulin secretion.[4, 7–11] Vitamin D may also have a direct effect on beta-cell function, which seems to be exerted by binding of its circulating active form to the vitamin D receptor (VDR) that is expressed in pancreatic beta-cells.[12] (Figure 1) Interestingly, mice lacking a functional VDR show an impaired insulin secretion following a glucose load. Such impairment appears associated with a decrease in insulin synthesis by the beta-cell resulting in a reduction in the amount of stored insulin [13]. Activation of vitamin D mediated by the 25(OH) D-1α-hydroxylase enzyme (CYP27B1) also occurs within the pancreatic beta cell allowing for an important paracrine effect of circulating 25-hydroxyvitamin D [14]. An additional effect of vitamin D on the pancreatic beta cell is the regulation of extracellular calcium concentration and flux through the beta cell. [15] Insulin secretion is a calcium-dependent process [16], therefore, alterations in calcium flux could have an effect on insulin secretion. [17–19] Vitamin D also regulates the function of calbindin, a cytosolic calcium-

binding protein found in pancreatic beta cells[12, 20] and acts as a modulator of depolarization-stimulated insulin release *via* regulation of intracellular calcium. [21]

Vitamin D and insulin sensitivity

There are several ways in which vitamin D could affect insulin sensitivity. $1,25(OH)_2D$ appears to stimulate the expression of insulin receptors, which in turn will affect insulin sensitivity. [22–25] $1,25(OH)_2D$ enters insulin-responsive cells and interacts with the VDR activating the VDR-retinoic acid X-receptor (RXR) complex which binds to a vitamin D response element found in the human insulin receptor gene promoter region.(Figure 2) The result is an enhanced transcriptional activation of the insulin receptor gene increasing the total number of insulin receptors without altering their affinity. $1,25(OH)_2D$ may also enhance insulin sensitivity by activating peroxisome proliferator-activated receptor delta (PPAR-δ), which is a transcription factor that regulates the metabolism of fatty acids in skeletal muscle and adipose tissue [26]. Vitamin D has also been found to improve muscle oxidative phosphorylation after exercise. Another potential effect of $1,25(OH)_2D$ on insulin sensitivity might be exerted *via* its regulatory role in extracellular calcium concentration and flux through cell membranes. Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as muscle and fat [27, 28], with a narrow range of intracellular calcium needed for optimal insulin-mediated functions [29]. Changes in intracellular calcium in insulin target tissues may contribute to peripheral insulin resistance [29–36] *via* an impaired insulin signal transduction [36, 37] leading to a decreased glucose transporter activity. [36–38] Hypovitaminosis D also leads to an increase in the levels of parathyroid hormone (PTH), which has been associated with insulin resistance. [39, 40] Vitamin D may also affect insulin resistance indirectly through the renin-angiotensin-aldosterone system (RAAS), as described below. Finally, vitamin D insufficiency has been associated with increased fat infiltration in skeletal muscle, which appears independent of body mass and is thought to contribute to a decreased insulin action. [41]

Vitamin D and systemic inflammation

Vitamin D could directly and/or indirectly lessen the effects of systemic inflammation in patients with type 2 diabetes in several ways. For example, $1,25(OH)_2D$ may protect against beta cell cytokine-induced apoptosis by directly modulating the expression and activity of cytokines, hence improving insulin sensitivity.[42–45] One such pathway may be through the down-regulation of NF-kB, a major transcription factor for TNF-*alpha* and other pro-inflammatory molecules.[46] Another pathway that may mediate the effect of $1,25(OH)_2D$ on beta cell function is through counteracting cytokine-induced Fas expression, which in turn will have anti-apoptotic effects.[47] Several other immune-modulating effects of $1,25(OH)_2D$ such as blockade of dendritic cell differentiation, inhibition of lymphocyte proliferation, inhibition of foam cell formation and cholesterol uptake by macrophages and enhanced regulatory T-lymphocyte development[43, 48] may provide additional protective pathways against beta cell destruction mediated by the systemic inflammation caused by type 2 diabetes.

Association between vitamin D status and type 2 diabetes

Cross sectional studies

There are many cross-sectional observational studies that have examined the association between vitamin D and type 2 diabetes and most have reported an inverse association between vitamin D status (25OHD concentration) and prevalent diabetes. One of the largest such cohorts is the National Health and Nutrition Examination Survey (NHANES) in United States, which reported an inverse association between 25OHD concentration and prevalence of diabetes in non-Hispanic whites and Mexican-Americans, but not African-Americans.[49]

Similarly, this inverse association was seen in other large cohorts from the U.S.[40], Europe[50] and China.[51] The major limitation of cross-sectional studies is the potential of reverse causation; therefore, causality cannot be established.

Longitudinal studies

Longitudinal studies, where vitamin D status is assessed before the outcome (type 2 diabetes) is assessed have nearly universally shown an inverse association of vitamin D status and incident type 2 diabetes (Table 3).[52–67] In these studies, vitamin D status was assessed by self-reported vitamin D intake, predicted 25OHD concentration or measuring plasma or serum 25OHD concentration.

In one of the largest studies to date where vitamin D intake was the measure to assess vitamin D status, the Nurses' Health Study, after multivariate adjustment for age, BMI, and non-dietary covariates, women who consumed more than 800 IU/day of vitamin D had a 23% lower risk for developing incident type 2 diabetes compared to women who consumed less than 200 IU/day (RR 0.77, 95%CI 0.63–0.94; $p<0.01$).[53] However, after adjusting for dietary factors, the association became non-significant. Similarly, in the Women's Health Study, an intake of 511 IU/day or more of vitamin D was associated with 27% lower risk of developing type 2 diabetes compared with an intake of 159 IU/day or less. [52] The Women's Health Study analysis is limited by the lack of adjustments for risk factors of type 2 diabetes other than age.

In a nested case-control study conducted in Finland, which included 2 cohorts, participants in the highest quartile of 25OHD (mean 25OHD 27.6 ng/mL) had a 40% lower risk of developing incident type 2 diabetes, compared to those in the lowest quartile (mean 25OHD 8.9 ng/mL), after multivariate adjustment. However, the lower risk was only observed in men. [54] On the other hand, in the Nurse's Health Study, the odds ratio for incident type 2 diabetes in the highest (mean 25OHD, 33.4 ng/ml) compared to the lowest quartile (mean 25OHD, 14.4ng/ml) was 0.52 (95% confidence interval, 0.33, 0.83) after multivariate adjustment. The inconsistency between the Finnish and the US female population could be secondary to different baseline mean 25OHD (15 ng/ml versus 23 ng/ml respectively) suggesting that a threshold 25OHD concentration above which the risk of type 2 diabetes declines. In the Diabetes Prevention Program, which included a much larger number of participants at high risk for developing diabetes, those in the highest tertile of 25-hydroxyvitamin D (median concentration 30.1 ng/mL) had a hazard ratio of 0.72 (95%CI, 0.56 to 0.90) for developing diabetes compared to participants in the lowest tertile (median concentration 12.8 ng/mL) after multivariate adjustment. [64]

Recently, two meta-analyses of longitudinal observational studies have been reported with nearly identical results. Song et al included 21 studies and a total of 76,000 participants and calculated the risk of developing type 2 diabetes, according to baseline 25OHD level. There was a 38% lower risk of developing type 2 diabetes in the highest tertile of 25OHD compared to the lowest one (relative risk 0.62 [95% CI 0.54–0.70] (Figure 3), with little heterogeneity between studies.[68] The association was consistent regardless of diabetes diagnosis criteria, study size or follow-up duration and remained significant after adjustment for BMI and intermediate biomarkers. A linear trend analysis showed that a 4 ng/ml increment in 25OHD levels was associated with a 4% lower risk of type 2 diabetes (95% CI 3–6; P for linear trend, 0.0001). In another meta-analysis of 16 studies, Afzal et al estimated the odds ratio for type 2 diabetes to be 1.5 (95% CI, 1.33–1.70) for the bottom versus the top quartile of 25OHD concentration. [67]

Despite the consistency of these results, the observational nature of these studies precludes an assessment of cause and effect because residual confounding cannot be excluded.

The influence of vitamin D supplementation on type 2 diabetes

The effect of vitamin D supplementation on glycemia or incident type 2 diabetes has been reported in several trials with mixed results. (Table 4)

In trials that included participants with normal glucose tolerance at baseline, vitamin D supplementation had a neutral effect on measures of glycemia including fasting plasma glucose or hemoglobin A1c and insulin resistance measured by HOMA. [69–77] Similarly, vitamin D supplementation had no effect on incident type 2 diabetes in individuals with normal glucose tolerance at baseline. [71, 72] The major limitation in interpreting these results is that most were designed for non-glycemic outcomes and the analyses on vitamin D and type 2 diabetes were *post-hoc*. [69–72, 75] In addition, all trials with the exception of the Women's Health Initiative trial [71] and the RECORD trial [72] were underpowered for glycemic outcomes. It is also important to note that adherence to the intervention would have played a major role in interpreting the results. For example, in a *post-hoc* analysis of the RECORD study, a community-based effectiveness trial designed for bone outcomes, [72] supplementation with 800 IU/day of vitamin D_3 (given in a 2×2 factorial design with calcium carbonate) did not change the risk of self-reported type 2 diabetes; however, among study participants who were highly compliant with supplementation, there was a notable trend towards reduction in type 2 diabetes risk with vitamin D_3 (OR 0.68; 95%CI 0.40–1.16).

The potential effect of vitamin D supplementation appears to be more prominent among persons who are at high risk for diabetes (e.g., pre-diabetes). In a post-hoc subgroup analysis conducted using data from a completed trial designed for fractures, combined vitamin D_3 (700 IU/day) and calcium carbonate (500 mg/day) supplementation prevented the rise in insulin resistance (HOMA-IR) and fasting plasma glucose (FPG) in people with impaired fasting glucose, but not in individuals with normal fasting glucose at baseline,[70] suggesting that vitamin D may benefit only individuals at high risk for diabetes. In this study, the reduction in FPG over 3-years was similar to the reduction in FPG achieved with metformin or lifestyle, in the Diabetes Prevention Program, which was associated with a 31–58% decrease in incident diabetes.[78] In the Calcium and Vitamin D for type 2 Diabetes Mellitus (CaDDM) study, vitamin D supplementation (4,000 IU/day) in adults at risk for type 2 diabetes improved beta cell function and had a nearly statistically significant effect on the rise in A1c values. [79] Similarly, In another intervention study, where vitamin D was given without a placebo, insulin sensitivity improved after 4 weeks of vitamin D administration in persons with pre-diabetes.[80] In contrary, Davidson et al. found no effect of high dose vitamin D supplementation on insulin secretion, insulin sensitivity or incident diabetes in a population with impaired fasting glycemia or impaired glucose tolerance and low vitamin D levels. [81] In this study, the average daily dose of vitamin D supplementation was close to 12700 IU and the population was limited to non-Caucasians. According to the IOM, chronic administration of vitamin D in excess of 4,000 IU per day may not be beneficial. Therefore, the supra-physiologic dose of vitamin D supplemented in the study by Davidson et al and the difference in ethnicity could explain the discrepancy with other studies in persons with pre-diabetes.

In most trials that included participants with established type 2 diabetes, vitamin D supplementation had no effect on glycemic outcome measures after a follow-up period of 8–26 weeks.[82–89] However, these studies were underpowered and the effect of concurrent diabetes pharmacotherapy on the outcome measured was not reported.

Vitamin D and type 1 diabetes

Type 1 diabetes is characterized by autoimmune destruction of pancreatic islet beta cells, leading to absolute insulin deficiency. Many effects of vitamin D on the pathophysiology of type 1 diabetes have been described, including changes in the immune-mediated destruction, [90] but also the beta-cell itself. The latter effect may, at least in part, be mediated indirectly by the effect of vitamin D on calcium homeostasis. It has also been reported that specific vitamin D receptor polymorphisms interact with the HLADRB1 allele, which predisposes to type 1 diabetes.[91]. Evidence from animal studies in non-obese diabetic mice (NOD), which undergo destruction of pancreatic beta cells that mimics the pathogenesis of type 1 diabetes in humans, suggests that vitamin D deficiency is associated with development of diabetes while administration of 1,25-dihydroxyvitamin D to these mice prevented the development of diabetes. [92]

In humans, the prevalence of type 1 diabetes has been inversely correlated with ultra violet B radiation and altitude, suggesting that low vitamin D synthesis may be important in the pathogenesis of type 1 diabetes. Lack of vitamin D supplementation in infancy has been associated with increased risk of type 1 diabetes later in life. In the Finnish birth cohort study, children who regularly took the recommended dose of 2,000 IU/day of vitamin D had lower risk of developing diabetes compared with those who regularly received less than the recommended amount.[93] A meta-analysis based on five observational studies concluded that vitamin D supplementation in early childhood is associated with decreased diabetes risk. [94] Recently, Sorensen et al reported that lower maternal serum concentration of 25OHD during pregnancy was associated with an increased risk of childhood-onset type 1 diabetes, suggesting that in utero exposure to vitamin D may also be important. There are limited data from intervention studies with vitamin D in patients with type 1 diabetes. In patients with new onset type 1 diabetes, Gabbat et al reported that supplementation with 2000 IU per day of cholecalciferol over 18 months resulted in a favorable immunologic effect and a slower decline of residual beta-cell function but without any change in glycemia. [95] Two earlier studies of calcitriol supplementation in type 1 diabetes did not show a positive effect on beta cell residual function. [96, 97]

Although the data from animal and epidemiological studies seem promising, large trials evaluating the efficacy and safety of vitamin D supplementation in prevention or treatment of type 1 diabetes are lacking.

Summary

Findings from basic science suggest that vitamin D may play a significant role in both types of diabetes. In human studies, the evidence for a potential association is stronger for vitamin D and type 2 diabetes with much less data on type 1 diabetes. However, the evidence about type 2 diabetes in humans comes almost exclusively from observational studies, which may be confounded by a variety of factors and, therefore, these studies preclude an assessment of cause and effect. There are no published trials specifically designed to test the safety and efficacy of long-term vitamin D administration to reduce the risk of developing type 2 diabetes; therefore, firm conclusions cannot be drawn regarding the role of vitamin D for prevention or treatment of diabetes. On numerous occasions, encouraging findings from observational studies were not confirmed by well-designed clinical trials (e.g. hormone replacement therapy, vitamin E and other supplements) [98, 99] and prevailing clinical practice was overturned. Therefore, evidence from randomized controlled trials is needed to address the issue of causality and to rigorously assess the protective effect of vitamin D on type 2 diabetes.

There are several ongoing randomized trials to test the hypothesis that vitamin D supplementation lowers type 2 diabetes risk. The vitamin D and omega-3 trial (VITAL study, www.vitalstudy.org) is a large *community-based* 2×2 factorial trial that is testing the *effectiveness* of 2,000 IU/day of vitamin D3 vs. less than 800 IU/day (the other factor is omega-3 fatty acids vs. placebo) in primary prevention of cancer, cardiovascular disease and stroke. An ancillary study to VITAL will evaluate the effect of vitamin D supplementation on diabetes incidence, based on self-reported data among those with normal glucose tolerance at baseline. The vitamin D and type 2 diabetes study (D2d, www.d2dstudy.org) is a large multi-center clinical trial conducted in twenty cities around the United States, specifically designed to test whether vitamin D supplementation reduces risk of incident diabetes in patients with pre-diabetes. The D2d study will enroll approximately 2,400 participants will be followed for up to 4 years for development of diabetes.

If the results of these larger trials, and other ongoing studies, confirm a favorable benefit/harm ratio of vitamin D supplementation, vitamin D would likely be integrated into contemporary strategies for the prevention of type 2 diabetes in the more than 79 million Americans at risk of developing diabetes and to treatment in the more than 10 million Americans with established diabetes. Until then, vitamin D is a promising, yet unproven dietary intervention for type 2 diabetes.

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Key points

- Observational studies suggest a link between vitamin D and diabetes
- The potential effect of vitamin D appears to be more prominent among persons at risk for diabetes.
- The optimal blood 25-hydroxyvitamin D concentration associated with reduced risk of type 2 diabetes is not clear.
- The evidence from randomized controlled trials to support the hypothesis that vitamin D supplementation prevents type 2 diabetes is lacking.

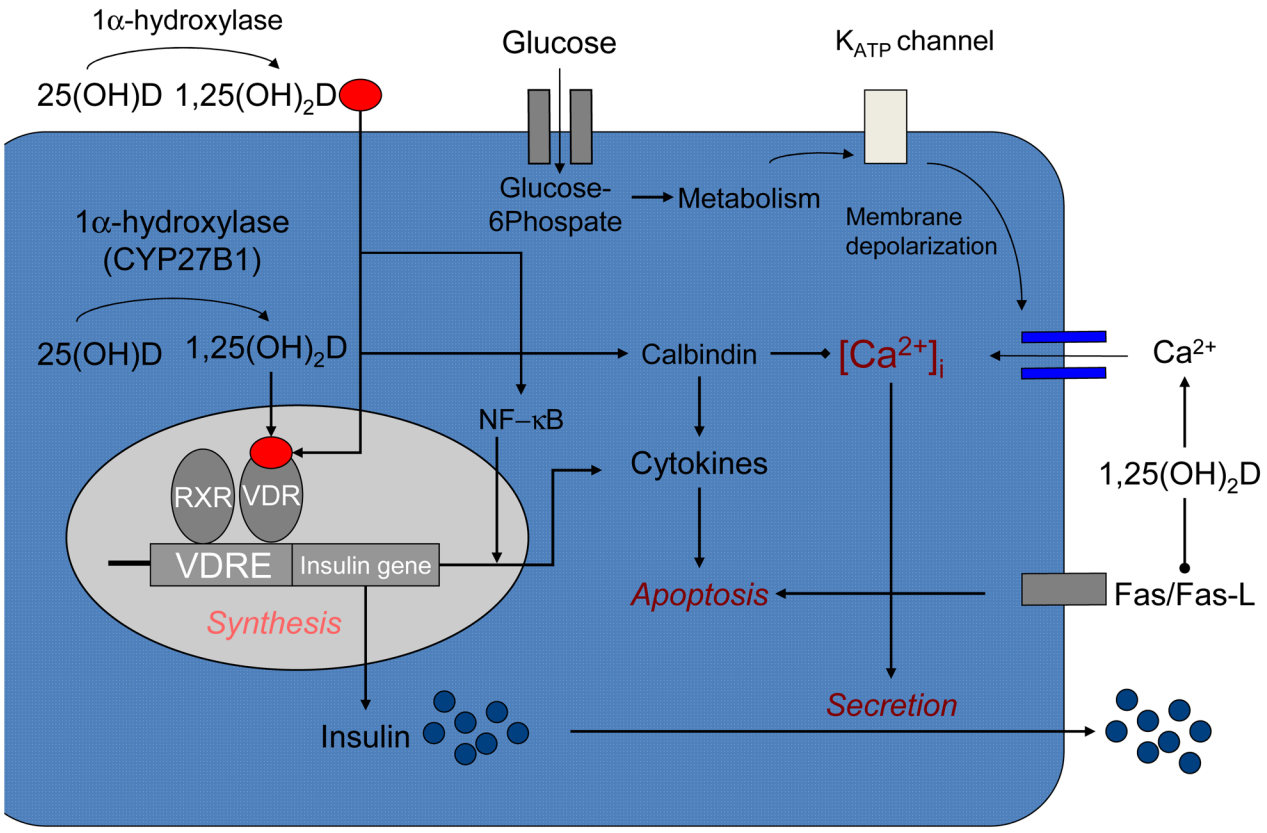

Figure 1.

Vitamin D and insulin secretion. Vitamin D can promote pancreatic beta cell function in several ways. The active form of vitamin D, (1,25OH2D), enters the beta cell from the circulation and interacts with the vitamin D receptor-retinoic acid x-receptor complex (VDR-RXR), which binds to the vitamin D response element (VDRE) found in the human insulin gene promoter, to enhance the transcriptional activation of the insulin gene and increase the synthesis of insulin. Vitamin D may promote beta-cell survival by modulating the generation (through inactivation of nuclear factor-kB [NF-kb]) and effects of cytokines. The anti-apoptotic effect of vitamin D may also be mediated by downregulating the Fas-related pathways (Fas/Fas-L). Activation of vitamin D also occurs intracellularly by 1-alpha hydroxylase, which is expressed in pancreatic beta cells. Vitamin D also regulates calbindin, a cytosolic calcium-binding protein found in beta cells, which acts as a modulator of depolarization-stimulated insulin release via regulatation of intracellular calcium. Calbindin may also protect against apoptotic cell death via its ability to buffer intracellular calcium. The effects of vitamin D may be mediated indirectly via its important and well-recognized role in regulating extracellular calcium (Ca2+), calcium flux through the beta cell and intracellular calcium (Ca2+)i. Alterations in calcium flux can directly influence insulin secretion, which is a calcium-dependent process.

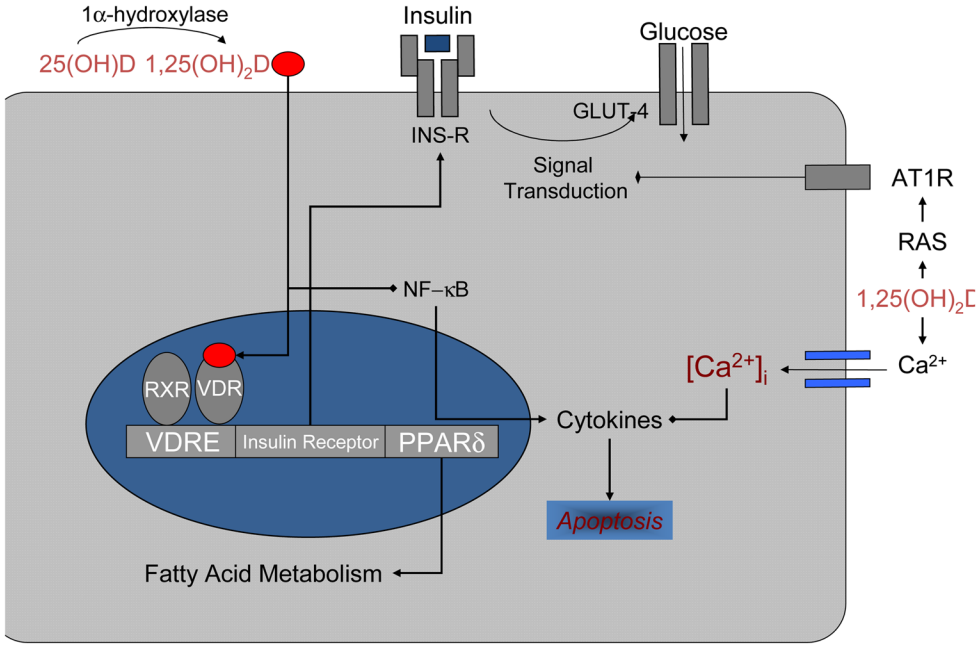

Figure 2.

Vitamin D and insulin action. In peripheral insulin-target cells, vitamin D may directly enhance insulin sensitivity by stimulating the expression of insulin receptors (INS-R) 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. The effects of vitamin D may be mediated indirectly via its important and well-recognized role in regulating extracellular calcium (Ca2+), calcium flux through the cell and intracellular calcium (Ca2+)i. Vitamin D may promote beta-cell survival by modulating the generation (through inactivation of nuclear factor-kB [NF-kb]) and effects of cytokines. Vitamin D may also affect insulin resistance indirectly through the renin-angiotensin (AII)-aldosterone system.

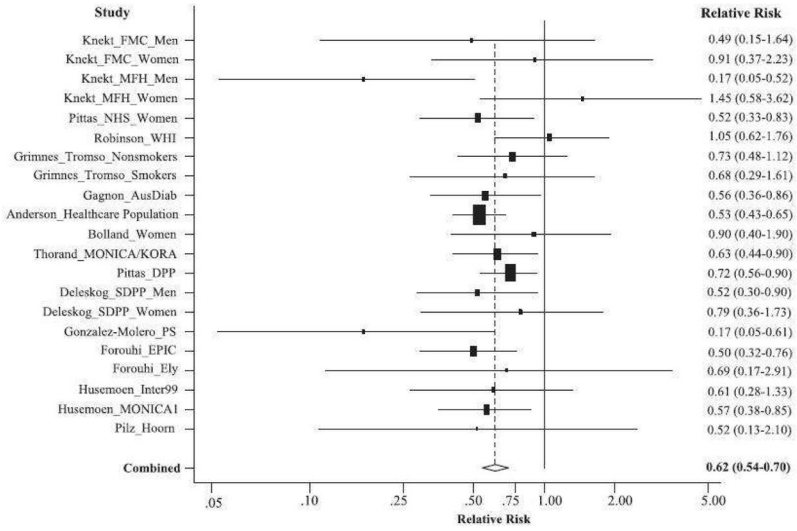

Figure 3.

A random-effects meta-analysis of 21 independent prospective studies with adjusted RR and 95% CI of type 2 diabetes in relation to serum 25(OH)D levels (the highest category versus the lowest category).

Table 1

Guidelines for vitamin D status by blood 25-hydroxyvitamin D concentration

Cut-off, ng/mL[1]	Institute of Medicine	Endocrine Society
<12	Deficiency	Deficiency
12 – 19	Inadequacy	Deficiency
20 – 29	Sufficiency	Insufficiency
30 – 49	Sufficiency	Sufficiency
>50	Reason for concern	Sufficiency

[1]To convert 25(OH)D concentration from ng/mL to nmol/L multiply by 2.459

Table 2

Vitamin D Recommended Intake*

	Institute of Medicine		Endocrine Society	
	RDA[1]	UL[2]	Daily requirement	UL
14–18 years	600 IU	4000 IU	600–1000 IU	4000 IU
19–70 years	600 IU	4000 IU	1500–2000 IU	4000 IU
> 70 years	800 IU	4000 IU	1500–2000 IU	10000 IU

*RDA for skeletal outcomes (fractures and falls) only under conditions of minimal sun exposure. Applicable to normal healthy population groups

[1]Recommended Dietary Allowance, intake that meets needs of 97.5% of healthy population

[2]Tolerable Upper Intake Level, above which potential risk of adverse effects may increase with chronic use.

Table 3

Observational longitudinal cohort studies of vitamin D status (plasma or serum 25[OH]D concentration, predicted 25[OH]D concentration or self-reported vitamin D intake) and incident type 2 diabetes

Study, Year (reference) Cohort [Country]	Male, %	Mean baseline age (range), y	White, %	n*/N (incidence)	Vitamin D measure; comparison†	Mean follow-up, y (start-end)	Results, Adjusted RR, OR, or HR (95% CI) P for trend	Outcome (ascertainment method)	Adjustments
Liu et al, 2005 Women's Health Study [US]	0	52 (45–75)	95	805/10,066 (8.0%)	Vitamin D intake (total); ≥511 vs. ≤159 IU/d	9 (ND)	0.73 (0.54, 0.99) § P=0.02	Type 2 diabetes (validated self-report)	Age
Pittas et al, 2006 [US]	0	46 (30–55)	98	4,843/83,779 (5.8%)	Vitamin D intake (total); >800 vs. ≤200 IU/d	20 (1980–2000)	0.87 (0.69, 1.09) P=0.67	Type 2 diabetes (validated self-report)	Age, BMI, exercise, residence, family history of diabetes, hypertension. calcium intake, smoking, alcohol, coffee, other diet
Knekt et al, 2008 Finnish Mobile Clinic Health Examination Survey [Finland]	100	ND (40–74)	100	105/1,628 (6.4%); nested case-control study with 206 control participants	25OHD concentration; 30 vs. 10 ng/mL (means)	22 (1973–1994)	0.49 (0.15, 1.64) P=0.06	Type 2 diabetes (medication-treated, registry-based)	Age, BMI, exercise, season, smoking, education, medications
	0	ND (40–74)	100	125/1,699 (7.4%); nested case-control study with 246 control participants	25OHD concentration; 25 vs. 9 ng/mL (means)		0.91 (0.37, 2.23) P=0.66		Age, BMI, exercise, season, smoking, education, medications
Knekt et al, 2008 Mini-Finland Health Survey [Finland]	100	53 (40–69)	100	83/1,948 (4.3%); nested case-control study with 245 control participants	25OHD concentration; 31 vs. 9 ng/mL (means)	17 (1978–1994)	0.17 (0.05, 0.52) P<0.001	Type 2 diabetes (medication-treated, registry-based)	Age, BMI, exercise, season, smoking, education, medications
	0	ND (40–69)	100	99/2228 (4.4%); nested case-control study with 289 control participants	25OHD concentration; 25 vs. 8 ng/mL (means)		1.45 (0.58, 3.62) P=0.83		Age, BMI, exercise, season, smoking, education, medications
Kirii et al, 2009 Japan Public Health Center-based Prospective Study [Japan]	100	57 (40–69)	NR (~100% Japanese)	634/25,877 (2.4%)	Vitamin D intake (total); 720 vs. 188 IU/d (means)	5 (1990–1998)	0.96 (0.74, 1.23) P=0.35	Type 2 diabetes (validated self-report)	Age, BMI, exercise, family history of diabetes, smoking, diet, hypertension
	0	57 (40–69)	NR (~100% Japanese)	480/33,919 (1.4%)	Vitamin D intake (total); 696 vs. 192 IU/d (means)	5 (1990–1998)	0.88 (0.67, 1.16) P=0.67	Type 2 diabetes (validated self-report)	
Liu et al, 2010 Framingham Offspring Study [US]	54	60	~100	133/2,956 (4.4%)	Predicted 25OHD score; 22 vs. 17 ng/mL (median)	7 (1991–2001)	0.60 (0.37, 0.97) P=0.03	Type 2 diabetes (medication-treated, laboratory-based)	Age, sex, waist circumference, ** family history of diabetes, hypertension, low HDL-cholesterol, high triglycerides, impaired fasting glucose, diet
Pittas et al, 2010 Nurses Health Study [US]	0	46 (30–55)	98	608/32,826 (1.8%); nested case-control study with 569 control participants	25OHD concentration; 33 vs. 14 ng/mL (median)	14 (1990– 2004)	0.52 (0.33, 0.83) P=0.008	Type 2 diabetes (validated self-report)	Age, BMI, exercise, season, race, fasting status, latitude, hypercholesterolemia, hypertension, family history of diabetes, smoking, physical

Study, Year (reference) Cohort [Country]	Male, %	Mean baseline age (range), y	White, %	n*/N (incidence)	Vitamin D measure; comparison†	Mean follow-up, y (start-end)	Results, Adjusted RR, OR, or HR (95% CI) P for trend	Outcome (ascertainment method)	Adjustments
									activity, alcohol, multivitamin use, diet
Anderson et al, 2010 Intermountain Healthcare system [US]	25	55	NR	NR/41,497 (NR);	25OHD concentration; ≤15 vs. >30 ng/mL (median)	1.3 (2000 –2009)	1.89 (1.54, 2.33) P<0.001	Diabetes (physician-diagnosed based on ICD-9 code)	Age, gender, hypertension, hyperlipidemia, heart failure, infection, depression, renal failure
Grimnes et al, 2010 Tromso study [Norway]	NR NR	60 (Non smokers) 57 (smokers)	NR (majority Caucasians) NR (majority Caucasians)	183/4157 64/1962	25OHD concentration; quartiles 25OHD concentration; quartiles	11 (1994–2005) 11 (1194–2005)	HR=0.95 (0.86–1.0) p NS HR=0.96(0.83–1.12) p NS	Type 2 diabetes (self-report verified by A1C and hospital discharge diagnosis) Type 2 diabetes (self-report verified by A1C and hospital discharge diagnosis)	Age, Sex, BMI, physical activity, month (stratified by smoking status) Age, Sex, BMI, physical activity, month (stratified by smoking status)
Bolland et al, 2010 Community dwelling women [Australia]	0	74 (>55)	100	15/1,471	25OHD concentration; <20 vs. ≥20 ng/mL	5 (1998–2003)	0.90 (0.4, 1.9) P=NS	Type 2 diabetes (self-reported)	Age, weight, smoking, season, treatment allocation
Gagnon et al, 2011 [Australia]	45	51 (xx)	92	199/6,537 (3.8%);	25OHD concentration; ≤19 vs. ≥32 ng/mL	5 (1999, 2005)	0.68 (0.43, 1.07) P=0.02	Type 2 diabetes (medication-treated, FPG or OGTT)	Age, gender, waist, exercise, race,
Robinson et al, 2011 WHI [US]	0	(50–79)		317/5,140 (6.2%); nested case-control study	25OHD concentration; < 20 vs. ≥30 ng/mL	7.3	1.14 (0.68, 1.90) P=0.873	Diabetes (self-report, medication-treated)	Age, BMI, season, race, others
Thorand et al, 2011 [Germany]	53	(35–74)	100%	416/1683 (25%) case-control	25OHD concentration; 11 vs. 68 ng/mL (median)	11	0.63 (0.44, 0.90) P=0.01	Type 2 diabetes (validated self-report)	Age, sex, survey, season, BMI, smoking, alcohol, physical activity, systolic blood pressure, total cholesterol/HDL cholesterol, parental history of DM.
Pittas et al, 2012 Diabetes Prevention Program [USA]	33	51	57%	/2040	25OHD concentration; ≤13 vs. ≥30 ng/mL	2.7 yr	0.72 (0.56, 0.90) p=0.0054	Type 2 diabetes (OGTT)	Age, gender body mass index, race, family history of diabetes, personal history of hypertension at baseline, smoking status at baseline, alcohol consumption, C-reactive protein, kidney function, self-reported physical activity, calcium intake and treatment arm
Deleskog et al, 2012 [Denmark]	100	(35–56)	100%	145/1011	25OHD concentration; >28 vs. < 18 ng/mL (means)	10	0.38 (0.21, 0.71)	Type 2 diabetes (OGTT)	Age, gender, BMI, exercise, season, BP, family history of diabetes
Forouhi et al, 2012 EPIC-Norfolk [Europe]	52%	58	>90%	621/826 nested case-control study	25OHD concentration; >32	10	0.50 (0.32, 0.76)	Type 2 diabetes (validated self-report)	Age, gender, BMI, exercise, season, family history of diabetes, cholesterol, alcohol,

Study, Year (reference) Cohort [Country]	Male, %	Mean baseline age (range), y	White, %	n*/N (incidence)	Vitamin D measure; comparison†	Mean follow-up, y (start-end)	Results, Adjusted RR, OR, or HR (95% CI) P for trend	Outcome (ascertainment method)	Adjustments
					vs. <20 ng/mL (means)				smoking, education, supplement use
Afzal et al, 2013 Copenhagen City Heart Study [Europe]	43%	56	100%	810/9841	25OHD concentration Quartiles value NR	29	1.35 (1.09–1.66)	Type 2 diabetes (Self report, medication treated, non fasting glucose, registry based)	sex, age, smoking status (never/ever), BMI, income, and duration and intensity of leisure time physical activities.

*number of cases if nested case-control study

†highest/lowest risk category versus reference category

§estimated from reported data

25OHD, plasma or serum 25-hydroxyvitamin D; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HR, hazard ratio; IU, international units; ND, no data; OR, odds ratio; RR, relative risk

To convert 25OHD concentration from ng/mL to nmol/L multiply by 2.459

Data from Refs [52–67].

Table 4

Randomized controlled trials of the effect of vitamin D (cholecalciferol [D_3] or ergocalciferol [D_2]) supplementation (with or without calcium) on glycemic measures

Study, First author, Year [Country]	Men, %	Mean baseline age and/or range	BMI	Participants	Mean baseline 25(OH)D concentration, ng/mL calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs. placebo [p value]
Nilas and Christiansen, 1984 [Denmark]	0	45–54	ND	Postmenopausal healthy n=151	ND	D_3, 2000 IU/d (n=25) vs. $1(OH)_2D_3$ 0.25 mcg/d (n=23) vs. placebo (n=103). All received calcium, 500 mg/d	2 y	↔FPG 2.16 vs. −5.94 vs. 2.34 mg/dL
Pittas et al., 2007 [US]	38	71 (≥65)	27	Normal fasting glucose n=222	30 Calcium intake, 750 mg/d	D_3, 700 IU/d plus calcium citrate, 500 mg/d (n=108) vs. placebo (n=114)	3 y	↔FPG change, 2.70 vs. 2.16 mg/dL [p=0.55] ↔ IR_{HOMA}
	52	71		Impaired fasting glucose n=92	30 Calcium intake, 680 mg/d	D_3, 700 IU/d plus calcium citrate 500 mg/d (n=45) vs. placebo (n=47)	3 y	↓FPG change, 0.36 vs. 6.13 mg/dL [p=0.042] ↓ IR_{HOMA}
De Boer et al., 2008 [US]	0	62 (50–79)		Post-menopausal without diabetes	<32 (for 89% of participants)	D_3, 400 IU/d plus calcium carbonate 1,000 mg/d (n=16,999) vs. placebo (n=16,952)	7 y	↔Incidence of Diabetes (self-reported), HR 1.01 (0.94 to 1.10) [p=0.95]; ↔Insulin secretion ↔ IR_{HOMA}
	0	50–79		Normal fasting glucose n=1,637		D_3, 400 IU/d + calcium carbonate 1,000 mg/d (n=866) vs. placebo (n=771)	6 y	↔FPG change, 3.80 vs. 4.61mg/dL [p=0.32]
	0	50–79		Impaired fasting glucose n=1,457		D_3, 400 IU/d + calcium carbonate 1,000 mg/d (n=718) vs. placebo (n=739)	6 y	↔FPG change, 3.93 vs. 4.69 mg/dL [p=0.79]
Avenell et al., 2009 [UK]	15	77 (≥70)	ND	History of fracture	ND	D_3, 800 IU/d (n=2,649) vs. placebo (n=2,643) (2×2 factorial design with calcium carbonate 1,000 mg/d)	2–5 y	↔Incidence of Diabetes (self-reported), intention-to-treat HR 1.11 (0.77 to 1.62) [p=0.57] ↔Incidence of Diabetes (self-reported), compliant HR 0.68 (0.40 to 1.16) [p=0.16]
Zittermann et al., 2009 [Germany]	33	48 (18–70)	33	Healthy; BMI>27 kg/m^2 n=200	12	D_3, 3,332 IU/d (n=82) vs. placebo (n=83). All received weight	1 y	↔Hemoglobin A1c change, −0.25% vs. −0.25% [p=0.96]

Study, First author, Year [Country]	Men, %	Mean baseline age and/or range	BMI	Participants	Mean baseline 25(OH)D concentration, ng/mL calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs. placebo [p value]
						reduction advice for 24 wk		↔FPG change, −0.21 vs. −0.27 mmol/L (−3.8 vs. −4.9 mg/dL) [p=0.39]
Von Hurst et al., 2010 [New Zealand]	0 Indian (91%)	42 (23–68)	27.5	Insulin resistance, no diabetes; 25(OH)D<20 ng/mL n=81	8	D_3, 4,000 IU/d (n=42) vs. placebo (n=39)	26 wk	↔FPG change, 0.1 vs. 0.1 mmol/L (1.8 vs. 1.8 mg/dL) [p=0.82]; ↓ IR_{HOMA} (change from baseline) −0.2 vs. 0.2; p=0.02; (highest effect seen when final 25OHD>80 nmol/L) ↓ Insulin ↔ HOMA2%B; C-peptide
Jorde et al, 2010 [Norway]	36	38 (21–70)	35	Overweight/Obese; no diabetes n=438	23	D_3, 40,000 IU/wk (equivalent to 5,714 IU/d) (n=150) vs. D_3, 20,000 IU/wk (equivalent to 2,857 IU/d) (n=139) vs. placebo (n=149). All received calcium 500 mg/d	1 y	↔Hemoglobin A1c change, 0.09% vs. 0.11% vs. 0.09% (0.4 vs. 1.4 vs. 1.4 mg/dL) [p=NS]; post-hoc ↔FPG change, 0.02 vs. 0.08 vs. 0.08 mmol/L [p=NS]; post-hoc ↔2hPG change, 0.15 vs. 0.36 vs. −0.02 mmol/L (2.7 vs. 6.5 vs. −0.4 mg/d) [p=NS]; post-hoc ↔ IR_{HOMA} 0.23 vs −0.05 vs 0.36, p=NS ↔ QUICKI
Wood et al, 2012 [UK]	0	64	26	Healthy (NGT) post-menopausal women; n=305	13	D_3 1,000 IU/d orally (n=101) vs. D_3 400 IU/d orally (n=102) vs. placebo (n=102)	48 w	↔FPG change, −1.1 vs. 0.9 vs. −2.3 mg/dL [p=0.23) ↔HOMA-IR change
Nagpal et al, 2009 [India]	100	43 (>35)	26	Healthy; Central obesity; N=71	15	D3 120,000 IU three times (equivalent to 8,571 IU/d) [N=35] vs. Placebo [N=36]	6 w	↑OGIS (change from baseline, ml/min*kg) 21.17 vs. −8.89 p=0.055 ↔HOMA (change from baseline) 0.14 vs. 0.16 p=0.95 ↔QUICKI 0 vs 0 p= 0.9
Mitri et al, 2011 [US]	53	57	32	Pre-diabetes; n=92	24	D_3 2000 IU/d vs. placebo-vitamin D (n=46); 2×2 factorial design with calcium 800 mg/d vs. placebo-calcium (n=46)	16 w	↔ A1c change, 0.06 vs. 0.14% [p=0.08] ↔ FPG change, 2.4 vs. 5.6 mg/dL [p=0.172) ↔ 2hPG change, −7.2 vs. 1.2 mg/dL [p=0.22] ↑ DI change 300 vs −126 in D_3 vs non D_3, [p=0.011]

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Study, First author, Year [Country]	Men, %	Mean baseline age and/or range	BMI	Participants	Mean baseline 25(OH)D concentration, ng/mL calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs. placebo [p value]
								↑ SI change −0.3 vs −0.9 in D_3 vs non D_3, [p=0.16] ↑ AIR change, 34 vs −53 in D_3 vs non D_3 [p=0.074]
Nazarian et al, 2011 [US]	38	34–62	23–45	Pre-diabetes (FPG 100–125 mg/dL); 25OHD≤30 ng/mL (n=8)	20	D_3 10,000 IU/d for 4 weeks (n=8)	4 w	No glycemic data ↔ DI (% from baseline) 21 [p=NS] ↑ SI (% from baseline) 42 [P=0.012] ↓ AIRg (% from baseline) 20 [P=0.011]
Davidson et al, 2012 [US]	32	52 (ND)	32	Pre-diabetes (FPG 110–125 mg/dL; 2hPG 140–199 mg/dL); 25OHD<30 ng/mL; Latino and African-American; n=117	22	D3, orally weekly titrated to achieve 25OHD 65–90 ng/mL (mean dose required equivalent to 12,700 IU/d) (n=56) vs. Placebo (n=53)	12 m	↓ Hemoglobin A1c change, −0.1 vs. 0.1% [p=0.004] ↔FPG change, 1 vs. 4 mg/dL [p=0.27) ↔ 2hPG change, −11 vs. −9 mg/dL [p=0.64] ↔ DI1 change, 0.2 vs. 0 [p=0.39] ↔ DI2 change, −0.1 vs. 0 [p=0.32] ↔ Proportion with diabetes [p=NA]
Harris et al, 2012 [US]	35	56 (NR)	32	Pre-diabetes/early diabetes (FPG>100 mg/dL; A1c 5.8–6.9%); Overweight; African-American; n=89		D_3, 4,000 IU/d orally (n=43) vs. Placebo (n=46)	12 w	↔Hemoglobin A1c change, −0.05 vs. 0.05% [p=0.97] ↔FPG change, −0.18 vs. −0.54 mg/dL [p=0.81) ↔ 2hPG change, −7.2 vs. −6.5 mg/dL [p=0.98] ↓ Insulin sensitivity change (%),−4 vs. 12 [p=0.004] ↑ Insulin secretion change (%), 12 vs. 2 mg/dL [p=0.27) ↔ DI change, −11 vs. −9 mg/dL [p=0.64]
Witham et al, 2010 [United Kingdom]	ND	65 (>18)	31	Type 2 diabetes; 25OHD<40 ng/mL n=61	18	D_3, 100,000 IU orally once (equivalent to 892 IU/d) (n=19) vs. D_3, 200,000 IU orally once (equivalent to 1,785 IU/d) (n=20) vs. placebo (n=22)	16 wk	↔Hemoglobin A1c change, “no change” (data NR) ↔FPG change, “no change” (data NR) ↔IR_{HOMA} change, “no change” (data NR)
Sugden et al, 2008 [UK]	53	64	31	Stable type 2 diabetes; 25(OH)D<20 ng/mL n=34	15	D_2, 100,000 IU once (equivalent to 1,785 IU/d) (n=17) vs. placebo (n=17)	8 wk	↔Hemoglobin A1c change, 0.01% vs. −0.05% [p=0.74] ↔IR_{HOMA} change, −39.7 vs −25.6 [p=0.72]

Study, First author, Year [Country]	Men, %	Mean baseline age and/or range	BMI	Participants	Mean baseline 25(OH)D concentration, ng/mL calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs. placebo [p value]
								IR_{HOMA} significantly improved if 25OHD rise >11 nmol/l
Jorde and Figenschau 2009 [Norway]	50	56 (21–75)		Stable type 2 diabetes n=32	24	D3, 40,000 IU/wk (equivalent to 5,714 IU/d) (n=16) vs. placebo (n=16)	26 wk	↔Hemoglobin A1c change, 0.2% vs. −0.2% [p=0.90] ↔FPG change, −0.2 vs. 0.4 mmol/L (−3.6 vs. 7.2 mg/dL) [p=0.43] ↔ IRHOMA 0.3 vs. −0.2, p=0.58
Nikooyeh et al, 2011 [Iran]	40	51	29	Type 2 diabetes (FPG≥126 mg/dL)	12	D_3 1000 IU/d in yogurt drink with 250 mg of calcium (n=30) vs. D_3 1000 IU/d in yogurt drink with 500 mg of calcium (n=30) vs. placebo (plain yogurt drink; n=30)	12 w	↓ A1c change, −0.5 vs. 1.2% [p<0.01] ↓ FPG change, −9 vs. 16 mg/dL [p=0.01)
Soric et al, 2012 [Ohio, US]	45	54 (21–75)	ND	Type 2 diabetes (A1c >7%); n=37	ND	D_3, 2,000 IU/d orally (n=19) vs. Vitamin C, 500 mg/d orally (n=18)	12 w	↔Hemoglobin A1c change, −0.4 vs. 0.1% [p=0.16] ↓ Hemoglobin A1c change, −1.4% vs. 0.2% [p=0.013] when baseline A1c>9%
Punthakee et al, 2012 [33 countries]	60	66		Type 2 diabetes (A1c 7.4%) [TIDE study) N=1,221	ND	D_3, 1,000 IU/d orally (n=607) vs. placebo (n=614)	40 m	↔Hemoglobin A1c “NR ↔FPG change NR cancer; all-cause death, 0.3% vs. 0.5%
Heshmat, et al., 2012 [Iran]	36	56.2(37–79)	27.7	Type 2 diabetes on diet or oral agents (A1c <7.5%) [TIDE study) N=42	46.9	D3, 300,000 IU/d orally x1 dose (n=21) vs. placebo (n=21)	3 m	↔Hemoglobin A1c −0.05 % vs −0.2% p=0.495 ↑ FPG 16.2 vs −9.7 (p=0.007) ↑ HOMA 0.2 vs −0.9 p=0.017

25(OH)D, plasma or serum 25-hydroxyvitamin D; 2hPG, plasma glucose 2 hours after 75 gram glucose load; D_3, cholecalciferol; D_2, ergocalciferol; FPG, fasting plasma glucose; HR, hazard ratio; ND, no data;

GLU_{AUC}, glucose area-under-the-curve after 75 gram glucose load; INS_{AUC}, insulin area-under-the-curve after 75 gram glucose load; INS_{120}, Insulin value at 120′ after glucose load is given; IR, insulin resistance; IR_{FI}, Insulin resistance by fasting insulin; IR_{HOMA}, Insulin resistance by homeostasis model assessment-; IR_M, Insulin resistance after euglycemic hyperinsulinemic clamp; IR_{IVGTT}, insulin resistance after intravenous glucose tolerance test;

↓ decreased (statistically significant), ↑ increased (statistically significant), ↔ no difference (no statistical significance);

To convert 25(OH)D concentration from ng/mL to nmol/L multiply by 2.459; to convert FPG form mg/dL to nmol/L, multiply by 0.0555

Data from Refs [69–77,79–83,85–89,100].

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