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REVIEW ARTICLE

# Vitamin D and diabetes mellitus

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**Abstract** Better understanding of the physiological role of the vitamin-D system, in particular its potential effects on inflammatory and autoimmune conditions as well as on insulin secretion and possibly also on insulin resistance, increased the interest in its potential role in prevention and control of the diabetic condition, both type-1 and -2 diabetes. Both these conditions are associated with inflammation and type-1 diabetes also with an autoimmune pathology. Indeed, animal and human studies support the notion that adequate vitamin-D supplementation may decrease the incidence of type-1 and possibly also of type-2 diabetes mellitus and may improve the metabolic control in the diabetes state. However, the exact mechanisms by which vitamin-D and calcium supplementation exert their beneficial effects are not clear and need further investigation.

**Keywords** Type-1 diabetes · Type-2 diabetes · Calcium · Vitamin-D · PTH

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## Introduction

Diabetes is the fifth leading cause of death in the US and the number of people with diabetes in the world is expected to approximately double between 2000 and 2030 [1]. In view of this data, it becomes imperative to discover and implement preventive measures to address this growing epidemic. While universally recognized measures for the prevention of type-1 diabetes mellitus (DM) remain elusive, many modifiable environmental risk factors have been indentified for type-2 DM [2]. Recent epidemiological data have suggested that the majority of cases of type-2 DM could be avoided by behavior modification [2, 3]. Among these risk factors, obesity remains number one [2]. For decades, multiple studies have looked at a potential link between calcium, PTH, and DM [4–9]. More recently, animal and human studies have suggested that vitamin D is a potential modifier of diabetes risk [10–15]. Vitamin D has been shown to play an important role in the disorders of glucose and insulin metabolism [16–18]. It has been observed that vitamin D with calcium supplementation produces a significant decrease in fasting glucose and insulin resistance in patients with impaired fasting glucose [19] and vitamin D supplementation has been suggested to have a role in improving and even preventing type-1 DM in both human [20, 21] and animal models [8, 9]. This evidence gives hope for a new avenue of primary prevention for both type-1 and -2 DM. The purpose of this review is to assess the role of vitamin D as a potential modifier of diabetes risk and to provide an overview of the possible mechanisms of its action.

## Vitamin D metabolism and biological function

Only a small amount of vitamin D is obtained from the diet, since it is contained in only a few food sources [22].

The major food sources of vitamin D are oily fish, vitamin D fortified dairy products, and egg yolk [23]. Most of the needed vitamin D is derived from the synthesis of cholecalciferol (vitamin D3) in the skin [24]. Vitamin D3 is derived from the skin 7-dehydrocholesterol through exposure to sunlight [25]. The production of vitamin D3 in the skin is dependent on the ultraviolet radiation wavelength (290–315 nm) and the number of the photons absorbed by the 7-dehydrocholesterol in the skin [22]. A multitude of factors affect this process, including increased skin pigmentation, the use of sunscreen, and the angle of sunlight reaching the Earth's surface (zenith angle) [26–29]. The zenith angle is dependent on the time of the day, season, and latitude [29, 30]. The ultraviolet radiation needed to synthesize vitamin D is blocked by the atmosphere when the sun fails to rise over 35° above the horizon [31]. Therefore, Vitamin D3 synthesis is impaired in the morning and the evening hours, during the winter months and more so in countries of higher latitude [32, 33].

Once vitamin D3 is produced in the skin or consumed in food, it is converted in the liver to 25-hydroxyvitamin D3 (25(OH)D3) by vitamin D-25-hydroxylase [34]. A second hydroxylation to the main physiologically active metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D3$), occurs predominantly in the kidney through the action of 1α-hydroxylase [35]. This process is regulated by PTH, calcitonin, calcium, phosphorus, and fibroblast growth factor 23 as well as by $1,25(OH)_2D3$ itself [36, 37]. Both of these hydroxylases belong to the P450-dependent steroid hydroxylases [38]. After $1,25(OH)_2D3$ is synthesized it is transferred to its target tissues by binding to Vitamin D binding protein (DBP) [39]. The accepted way to determine vitamin D nutritional status is by measurement of the level of 25(OH)D3, which has a slower rate of clearance (biological half life of approximately 3 weeks) as compared to vitamin D3 (approximately 24 h) and $1,25(OH)_2D3$ (approximately 4–6 h) [40, 41].

Vitamin D has been shown to have actions at multiple sites, and thus have additional potential effects other than that on calcium homeostasis [42]. Vitamin D receptors (VDR) exist in almost all tissues. They have been identified in bone and kidney cells, skeletal, heart, and smooth muscles, intestinal epithelial cells, stomach, liver, skin keratinocytes and hair follicular cells, breast, pancreatic islets (β cells), thyroid, parathyroid, adrenal and pituitary glands, immune cells, brain, prostate, ovaries and testes [42, 43]. Some sites such as proximal renal tubular cells, pancreatic β cells, skin keratinocytes, immune cells, granulomatous tissue in sarcoidosis and cancer cells such as colon, lung, prostate and breast cancer have also been demonstrated to possess the 1α-hydroxylase enzyme [44–51]. These findings are consistent with a more complex role of vitamin D in human biology, that includes among others also regulation of insulin synthesis and secretion [52], modulation of the inflammatory response, cell maturation, and cell differentiation [22, 42]. Vitamin D has been shown to have a potential role in cancer prevention, including colon, breast, prostate, and ovarian cancer [53] most likely by its effect on cell maturation and differentiation. The role of vitamin D in autoimmune and inflammatory conditions is currently aggressively studied [42].

## Vitamin D modulation of the immune and inflammatory reaction in diabetes

Type-1 and -2 DM, which have different pathogenesis, share a common denominator an inflammatory process.

Type-1 DM is characterized at the early stages of the disease by an autoimmune destruction of the pancreatic islets. Type-2 DM was found to be associated with an increase in the levels of tumor necrosis factor-α and β, C reactive protein, plasminogen activator inhibitor-1 (PAI-1), and interleukin-6 (IL-6) [54–60]. The increase in these inflammatory mediators may precede and even predict the development of type-2 DM [54].

Animal studies on the effect of vitamin D on the immune and inflammatory systems suggest that it may modulate the pathogenesis of type-1 DM [11–14]. Its immunomodulatory and anti-inflammatory actions may reduce the inflammatory reaction in the pancreatic islets and decrease the autoimmune insulinitis characteristic for type-1 DM [13]. In support of this concept is the finding that VDR has been found on almost all cells of the immune system [61] and vitamin D can repress type 1 cytokines, inhibit dendritic cell maturation, and upregulate regulatory T cells [10]. Furthermore, immune cells, such as macrophages, contain 1α-hydroxylase [47] that can be up regulated by inflammatory mediators and not PTH [62].

Vitamin D also suppresses the antigen-presenting capacity of macrophages, modulates the development of CD4 lymphocytes [61] and inhibits the production of IFNγ (interferon γ) and IL-2 (interleukin 2) [63–65] among other cytokines. These cytokines are known to activate macrophages and cytotoxic T cells, which in turn can lead to the destruction of the pancreatic islets seen in Type-1 DM [66]. Through its anti-inflammatory effects, vitamin D may reduce the cytokine induced islet cell death [67].

By modulation of the immune and inflammatory process, vitamin D may also decrease insulin resistance and increase insulin secretion in type-2 DM [68], two characteristic defects in this condition.

## Effect of vitamin D on insulin secretion

Pancreatic islets have both VDR and vitamin D-dependent calcium-binding proteins (CaBP) [69, 70], suggesting a role for vitamin D in insulin secretion. Vitamin D affects more the $\beta$ cells than the $\alpha$ cells' function [71, 72]. Its effect on the $\beta$ cells is by increasing insulin response to glucose stimulation, but it does not affect basal insulin secretion [16].

Vitamin D-deficient rats have been found to have reduced insulin secretion [73] and after a single subcutaneous injection of vitamin D, glucose tolerance and insulin secretion significantly improved [74]. Furthermore, in mice with non-functioning VDRs, serum insulin concentrations as well as cellular insulin mRNA levels were found to be reduced, while blood glucose levels were increased, as compared to wild-type mice [75]. It was suggested that the effect of the vitamin D on insulin secretion and synthesis was independent of the effects of calcium levels [75].

The relationship between vitamin D and $\beta$ cell functions may be reciprocal in nature. In streptozotocin-induced diabetic rats with $\beta$ cell destruction, plasma calcium levels, DBP, circulating vitamin D, and bone mass were reduced [76–78]. After insulin therapy, plasma 25(OH)D3 was fully restored [77].

Insulin secretion is a process dependent on changes in intracellular calcium concentration [4]. The effects of vitamin D on $\beta$ cells may be by its regulation of extracellular calcium and calcium flux through the $\beta$ cell [79, 80] or through calcium-independent pathways [71, 75]. Whether or not acting independently, vitamin D or calcium deficiency may alter the balance between intracellular and extracellular calcium in $\beta$ cells, interfering with insulin secretion and possibly synthesis.

Vitamin D deficiency may also impair insulin secretion through its associated increase in PTH levels. It was proposed that vitamin D deficiency-associated hyperparathyroidism may actually cause a paradoxical increase in intracellular calcium level [Ca]i [81]. This PTH-induced increase in [Ca]i may in turn impair the calcium signal needed for glucose-induced insulin secretion [81].

Of significance is the finding that vitamin D potentiation of glucose-induced insulin secretion is seen in normal individuals but not in patients with established Type-2 DM [71, 72]. This could be because type-2 diabetes by itself may be a condition of impaired intracellular calcium homeostasis [8, 9].

Whether insulin secretion is influenced by the direct action of vitamin D through its receptor, or through changes in calcium, or PTH, is a matter of ongoing studies. It is also possible that insulin secretion may be influenced by a combination of the different mechanisms.

## Effect of vitamin D on insulin sensitivity

Systemic inflammation has been found to increase insulin resistance [82]. Obesity and Type-2 DM are conditions of increased inflammatory reaction [82] and therefore vitamin D may reduce the insulin resistance in these conditions by its immunomodulatory and anti-inflammatory effects [68].

Vitamin D deficiency is often associated with obesity and Type-2 DM [83, 84]. The deposition of vitamin D in the fat stores where it becomes less bioavailable is a presumed mechanism explaining this finding [85]. Vitamin D-deficient obese subjects also have elevated PTH levels [68, 86]. Increased PTH can decrease insulin sensitivity [7, 87]. There is evidence that hyperparathyroidism is associated with reduced insulin sensitivity and increased prevalence of impaired glucose tolerance (IGT) and DM in patients [5] and parathyroidectomy improves fasting and 2 h post-prandial plasma glucose levels [88]. Therefore, the increased insulin resistance found in elevated PTH states seems to be reversible.

The mechanism by which elevated PTH may increase insulin resistance may involve the "calcium paradox" (disproportionate increase in [Ca]i as a result of elevated PTH) [81]. It has been suggested that an optimal concentration of [Ca]i (between 140 and 370 nM) is needed for insulin to mediate its effects on its target tissue [6]. Higher basal intracellular calcium levels may result in a diminished cellular response to insulin [6, 89]. The paradoxical increase in [Ca]i due to elevated PTH [81] stimulated by vitamin D deficiency and hypocalcemia may therefore lead to elevated basal [Ca]i and impair insulin action.

Results from studies trying to determine whether vitamin D has an independent contribution in improving insulin sensitivity are inconsistent [90]. Studies looking at specific populations, such as patients with chronic renal failure on dialysis, have suggested a role of vitamin D [90]. These patients often have decreased insulin secretion and increased insulin resistance [91]. Treatment with vitamin D in these patients has been shown to improve glucose tolerance and insulin secretion [92]. These findings seem to be independent of PTH and calcium effects [92].

However since the regulatory factors of calcium homeostasis are linked together and evidence suggests that elevated PTH, vitamin D deficiency as well as hypocalcemia all may contribute to increased insulin resistance, it is not always possible to determine which factor contributes most.

## Vitamin D and type-1 DM

### Human studies

Several observational studies have described a link between geographical latitude and the incidence of type-1DM [32, 33,

93]. A seasonal pattern has also been described [32, 94], suggesting an inverse correlation between the incidence of diabetes and the effective exposure to sunlight. These findings could also suggest a link between the amount of vitamin D formation in the skin and the Type-1 DM.

There is evidence that increased vitamin D intake by infants may reduce the risk of developing type-1 DM [15]. The European Community sponsored Concerted Action on the Epidemiology and Prevention of Diabetes study found a 33% reduction in the risk of developing childhood-onset type-1 DM in children who received vitamin D supplementation compared with non-supplemented children [21]. Furthermore, a birth-cohort study showed that an intake of 2000 IU of vitamin D during the first year of life diminished the risk of developing type-1 DM, and found that the incidence of childhood diabetes was thrice higher in subjects with suspected rickets [95]. This benefit may also extend to children of mothers with higher vitamin D intake during the third trimester of pregnancy, as maternal intake of vitamin D during pregnancy may have a protective effect on the appearance of islet autoimmunity [96]. It was found that cod liver oil, an important source of vitamin D, taken by pregnant mothers was associated with reduced risk of type-1 DM in the offspring [20]. It is interesting to note that subjects that received the cod liver oil between 7 and 12 months had lower chances of developing type-1 DM than those supplemented between 0 and 6 months of age [20]. In spite of some inconsistencies in the reports, a recent meta-analysis by Zipitis and Akobeng [15] concluded that vitamin D supplementation in infancy might be protective against the development of type-1 DM. The apparent reduction of type-1 DM may be due to the immunomodulatory effects of vitamin D, thereby protecting from or arresting the immune process which contributes to its development [21].

In adult patients with recent onset type-1 DM, an open-label randomized trial also found a benefit in supplementation with calcitriol, which temporarily reduced the required insulin dose [97].

### Animal studies

In non-obese diabetic mice (NOD), an animal model for type-1 DM, which spontaneously develops autoimmune diabetes [10] the administration of $1,25(OH)_2D3$, was found to inhibit the onset of the autoimmune diabetes [12].

It was also found that vitamin D deficiency in the early life of NOD mice accelerates the appearance of the type-1 DM condition in the animals [14].

Additionally, an analog of vitamin D, KH1060, has been shown to prevent the onset of diabetes in NOD mice [11] and a similar compound was found to inhibit ongoing insulinitis [13].

These animal studies suggest that vitamin D may have a role in not only blocking the onset of Type-1 DM, but may also have a role in arresting the disease process.

## Vitamin D and type-2 DM

### Human studies

Similar to the findings for type-1 DM, observational studies have shown that glycemic control in patients with type-2 diabetes has a seasonal variation, being worse in the winter [98]. This variation may be explained in part also by fluctuations in vitamin D concentrations as a result of fluctuations in exposure to ultraviolet radiation [98, 99].

There are several contributing factors that can lead to the development of type-2 DM, including defects in pancreatic $\beta$-cell function, decrease in insulin sensitivity, and systemic inflammation [100, 101]. Vitamin D, as discussed above, has been shown to influence these mechanisms and therefore may be of significance in the development and the metabolic control of type-2 DM.

Two large randomized controlled trials that used combined calcium and vitamin D treatment found that it may lower the risk of type-2 DM [102, 103]. This suggests that calcium, vitamin D, or both may have a role in the treatment of type-2 DM.

There is evidence that in patients with osteomalacia, treatment with vitamin D improves blood glucose levels [104] and studies have found an inverse correlation between vitamin D levels and fasting blood glucose [105] and between vitamin D levels and glucose concentrations after oral glucose load [18]. A positive correlation between vitamin D levels and insulin sensitivity has also been shown [106].

Population-based studies have looked at hypovitaminosis D in relation to type-2 DM and metabolic syndrome [107]. In a large cross-sectional study involving 23,000 adults, after adjusting for age, sex, BMI, physical activity, and season, insulin resistance was found to be inversely correlated with serum vitamin D levels in Caucasians and Mexican Americans [108]. African Americans did not have a correlation between insulin resistance and vitamin D levels [108]. This finding may have been due to a previously described possible decreased sensitivity to vitamin D, PTH, or calcium in Blacks as compared to Whites [109]. Other cross-sectional studies have also found an association between low vitamin D levels and type-2 DM [110–112] and between low vitamin D levels and IGT [111, 112].

Studies and case reports have suggested that in vitamin D deficient populations with IGT and with type-2 DM, vitamin D replenishment may improve insulin secretion and glucose tolerance [113–115] as well as HBA1C levels

[116]. Also, from data in an observational study, the authors suggested that by extrapolation, vitamin D replenishment in vitamin D deficient healthy adults may improve insulin sensitivity by as much as 60% [106] and that this effect is more potent than either rosiglitazone or metformin treatment [106]. Additionally, in a cohort study with a 17-year follow-up period, a significant inverse association was found between 25(OH)D3 levels and the incidence of type-2 DM [117] and in pooled data from two cohorts with a 17–22-year follow-up period, high vitamin D status was found to provide protection against type-2 DM [118]. The data are often conflicting, because some studies found no benefit in vitamin D replenishment on fasting blood glucose, glucose tolerance, or insulin sensitivity [119–123]. In two prospective short-term studies looking at non-diabetic men and women, no change was found in fasting blood glucose or insulin sensitivity after vitamin D supplementation [122, 123]. Another prospective study looking at vitamin D-deficient population with IGT, found no benefit of vitamin D replenishment [119], and in postmenopausal non-diabetic women, vitamin D supplementation was also found to have no effect on fasting blood glucose [120]. The discrepancy in results is difficult to account for, but this may be explained by the different populations studied [68], a possibility that there may be a different response to vitamin D among different ethnic groups [105] and the existence of DNA sequence variations (polymorphisms) for the VDR gene which may account for a variability in the endocrine action of vitamin D [68, 124].

Additionally, the studies looking at the relationship between vitamin D and type-2 DM are often limited due to short duration, few subjects, lack of standard protocol for replacement, and the existence of few prospective or randomized controlled trials specifically targeting vitamin D as a modifier of type-2 DM risk [125]. Also, an independent role of calcium itself on insulin resistance [126] can influence the results.

Nonetheless, in a recent large meta-analysis, Pittas et al. [125] suggested that vitamin D and calcium may promote $\beta$ cell function and insulin sensitivity. It remains unclear whether these effects are additive or synergistic [125].

### Animal studies

The association between vitamin D and type-2 DM was studied in animal models.

Vitamin D-deficient rats have been found to have reduced insulin secretion [73] and upon vitamin D replacement, insulin secretion was found to improve in response to glucose tolerance testing [127]. This improvement was independent of calcium, as calcium replacement by itself in vitamin D-deficient rats failed to improve insulin secretion [127]. Also, in an experimental animal model of type-2 DM (obese Wistar rats) without vitamin D deficiency, vitamin D3 was found to decrease plasma glucose concentrations by as much as 40% [128].

## Conclusion

Vitamin D has been found to have additional biologic roles to the well-known effects, it has on calcium homeostasis. Studies looking at both mechanisms of action and clinical relevance have suggested that vitamin D may play a role in the prevention and treatment of both type-1 and -2 DM. There is compelling evidence that vitamin D may achieve this through actions on systemic inflammation, insulin secretion, and insulin resistance.

The mechanism of action of vitamin D may be direct or interlinked with the actions of calcium and/or PTH. Often, this relationship is inferred, as direct evidence of the mechanism of action at the molecular level is not always attainable. Further studies are needed to elucidate this aspect as well as to explore what type and what dose of vitamin D supplementation provides the best clinical outcome.

The prevalence of vitamin D deficiency is high and evidence has shown that it may be associated with an increased incidence of both type-1 and -2 DM. The potential role of vitamin D and calcium supplementation in the alleviation of the alarmingly increasing rate of diabetes worldwide needs to be further studied.

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