Diabetes mellitus is one of the most common endocrine diseases, characterized by an increase in plasma glucose. Different forms of diabetes with very distinct pathogenesis exist. Over time, diabetes can lead to blindness, kidney failure, and nerve damage. Diabetes is also an important factor in accelerating atherosclerosis, leading to stroke, coronary heart disease, and other large blood vessel diseases, all ultimately associated with increased mortality risks.

The most prevalent form of diabetes is type 2 diabetes (T2D), currently affecting more than 300 million people worldwide. T2D is characterized by the combination of insulin resistance and failing β-cell function. Type 1 diabetes (T1D), on the other hand, is an autoimmune disease in which the body’s own immune system mistakenly attacks and destroys the insulin-producing β cell in the pancreas. T1D typically occurs in young, lean individuals, but older patients can also be affected. This subgroup is referred to as latent autoimmune diabetes in adults (LADA). LADA is a slow, progressive form of T1D. Other forms of diabetes include gestational diabetes (GD), secondary diabetes due to pancreatic diseases or surgery, and genetic forms of diabetes.

Vitamin D is a secosteroid that is generated from 7-dehydrocholesterol in skin under the influence of UV light. Therefore, by definition, vitamin D cannot be considered a true vitamin but rather a prohormone, as the natural source of vitamin D in evolution of vertebrates and primates is photosynthesis in the skin. Indeed, the normal human diet is usually poor in vitamin D except for fatty fish. Regardless of the source of vitamin D, it needs to be hydroxylated twice to become biologically active. Vitamin D is first hydroxylated in the liver by 25-hydroxylases (25(OH)ase), consisting of
cytochrome P450 (CYP) isoforms (the mitochondrial CYP27A1 and the microsomal CYP2R1 [the most critical enzyme], CYP3A4, and CYPJ3) into 25-hydroxyvitamin D (25(OH)D). The second hydroxylation occurs in the kidney, by 1\(\alpha\)-hydroxylase (1\(\alpha\)(OH)ase, CYP27B1), as this tissue is normally the only one capable of the secretion of its end product, 1,25(OH)\(_2\)D, into the blood circulation. Vitamin D and its metabolites are bound to a carrier protein (vitamin D binding protein; DBP) when transported through the circulation. Another multifunctional hydroxylase, 24-hydroxylase (24(OH)ase, CYP24A1), catabolizes vitamin D metabolites. Vitamin D exerts its action via a nuclear receptor (vitamin D receptor; VDR), present in nearly all nucleated cells, but with the highest concentration in the epithelial cells of the gut. However, most of these enzymes and proteins essential for the action of vitamin D are also present in many tissues not related to bone and calcium metabolism, such as the immune system.\(^7\),\(^8\)

Over many years, links between vitamin D status and diabetes mellitus have been identified. As early as the 1980s, it was shown that vitamin D deficiency in rodents and rabbits inhibits pancreatic insulin secretion, indicating that vitamin D is essential for the function of the endocrine pancreas.\(^9\) Later, the connection between vitamin D and diabetes was reinforced by the discovery of the VDR and DBP in pancreatic tissue (more specifically in the insulin-producing \(\beta\) cells) and also in various cell types of the immune system. Thus, vitamin D has been proposed as a possible therapeutic agent in the prevention and treatment of T1D and T2D.\(^8\)

**TYPE 1 DIABETES**

T1D is a chronic autoimmune disease that results from the immune-mediated destruction of pancreatic \(\beta\) cells, thus resulting in insulin deficiency. The autoimmune process most commonly initiates in childhood and progresses for a variable period of months and even years before it leads to hyperglycemia and, thus, diagnosis. By the time of diagnosis only 10% to 30% of functional \(\beta\)-cell mass remains.\(^10\),\(^11\) T1D is the second most common chronic disease in children, second only to asthma, and is considered as a complex genetic trait; not only do numerous genetic loci contribute to susceptibility, but environmental factors also play an important role in determining risk.

**Vitamin D and Genetic Predisposition to T1D**

In T1D the major genetic determinant is located in the major histocompatibility complex (MHC) region on chromosome 6p21,\(^12\) although multiple non-MHC genes also contribute to T1D disease susceptibility.\(^13\) Refining genetic mapping particularly of the non-MHC loci may improve the ability to predict the risk of T1D and facilitate the testing of more aggressive preventive therapies.\(^14\) In this context, associations of T1D with polymorphisms in the CYP27B1 gene on chromosome 12q13.1-q13.3\(^{15-17}\) may be useful. It is hypothesized that presence of polymorphisms in the CYP27B1 gene may reduce the (local) expression of 1\(\alpha\)(OH)ase and consequently the conversion of 25(OH)D to 1,25(OH)\(_2\)D, leading to increased predisposition to T1D.

In the past, it has been shown that allelic variations in the VDR gene are an important determinant for the amount of VDR expressed,\(^18\) and which in turn may influence the immune-modulatory function of the VDR. Several authors have demonstrated that VDR polymorphisms are able to influence the immune response in either healthy individuals or T1D patients.\(^19,20\) In epidemiologic studies, clear associations between VDR polymorphisms and T1D have been reported in South Indian, German, and Taiwanese populations,\(^21-23\) but were not found in a large combined population sample of British,
Portuguese, and Finnish origin. In a recent study it was shown that specific VDR polymorphisms interact with the predisposing HLA DRB1 allele through vitamin D response element present in the promoter region of the DRB1*0301 allele, which may be detrimental for the manifestation of T1D, particularly in the case of vitamin D deficiency in early childhood due to poor expression of DRB1 0301 in the thymus.

1,25(OH)2D is biologically inactivated through a series of events starting with 24-hydroxylation. The 24(OH)ase enzyme is encoded by the CYP24A1 gene located on chromosome 20q13.2-q13.3. At present, no associations between CYP24A1 gene polymorphisms and T1D have been found.

Vitamin D as an Environmental Risk Factor

T1D has been linked to a clear north-south gradient as well as to a deficiency in vitamin D concentrations. Indeed, the incidence of T1D is higher in countries of northern latitude, this trend being reversed in the southern hemisphere. Latitude itself is unlikely to be an independent risk factor for T1D onset. On the other hand, UV-B irradiation, which follows a north-south gradient, is known to convert 7-dehydrocholesterol to vitamin D in the skin, and has protective properties against autoimmunity. A more significant correlation of T1D has been observed with erythemal UV-B irradiance than with latitude. Recently, Mohr and colleagues assessed the T1D incidence data for children younger than 14 years during 1990 to 1994 in 51 regions worldwide. This investigation found that incidence rates of T1D approached zero in regions worldwide with high UV-B irradiance. Furthermore, seasonality of T1D onset is well known. Kahn and colleagues reported that spring births were associated with increased likelihood of T1D, which might reflect insufficient maternal/neonatal vitamin D levels during a critical fetal/neonatal programming period. Indeed, vitamin D has been shown to have a role in development and function of the immune system. In fact, inadequate vitamin D and other nutrients during immune system development (from gestation up to the second year of life) may play a critical role in the development of autoimmune diseases. Therefore, it is thought that restoration of vitamin D levels (either by supplementation with vitamin D or by administration of [less hypercalcemic analogues of] the active hormone 1,25(OH)2D) may reduce the risk of T1D. How vitamin D interferes with the pathogenesis of T1D is still not fully elucidated, though some possible mechanisms have been suggested.

Vitamin D as an Immune System Modulator

There is increasing evidence that active vitamin D (1,25(OH)2D) acts as a modulator of the immune system. One of the first indications for this role was the finding of VDR expression in a wide range of immune cells (eg, monocytes, activated lymphocytes). Also, activation of the nuclear VDR is known to modify transcription via several intracellular pathways and influence proliferation and differentiation of immune cells.

Antigen-presenting cells: dendritic cells

Dendritic cells (DCs), which are highly specialized antigen-presenting cells, are known to be important for the priming of CD4+ T cells. DCs act as sentinels in lymphoid and nonlymphoid organs, capturing and processing antigens; once the antigen is captured the DCs will mature, increasing the expression of costimulatory molecules. For activation of T cells, appropriate interaction between the T-cell receptor and antigen/MHC complex as well as costimulatory signals are necessary. However, when there is a disruption in these interactions, T cells become anergic. There is increasing evidence that by hampering the costimulatory capacity of DCs, a shift from
immunogenicity to tolerance can be achieved. 1,25(OH)₂D₃ has dramatic effects on antigen presentation, whereby it reduces antigen presentation by suppressing the expression of MHC-II molecules as well as costimulatory molecules. Many studies have shown the immunosuppressive properties of 1,25(OH)₂D₃ on DCs. For instance, in vitro exposure of the cultured immature DCs to 1,25(OH)₂D₃ can inhibit their maturation, decrease their production of interleukin (IL)-12, and increase the production of IL-10, thus leading to an immune-modulatory DC. 1,25(OH)₂D₃ not only inhibits maturation of DCs but also increases the apoptosis of mature DCs. Furthermore, coculture of 1,25(OH)₂D₃-treated DCs with autoreactive T-cell clones isolated from T1D patients inhibited T-cell proliferation and showed selective apoptosis of the autoreactive T cells. 

Extensive proteomic analysis of DCs treated with TX527, a 14-epivitamin D₃ analogue, showed that DCs are not merely locked in an immature state but adopt a tolerogenic phenotype with special migratory and endocytic properties compared with mature or immature DCs. Furthermore, these 1,25(OH)₂D₃-treated DCs may induce Treg cells and inhibit autoimmune diseases such as T1D. However, most of these studies do not exclude that 1,25(OH)₂D₃ could have a direct action on T-cell modulation as well.

**T lymphocytes**

VDR expression was first described in activated T cells, and early work suggested that vitamin D exerted its immune-modulatory effects on these cells. In the 1980s, several...
studies reported that 1,25(OH)₂D₃ could inhibit proliferation of mitogen-stimulated T-cell cultures.⁵²⁻⁵⁵ In 1987, Rigby and colleagues⁵⁶ described that 1,25(OH)₂D₃ treatment inhibited IL-2 and interferon (IFN)-γ production by human T cells. Others demonstrated inhibition of the aforementioned cytokines as well as IL-12, a known T-cell stimulating factor that is involved in the differentiation of naïve T cells into Th0 cells, which further develop into either Th1 cells or Th2 cells. In addition, an enhancement of Th2-related cytokines (IL-4, IL-5, and IL-10) was observed.⁵⁷,⁵⁸ As already mentioned, 1,25(OH)₂D₃ can also induce Treg cells in vitro and in vivo.⁵¹,⁵⁹,⁶⁰

Until recently, most of these studies were performed on peripheral blood mononuclear cells (PBMC) consisting of lymphocytes and monocytes. As such, direct effects of 1,25(OH)₂D₃ on T cells could not be proven.⁶¹,⁶² Work by Jeffery and colleagues⁶³ on isolated CD4⁺ cells demonstrated that 1,25(OH)₂D₃ can directly modulate T-cell responses. 1,25(OH)₂D₃ inhibited the production of IFN-γ, IL-17, and IL-21 inflammatory cytokines by CD4⁺ T cells, and induced development of Treg cells expressing CTLA-4 and FoxP3. T cells cultured in the presence of both 1,25(OH)₂D₃ and IL-2 expressed the highest levels of CTLA-4 and FoxP3, and possessed the ability to suppress proliferation of resting CD4⁺ T cells. Of interest, a different study showed that exposure of the skin to the topical vitamin D analogue calcipotriol before immunization with ovalbumin (OVA) and CpG DNA as an immune-stimulatory adjuvant induces Treg cells that prevent consequent antigen-specific CD8⁺ T-cell proliferation and IFN-γ production.⁶⁰

**B lymphocytes**

Resting B lymphocytes normally do not express VDR.⁶⁴ On activation, however, VDR expression has been reported.⁶⁴ Administration of 1,25(OH)₂D₃ decreases proliferation and immunoglobulin (Ig) production, and induces apoptosis.⁶⁴ Although 1,25(OH)₂D₃ has potent direct effects on B lymphocytes in vitro, indirect mediation by T cells and monocytes or macrophages has been suggested as its most important mechanism of action.⁶⁴,⁶⁵

**Cytokines**

Active vitamin D has also been reported to down-regulate the production of several cytokines, in particular, inflammatory cytokines such as IL-2, IL-6, IL-12, IFN-γ, tumor necrosis factor (TNF)-α, and TNF-β, while enhancing anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β.⁶⁶,⁶⁷ This finding is of great relevance for the pathogenesis of T1D, as especially IFN-γ and IL-12, which are markers of Th1 immune responses, are known to enhance inflammatory processes and participate in immune-mediated destruction of insulin-producing β cells.⁶⁸ Recently, low-intensity chronic inflammation related to obesity has been linked to insulin resistance, the major cause of T2D. It is suggested that the relationship between vitamin D and low-intensity chronic inflammation and insulin resistance in T2D can be mediated in part by the immune-modulating properties of 1,25(OH)₂D₃.⁶⁹

**Vitamin D and the β cell**

Exposure of pancreatic β cells to proinflammatory cytokines induces endoplasmic reticulum stress, leading to death by apoptosis.⁷⁰ Treatment of β cells with 1,25(OH)₂D₃ has been reported to directly protect against β-cell death by reducing expression of MHC class I molecules,⁷¹ inducing expression of antiapoptotic A20 protein and decreasing expression of Fas.⁷²,⁷³ The latter is a transmembrane cell surface receptor, transducing an apoptotic death signal and contributing to the pathogenesis of several autoimmune diseases including T1D. Of note, in vitro treatment of
pancreatic islets with 1,25(OH)\textsubscript{2}D\textsubscript{3} was also shown to decrease IL-1β and IL-15 cytokine as well as IP-10 chemokine (IFN-γ-inducible protein 10) expression in pancreatic β cells, indicating that 1,25(OH)\textsubscript{2}D\textsubscript{3} treatment could reduce the migration and recruitment of effector T cells and macrophages to the islets.\textsuperscript{74}

**Animal Models**

The immune-modulatory properties of active vitamin D suggest that vitamin D (metabolites or analogues) could be potential therapeutic agents for the prevention or cure of T1D. Treatment of NOD mice, an animal model for T1D, with high doses of 1,25(OH)\textsubscript{2}D\textsubscript{3} (5 μg/kg/2 d) showed a decrease in insulitis and diabetes development.\textsuperscript{75,76} Decreased numbers of effector T cells, as well as induction of Treg cells, was shown to be the basis for this protection.\textsuperscript{59} Later, the authors demonstrated that the arrest of insulitis and block of T-cell infiltration into the pancreas by treatment of prediabetic NOD mice with 1,25(OH)\textsubscript{2}D\textsubscript{3} was associated with reduced chemokine production by islet cells.\textsuperscript{74} Treatment of prediabetic NOD mice with 1,25(OH)\textsubscript{2}D\textsubscript{3} increased deletion of T lymphocytes in the thymus, allowing activation-induced cell death (AICD)-sensitive T lymphocytes to reach the periphery.\textsuperscript{77} Culture of DCs and thymic T lymphocytes from 1,25(OH)\textsubscript{2}D\textsubscript{3}-treated animals separately, however, demonstrated that both cell types needed to be exposed to 1,25(OH)\textsubscript{2}D\textsubscript{3} to obtain the apoptosis-restorative effect. Moreover, transfer experiments demonstrated that T lymphocytes from 1,25(OH)\textsubscript{2}D\textsubscript{3}-treated NOD mice were not able to transfer diabetes into young irradiated NOD mice, in contrast to age-matched untreated mice.\textsuperscript{78} The latter indicates that 1,25(OH)\textsubscript{2}D\textsubscript{3} is able to directly modulate immune cell responses. The authors also found that 1,25(OH)\textsubscript{2}D\textsubscript{3} is a potent inducer of thymic DC differentiation in NOD mice, consisting in modulation toward a more pronounced lymphoid phenotype and up-regulation of CD86.\textsuperscript{77} Moreover, NOD DCs generated from bone marrow in the presence of in vitro 1,25(OH)\textsubscript{2}D\textsubscript{3} exhibit dedifferentiation features of tolerogenic DCs.\textsuperscript{46}

Unfortunately, the doses needed for disease prevention in NOD mice lead to hypercalcemia and bone decalcification.\textsuperscript{37} This issue can be (partially) solved by using structural analogues of 1,25(OH)\textsubscript{2}D\textsubscript{3}.\textsuperscript{37} In fact, administration of vitamin D\textsubscript{3} analogues, specifically selected for their enhanced immune effects and decreased calcemic effects, was shown to delay or even inhibit the development of insulitis and the onset of T1D in NOD mice.\textsuperscript{79} The proposed mechanism of action was a restoration of suppressor-cell functionality.

In the streptozotocin-induced diabetes model, which is an inflammation-driven model of diabetes, 1,25(OH)\textsubscript{2}D\textsubscript{3} also induced a reduction in the incidence of diabetes.\textsuperscript{80} In the case of overt diabetes, 1,25(OH)\textsubscript{2}D\textsubscript{3} has little effect in reverting the disease. It is possible that at this point the number of remaining β-cell mass is simply not sufficient to restore insulin needs.\textsuperscript{81} Therefore, an alternative option to insulin therapy is islet or β-cell transplantation. In that regard, it has been shown that overtly diabetic NOD mice that received syngeneic islets and were treated with KH1060 (a 20-epivitamin D\textsubscript{3} analogue) together with cyclosporine displayed a significant prolongation of islet graft survival compared with untreated controls.\textsuperscript{82} The authors also demonstrated that this analogue in combination with cyclosporine was able to prevent early graft failure and delay graft rejection of xenogeneic islets transplanted in spontaneously diabetic NOD mice.\textsuperscript{83} More recently, a combination therapy using TX527, a 14-epivitamin D\textsubscript{3} analogue, with cyclosporine or IFN-β also induced a significant delay in diabetes recurrence after syngeneic islet transplantation, with an increase of IL-10 expression in islet grafts.\textsuperscript{84} Work by Adorini\textsuperscript{50} in an allogeneic islet transplantation model also confirmed that 1,25(OH)\textsubscript{2}D\textsubscript{3} treatment in combination with
mycophenolate mofetil was able to reduce graft rejection, possibly by inducing tolerogenic DCs and/or Treg cells. Taken together, 1,25(OH)2D3 and its structural analogues display attractive anti-inflammatory properties that open new avenues for the primary, secondary, or tertiary prevention of T1D and other autoimmune diseases.

Nevertheless, despite all the work showing the beneficial effects of vitamin D in T1D prevention, data from VDR knockout mice show conflicting results. Zeitz and colleagues85 showed in their model that mice presented higher concentrations of blood glucose and lower levels of circulating insulin, whereas Mathieu and colleagues83 and Gysemans and colleagues86 did not observe major alterations in glucose tolerance or diabetes incidence in their VDR knockout mouse models. However, these contradictory data could result from the different genetic background of the mice or the control of serum calcium homeostasis, but could also point toward redundancy of vitamin D signaling pathways, and may suggest that compensatory mechanisms are taking place when VDR is completely abrogated from early life onwards.

Clinical Interventions

Large-scale trials evaluating the efficacy of vitamin D in the prevention of T1D are still lacking, but interesting data can be obtained from epidemiologic observations and small-scale trials.

Several retrospective studies found beneficial effects of supplementation with regular vitamin D in early life on the later lifetime risk of T1D. Hypponen and colleagues87 found a significantly reduced risk of T1D development in a birth-cohort study when high doses of vitamin D supplementation (up to 2000 IU/d) were given during infancy. In addition, 2 studies by Stene and colleagues88,89 showed that use of cod liver oil, which is rich in vitamin D, during the first year of life was associated with a lower risk of developing T1D later in life. Finally, the European Community-sponsored Concerted Action on the Epidemiology and Prevention of Diabetes showed a 33% reduction of T1D in children who received vitamin D supplementation early in life.90 A meta-analysis of data from 4 case-control studies and one cohort study revealed lately that the risk of T1D was significantly reduced (29% reduction) in infants who were supplemented with vitamin D as compared with those who were not supplemented (pooled odds ratio 0.71, 95% confidence interval [CI] 0.60–0.84).91 There was also some evidence of a dose-response effect, with those using higher amounts of vitamin D being at lower risk of developing T1D. Some studies were not able to show an association with a reduced T1D risk, but none of them were associated with an increased risk.

Vitamin D supplementation during pregnancy has also yielded contradictory results. In 2000, Stene and colleagues88 documented in a pilot case-control study that cod liver oil, taken by the mother during pregnancy, was associated with a lower risk of T1D in their offspring. In a larger case-control study, Stene and colleagues89 could not confirm their initial results and were unable to find an association between the use of cod liver oil or other vitamin D supplements during pregnancy and T1D risk. Nevertheless, Fronczak and colleagues92 reported lower levels of anti-islet cell auto-antibodies in almost two-thirds of children whose mothers had higher vitamin D intake during the third trimester. Taking into account that T1D susceptibility has been linked to certain HLA genotypes, Wicklow and Taback intend to pursue a trial using 2000 IU of regular vitamin D per day in newborn babies with increased HLA-associated risk. So far they have shown in a few babies that this dose of supplementation seems safe, and did not cause alterations in serum and urine calcium measurements93 (Table 1).
Data on intervention with active vitamin D (1,25(OH)₂D) starting when β-cell damage is already present are disappointing. A small intervention trial in which newly-onset diabetic children were given a small dose (0.25 mg) of 1,25(OH)₂D or nicotinamide showed that although insulin requirements decreased in the group treated with 1,25(OH)₂D, they had no improvement in C-peptide levels. LADA is considered to be a subtype of T1D, in which the clinical manifestation begins and progresses slowly in adulthood. As in T1D, patients with LADA exhibit the presence of autoantibodies to the islets, especially those against glutamic acid decarboxylase.

Li and colleagues described results of a pilot study in which LADA patients were given a synthetic analogue of vitamin D₃, 1α(OH)D₃, in addition to insulin treatment. The patients who received the analogue exhibited a better ability to preserve β-cell function in comparison with patients treated with insulin alone.

### Table 1

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Subjects’ Characteristics</th>
<th>Study Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D supplements (first year of life)</td>
<td>1429 cases; 5026 controls</td>
<td>Risk T1D ↓ (OR = 0.83) age &lt;5 y</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Age &lt;14 y</td>
<td>Risk T1D ↓ (OR = 0.81) age 5–9 y</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Risk T1D ↓ (OR = 0.47) age 10–14 y</td>
<td></td>
</tr>
<tr>
<td>Cod liver oil (pregnancy) (first year of life)</td>
<td>78 cases; 980 controls</td>
<td>Risk of T1D ↓ offspring (OR = 0.63)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
<td>Risk of T1D ↓ cod-liver oil fed-infants (OR = 0.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Offspring &lt;15 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 IU/d (first year of life)</td>
<td>81 cases; 10,285 controls</td>
<td>Insulin and C-peptide ↑ Risk of T1D ↓ (RR = 0.22)</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Age 1–31 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod liver oil (first year of life)</td>
<td>95 cases; 346 controls</td>
<td>Risk of T1D ↓ Supplementation during 7–12 mo (OR = 0.55)</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Age &lt;15 y</td>
<td>Supplementation during 0–6 mo (OR = 0.80)</td>
<td></td>
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<tr>
<td>Vitamin D (food) (pregnancy)</td>
<td>Offspring</td>
<td>Insulin autoantibodies ↓ (OR = 0.49)</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Age &lt;5 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25 μg 1,25(OH)₂D₃ every 2 d or 25 mg nicotinamide/kg/d (1 y)</td>
<td>70 Recently diagnosed T1D Age &gt;5 y</td>
<td>Insulin needs ↓ 1,25(OH)₂D₃-treated group at 3–6 mo</td>
<td>94</td>
</tr>
<tr>
<td>Vitamin D supplements (lactation)</td>
<td>159 cases; 318 controls</td>
<td>Risk of T1D ↓ (OR = 0.33)</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Age 0–29 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 μg 1α(OH)D₃/d (1 y) (1 y)</td>
<td>35 LADA Adults</td>
<td>C-peptide ↑ β-Cell function ↑</td>
<td>96</td>
</tr>
<tr>
<td>2000 IU vitamin D first year of life</td>
<td>7 newborns HLA-associated T1D risk Age &gt;1 y</td>
<td>Serum and urine calcium =</td>
<td>93</td>
</tr>
</tbody>
</table>

In column 1, intervention period is given in parentheses. Abbreviations: OR, odds ratio; RR, relative risk.

Data on intervention with active vitamin D (1,25(OH)₂D) starting when β-cell damage is already present are disappointing. A small intervention trial in which newly-onset diabetic children were given a small dose (0.25 μg) of 1,25(OH)₂D or nicotinamide showed that although insulin requirements decreased in the group treated with 1,25(OH)₂D, they had no improvement in C-peptide levels. LADA is considered to be a subtype of T1D, in which the clinical manifestation begins and progresses slowly in adulthood. As in T1D, patients with LADA exhibit the presence of autoantibodies to the islets, especially those against glutamic acid decarboxylase. Li and colleagues described results of a pilot study in which LADA patients were given a synthetic analogue of vitamin D₃, 1α(OH)D₃, in addition to insulin treatment. The patients who received the analogue exhibited a better ability to preserve β-cell function in comparison with patients treated with insulin alone (see Table 1).

**TYPE 2 DIABETES**

T2D is a disorder that results from defects in both insulin secretion and insulin sensitivity, and accounts for 90% of all diabetes cases. The growing rate of T2D is
Vitamin D and Diabetes

The number one risk factor for T2D is obesity. However, weight loss is difficult to achieve and maintain in a long term. Identification of easily modifiable risk factors is, therefore, urgently needed for primary prevention of T2D. It is interesting that obesity is often related to hypovitaminosis D. Indeed, the absolute fat mass has an inverse relation with the serum 25(OH)D concentration and correlates positively with the serum parathyroid hormone (PTH) level. This relationship may be caused by the great capacity of adipose tissue of storing vitamin D, thus making it biologically unavailable. An increased PTH level and a decreased amount of serum 25(OH)D as well as 1,25(OH)2D3 can increase intracellular calcium in adipocytes, which then stimulates the lipogenesis and predisposes to further weight gain. Therefore, it is presently unclear whether (mild) vitamin D deficiency is contributing to or is the consequence of obesity.

Vitamin D deficiency has been associated with higher risks for metabolic syndrome and T2D. Population studies suggest that vitamin D (and calcium) may play a significant role in promoting β-cell function and insulin sensitivity, important issues in the pathogenesis of T2D. The National Health and Nutrition Examination Survey (NHANES), a large cross-sectional study, showed an inverse correlation between serum 25(OH)D and incidence of T2D and insulin resistance. In a prospective examination of the Medical Research Council Ely Study 1990 to 2000, an inverse relationship between 25(OH)D and glycemic status was found. Supporting these data, a positive correlation between plasma 25(OH)D and insulin sensitivity in healthy subjects subjected to glucose tolerance tests was also reported. On the other hand, prolonged treatment of osteomalacia with vitamin D can increase insulin secretion and improve glucose tolerance.

Vitamin D deficiency in obese patients has been linked to secondary hyperparathyroidism, which can contribute to T2D development, as elevated levels of PTH have been associated to glucose intolerance and cardiovascular complications. Current data suggest that T2D patients with vitamin D insufficiency have increased C-reactive protein, fibrinogen, and hemoglobin A1c compared with healthy controls, indicating that inflammation provoked by immune cells (eg, macrophages) are implicated in insulin resistance and T2D. The authors reported that administration of vitamin D ameliorates markers of systemic inflammation, which are typically found in T2D patients, thereby possibly improving β-cell survival.

Another intriguing observation is that insulin resistance in skeletal muscle has a positive correlation with T2D, for which a possible explanation has recently been proposed. Oh and colleagues observed that up-regulation of caveolin-1 (highly likely to be involved in nongenomic vitamin D signaling) significantly improved...
insulin sensitivity and improved glucose uptake in the skeletal muscle. Therefore, it would be interesting to investigate whether vitamin D supplementation in the nonobese T2D mouse model would improve insulin sensitivity and whether this would be correlated to caveolin-1 expression.

**Vitamin D and Genetic Predisposition to T2D**

T2D is a polygenic disorder, but monogenic disorders closely related to T2D also exist. Monogenic forms of T2D are rare and include subtypes of maturity onset diabetes (MODY). The majority of proteins that are linked to MODY are transcription factors (such as HNF-4α, HNF-1α, IPF-1, HNF-1β, and NEUROD1). On the other hand, causative genes in the more common polygenic forms of T2D are harder to be identified. However, there are several indications that polymorphisms of the DBP and VDR are related to impaired glucose tolerance and obesity. Even though these correlations vary according to age, lifestyle, and ethnicity of the subjects, there seems to be a fair amount of evidence to support this theory.

The DBP protein (also known as group-specific component protein, or GC) located on chromosome 4q12 is a highly polymorphic serum protein, mainly produced in the liver, with 3 common alleles (Gc1F, Gc1S, and Gc2) and more than 120 rare variants. Few studies have examined DBP polymorphisms and the risk of vitamin D-related diseases. In this regard, the DBP protein has been linked to abnormalities in glucose metabolism and obesity-related traits in different populations. Hirai and colleagues evaluated the variations of the DBP gene (Gc1F, Gc1S, and Gc2) in Japanese individuals with normal glucose tolerance. These investigators demonstrated that people with Gc1S/Gc2 and Gc1S/Gc1S had significantly higher fasting plasma concentrations than those with Gc1F/Gc1F. The same group also reported that Japanese T2D patients had higher frequencies of the Gc1S/Gc2 genotype and lower frequencies of the Gc1F allele in comparison with control subjects. Other studies in Caucasian patients of American or European origin could not confirm the relation between genetic variants of the DBP gene and the susceptibility to T2D. It has been suggested that DBP polymorphisms can perhaps influence bioactive 25(OH)D levels through changes in the ratio of free/bound hormones, by a differential affinity, or through effects on concentrations of the DBP/25(OH)D complex that can be internalized by receptor-mediated endocytosis and activate the VDR pathway.

The VDR gene is located on chromosome 12q13.11 and consists of 11 exons. Most VDR polymorphisms are located at the 3’ untranslated region of the VDR gene, such as the Bsml, Apal, and TaqI restriction fragment length polymorphisms. Several observational studies have reported associations between VDR polymorphisms and T2D, fasting glucose, glucose intolerance, insulin sensitivity, insulin secretion, and calcitriol levels. In the Rancho Bernardo study, polymorphism in Apal, Bsml, and TaqI in older Caucasian men was verified. The investigators observed that the frequency of aa genotype of Apal polymorphism was marginally higher in T2D patients. Also, fasting plasma glucose and prevalence of glucose intolerance were significantly higher in nondiabetic persons with aa genotype compared with those with AA genotype. Moreover, the bb genotype of Bsml polymorphism was associated with insulin resistance. Ortlepp and colleagues investigated the association of fasting glucose, low physical activity, and Bsml VDR polymorphism. In this study, males with low physical activity and gene carriers with the genotype BB had significantly higher levels of fasting glucose than gene carriers with the genotype Bb or bb. Of note, this effect was not seen in individuals with high physical activity. A recent study found that the Bsml polymorphism seems to influence body mass index (BMI;
weight in kilograms divided by height in meters squared), whereas the FokI seems to affect insulin sensitivity and serum high-density lipoprotein cholesterol (cHDL) level. It was found that BB carriers tend to have higher BMI and waist circumference compared with the bb genotypes. Similarly, FF and Ff carriers had higher fasting insulin levels than the ff carriers, and lower cHDL levels in comparison with ff genotypes. Ye and colleagues also describe a correlation between BMI/obesity and VDR polymorphism. This study found that T2D patients who were diagnosed at 45 years or younger with T-allele of TaqI and the b-allele of BsmI had higher BMI. More recently, Dilmec and colleagues could not find a correlation between VDR polymorphisms (ie, Apal and TaqI) and T2D risk in a study of 241 individuals (72 patients with T2DM and 169 healthy individuals). Regarding the matter of ethnicity, studies are inconclusive, as associations between VDR polymorphisms and the risk of T2D in different ethnic populations have produced variable results.

The pathophysiological mechanisms of these associations remain unexplained, but there seems to be a relation between the VDR genotype and certain traits of susceptibility to T2D. For instance, VDR polymorphisms are linked to obesity, and vitamin D itself has been reported to participate in adipocyte differentiation and metabolism. Moreover, polymorphisms of VDR might play a role in the pathogenesis of T2D by influencing the secretory capacity of \( \beta \) cells. The VDR genotype was associated with altered fasting glucose, confirming the importance of vitamin D in the modulation of insulin secretion (see next section).

Vitamin D and the \( \beta \) cell

There is strong evidence that vitamin D is important for glucose homeostasis and that this could be mediated by its direct action on \( \beta \)-cell function. Several studies in animals and humans indicate a positive correlation between vitamin D deficiency and glucose intolerance as well as impaired insulin secretion. Further, this deficiency seems to have a specific effect on insulin and not on other islet hormones such as glucagon. For instance, experiments on glucose- and sulfonylurea-stimulated islets obtained from rats kept on a vitamin D–deficient diet showed impaired insulin secretion and glucose tolerance. These defects were partially corrected by vitamin D replenishment. However, whether these defects are directly caused by lack of vitamin D or indirectly by hypocalcemia is not clear.

More convincing data on the beneficial effects of vitamin D on insulin secretion were obtained in experiments demonstrating that synthesis and release of insulin by islets isolated from normal animals could be enhanced by glucose challenge in the presence of high doses of 1,25(OH)\(_2\)D\(_3\). Stimulation of islets by 1,25(OH)\(_2\)D\(_3\) was shown to significantly increase the levels of cytosolic Ca\(^{2+}\), indicating that this could be a mechanism by which 1,25(OH)\(_2\)D\(_3\) is able to stimulate insulin secretion. Ca\(^{2+}\) is known to be important for the exocytosis of insulin from the \( \beta \) cell and for \( \beta \)-cell glycolysis, which participates in translating circulating glucose levels. Moreover, vitamin D could regulate insulin secretion and synthesis by facilitating the conversion of proinsulin to insulin, which is known to be dependent on the cleavage by \( \beta \)-cell calcium-dependent endopeptidases. It is also possible that high intracellular Ca\(^{2+}\) improves the binding of calmodulin to the insulin receptor substrate-1, thereby interfering with insulin-stimulated tyrosine phosphorylation and phosphoinositide-3 kinase activation. In this regard, PTH has been found to be inversely associated with insulin sensitivity. Another possible mechanism that has been suggested is that vitamin D could directly modulate \( \beta \)-cell growth and differentiation.

The effects of 1,25(OH)\(_2\)D\(_3\) and its analogues have been examined regarding binding to nuclear VDR and membrane VDR, through which they induce genomic
and nongenomic responses, respectively. Among these studies, Sergeev and Rhoten\textsuperscript{153} have reported that the administration of 1,25(OH)\textsubscript{2}D\textsubscript{3} evoked oscillations of intracellular Ca\textsuperscript{2+} in a pancreatic β-cell line within a few minutes. Later, Kajikawa and colleagues\textsuperscript{154} demonstrated that the 6-s-cis analogue, 1,25(OH)\textsubscript{2}lumisterol\textsubscript{3}, has a rapid insulinotropic effect, through nongenomic signal transduction via putative membrane VDR, which would be dependent on the augmentation of Ca\textsuperscript{2+} influx through voltage-dependent Ca\textsuperscript{2+} channels on the plasma membrane, being also linked to metabolic signals derived from glucose in pancreatic β cells.

As T2D has been recently associated with systemic inflammation, which is linked primarily to insulin resistance, vitamin D may also improve insulin sensitivity and β-cell function by directly modulating the generation and effects of inflammatory cytokines, as discussed previously.\textsuperscript{155}

**Animal Studies**

Experimental studies in animal models also suggest a role for vitamin D in the pathogenesis of T2D. Animal studies reveal that vitamin D deficiency is associated with impaired insulin sensitivity, while insulin secretion increases through vitamin D supplementation.

Chang-Quan and colleagues\textsuperscript{156} reported that T2D was associated with an abnormal vitamin D metabolism that was characterized by deficiency in 1,25(OH)\textsubscript{2}D and was related to renal injury. In the ob/ob mouse model, treatment with 1α(OH)D improved hyperglycemia, hyperinsulinemia, and fat tissue responsiveness to hormones.\textsuperscript{157} Anderson and Rowling\textsuperscript{158} demonstrated in Zucker Diabetic Fatty rats that vitamin D status was compromised due to poor vitamin D reabsorption in the kidney.

Considering that obesity seems to be an important risk factor to T2D, it was investigated whether vitamin D\textsubscript{3} had a beneficial effect on blood glucose in obese SHR and Wistar rats. Although vitamin D\textsubscript{3} supplementation in SHR rats did not alter the blood glucose levels in all rats, 40% of those rats had a reduction in glucose by 60%. In Wistar rats, a significant reduction in glucose levels in all animals supplemented with vitamin D\textsubscript{3} was found.\textsuperscript{159} In addition, feeding of cod liver oil to streptozotocin-induced diabetic rats partially improved their blood glucose levels as well as their cardiovascular and metabolic abnormalities.\textsuperscript{160} In another study, vitamin D\textsubscript{3} supplementation of spontaneously hypertensive rats normalized the membrane potential and contractility of aorta.\textsuperscript{161}

**Clinical Interventions**

In view of the cellular, preclinical data and observational studies in man, it seems reasonable to consider that vitamin D status influences the incidence of T2D and that vitamin D supplementation could prevent or ameliorate the disease, at least in cases of (mild) vitamin D deficiency. Despite this, trials in patients have yielded conflicting results (Table 2).

Vitamin D\textsubscript{3} supplementation of vitamin D–deficient T2D patients tended to reduce insulin requirements and lower serum triglycerides.\textsuperscript{177} Boucher and colleagues\textsuperscript{167} showed transient improvement of insulin secretion and C-peptide levels in at-risk patients treated with intramuscular vitamin D. In support to these findings, a small study in which a group of T2D women received 1332 IU of vitamin D\textsubscript{3} daily for 1 month showed an improvement on first-phase insulin secretion and a trend toward decreased insulin resistance.\textsuperscript{172} Moreover, the Nurses’ Health Study, which included 1,580,957 women over a period of more than 20 years with no history of diabetes, cardiovascular disease, or cancer at baseline, showed that a combined daily intake of greater than 1200 mg calcium and greater than 800 IU vitamin D was associated
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Subjects’ Characteristics</th>
<th>Study Results</th>
<th>Refs.</th>
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<tbody>
<tr>
<td>2000 IU vitamin D₃/d (2 y), n = 25</td>
<td>Postmenopausal women</td>
<td>Fasting glucose levels = 162</td>
<td></td>
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<tr>
<td>0.25 μg 1α(OH)D₃/d (2 y), n = 23</td>
<td>Age 45–54 y</td>
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<td>&gt;0.25 μg 1,25(OH)₂D₃/d (1 y), n = 40</td>
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<tr>
<td>2 μg 1α(OH)D₃/d (3 wk)</td>
<td>7 cases; 7 controls</td>
<td>Insulin secretion ↑ 163</td>
<td></td>
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<tr>
<td></td>
<td>T2D Japanese patients</td>
<td>Free fatty acid ↓</td>
<td></td>
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<td></td>
<td>Age ~ 54 y</td>
<td></td>
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<tr>
<td>2000 IU vitamin D₃/d (6 mo)</td>
<td>4 cases; 10 controls</td>
<td>Insulin secretion ↑ 164</td>
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<tr>
<td></td>
<td>Vitamin D deficient subjects</td>
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<tr>
<td></td>
<td>Age ~ 32 y</td>
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<tr>
<td>0.75 μg 1α(OH)D₃/d (3 mo)</td>
<td>65 Caucasian vitamin D sufficient men with impaired glucose tolerance</td>
<td>Glucose levels = 165</td>
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<td></td>
<td>Age 61–65 y</td>
<td>Insulin secretion =</td>
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<td></td>
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<td>Body weight ↓</td>
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<td></td>
<td></td>
<td>Urinary calcium ↑</td>
<td></td>
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<tr>
<td>2000 IU vitamin D/d (1 mo)</td>
<td>1 Vitamin D deficient hypocalcemic woman</td>
<td>Glucose tolerance ↑ 166</td>
<td></td>
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<tr>
<td></td>
<td>Age ~ 65 y</td>
<td>β-Cell function ↑</td>
<td></td>
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<tr>
<td>Single IV injection of 100,000 IU vitamin D₃</td>
<td>22 Vitamin D deficient subjects</td>
<td>Insulin and C-peptide ↑ 167</td>
<td></td>
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<tr>
<td></td>
<td>Age ~ 45 y</td>
<td></td>
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<tr>
<td>500 mg Ca²⁺ and/or 0.5 μg 1,25(OH)₂D₃/d (21 d)</td>
<td>17 Uremic men and women</td>
<td>First-phase insulin secretion and insulin sensitivity ↑ 168</td>
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<tr>
<td></td>
<td>Age ~ 50 y</td>
<td></td>
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<tr>
<td>Oral 1 μg 1,25(OH)₂D₃/d (4 d)</td>
<td>20 T2D men and women</td>
<td>Insulin secretion and C-peptide ↑ 169</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ~ 60 y</td>
<td>Urinary calcium ↑ in patients with short duration of diabetes</td>
<td></td>
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<tr>
<td>1.5 μg 1,25(OH)₂D₃/d (7 d)</td>
<td>18 Healthy young men</td>
<td>PTH concentration ↓ 170</td>
<td></td>
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<tr>
<td></td>
<td>Age ~ 26 y</td>
<td>Urinary calcium ↑</td>
<td></td>
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<tr>
<td>Single IM injection 300,000 IU vitamin D₂</td>
<td>3 T2D men and women</td>
<td>Insulin resistance ↑ 171</td>
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<tr>
<td>1332 IU vitamin D₃/d (1 mo)</td>
<td>10 T2D women</td>
<td>First-phase insulin secretion ↑ 172</td>
<td></td>
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<tr>
<td></td>
<td>Age ~ 54 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D and/or calcium supplementation</td>
<td>4843 cases; 1,576,114 controls Female nurses</td>
<td>23% ↓ risk of T2D when vitamin D consumption/d is ≥ 800 IU compared with &lt;200 IU/d 173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ~ 46 y</td>
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<tr>
<td>500 mg calcium and 700 IU vitamin D₃/d (3 y)</td>
<td>314 Nondiabetic Caucasians</td>
<td>Rise glycemia and insulin resistance ↓ in patients with impaired fasting glucose levels 174</td>
<td></td>
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<tr>
<td></td>
<td>Age ~ 71 y</td>
<td></td>
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</tr>
<tr>
<td>1000 mg Calcium and 400 IU vitamin D₃/d (6 y)</td>
<td>2291 cases; 31,660 controls</td>
<td>Insulin or glucose levels = 175</td>
<td></td>
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<tr>
<td></td>
<td>Postmenopausal women</td>
<td>Diabetes incidence =</td>
<td></td>
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<tr>
<td></td>
<td>Age 50–79 y</td>
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<td></td>
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<tr>
<td>3 doses of 120,000 IU vitamin D₃/fortnight (6 wk)</td>
<td>1000 healthy, centrally obese males</td>
<td>Insulin secretion = 176</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≥ 35 y</td>
<td>Insulin sensitivity ↑</td>
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</table>

In column 1, intervention period is given in parentheses.
with a 33% lower risk of T2D compared with an intake of less than 600 mg and 400 IU calcium and vitamin D. In 2008, 2 nested case-control studies, collected by the Finnish Mobile Clinic from 1973 to 1980, were pooled for analysis. These results supported the hypothesis that high vitamin D status provides protection against T2D. Recently, a New Zealand study found that South Asian women with insulin resistance improved markedly after taking vitamin D supplements. Optimal vitamin D concentrations for reducing insulin resistance were shown to be 80 to 119 nmol/L, providing further evidence for an increase in the recommended adequate levels.

On the other hand, some studies show no effect of vitamin D supplementation and improvement of T2D. For instance, the Women’s Health Initiative, in which low-dose calcium and 400 IU/d of vitamin D supplementation were given, did not show protection against diabetes. It was recently reported that daily oral administration of 800 IU (20 μg) vitamin D3 alone or in association with 1000 mg calcium to older people also failed to prevent T2D. In one study, Asian T2D patients with vitamin D deficiency even had a worsening of their condition through increased insulin resistance and deterioration of glycemic control. Another point to note is that, in general, no benefits in glucose tolerance have been seen with vitamin D supplementation in patients who are not vitamin D deficient. Of importance is that some of these studies reported elevation in calcium urinary excretion in vitamin D–supplemented individuals. The contradictory results of vitamin D supplementation in T2D suggest that dose and method of supplementation, as well as the genetic background and baseline vitamin D status of individuals, appear to be important for the efficacy of vitamin D supplementation against development of T2D.

GESTATIONAL DIABETES

GD is defined by β-cell dysfunction and insulin resistance during pregnancy. Women who have had GD have a 20% to 50% chance of developing T2D within 5 to 10 years. Several studies demonstrated that pregnant women are more susceptible to hypovitaminosis D and can suffer from insulin resistance. Studies on the role of vitamin D and the regulation of glucose homeostasis in pregnancy are scarce, and data are not always consistent. Nevertheless, Zhang and colleagues reported that each 5 ng/mL decrease in 25(OH)D levels relates to a 1.29-fold increase in GD risk. In addition, vitamin D depletion during pregnancy, aside from the classically known consequences such as decreased bone density and development of rickets in offspring, has also been associated with nonclassic consequences such as reduced fetal growth, disturbed brain development, and induction of T1D development. A study by Rudnicki and Molsted-Pederson, in which they injected pregnant GD-diagnosed women intravenously with 1,25(OH)2D, showed that these women had a transient decrease in fasting glucose levels but surprisingly also a decrease in insulin levels. These apparent contradictory results suggest that vitamin D could directly increase cellular glucose absorption by increasing insulin sensitivity.

VITAMIN D AND DIABETES COMPLICATIONS

Kidney Failure

Over time, hyperglycemia can have a damaging effect on the kidneys. Zhang and colleagues reported that the prodrug vitamin D analogue, doxercalciferol (1α(OH)D2), may protect kidneys in mice with diabetic nephropathy. This result suggests that vitamin D might be useful and preventative for the kidneys. The NHANES survey found that 25(OH)D levels were significantly lower in persons with severely decreased glomerular filtration rate when compared with healthy individuals.
In addition, persons with higher levels of 25(OH)D had decreased glucose homeostasis model assessment of insulin resistance (HOMA-IR), but 25(OH)D levels did not correlate with β-cell function (also estimated by HOMA). In a cross-sectional analysis of the 2001 to 2006 NHANES study, diabetic patients with nephropathy had a high prevalence of vitamin D deficiency and insufficiency. This finding may be worrisome, as recent work by Wolf and colleagues suggested that vitamin D deficiency in hemodialysis patients was associated with increased mortality risks. Of note, an independent association between vitamin D deficiency and insufficiency with the presence of diabetic nephropathy was seen. Given these findings, the improvement of the vitamin D status or pharmacologic intervention with vitamin D analogues for the prevention or treatment of renal failure needs further study.

Vision Loss and Blindness

Although not a sudden process, subjects with diabetes face a very real threat of vision loss, including blindness (diabetic retinopathy). Diabetes also increases the risk of developing cataracts (clouding of the eyes lenses) and glaucoma (damage to the optic nerves). In T2D patients, severity of retinopathy was inversely correlated with serum 1,25(OH)2D3 levels. Age-related macular degeneration (AMD) occurs when the macula, the area at the back of the retina that produces the sharpest vision, deteriorates over time. AMD is the most common cause of blindness among individuals older than 50 years. Levels of serum vitamin D were inversely associated with early AMD. These data suggest that vitamin D supplementation might have a beneficial effect on eye health.

Hypertension, Heart Attack, and Stroke

As many as 65% of diabetic patients will eventually die of heart failure or stroke. A wealth of recent data suggests a central role of the vitamin D endocrine system on blood pressure regulation and cardiovascular health. For this important topic, recent reviews discussing a potential link between low 25(OH)D levels and cardiovascular disease and the possible mechanisms mediating it have been published. Here it was summarized that severe vitamin D deficiency or resistance caused hypertension in animal models. In addition, mild vitamin D deficiency was associated with higher blood pressure in Caucasians, Hispanics, and African Americans. In recent years, Pilz and colleagues have demonstrated a clear association between low levels of 25(OH)D as well as of 1,25(OH)2D with prevalent myocardial dysfunction, deaths due to heart failure, and sudden cardiac death. In the Multi-Ethnic Study of Atherosclerosis, low 25(OH)D levels were linked to increased risk for developing incident coronary artery calcification. Also, direct effects of vitamin D on the cardiovascular system may be involved. Because various tissues such as cardiomyocytes, vascular smooth muscle cells, and endothelial cells express the VDR and vitamin D affects inflammation as well as cellular proliferation and differentiation, vitamin D may lower the risk of developing cardiovascular disease. A recent meta-analysis of 18 independent randomized controlled trials for vitamin D, including 57,311 participants, described that intake of regular vitamin D supplements (from 300 IU to 2000 IU) was associated with reduced mortality risk (relative risk 0.93; 95% CI, 0.87–0.99). Interventional trials are warranted to elucidate whether vitamin D replenishment is useful for prevention or treatment of cardiovascular diseases and other health outcomes.

Nerve Damage and Dementia

Neuropathy is a common complication in diabetic patients, with a hallmark of sensory neuropathy being the loss of sensation in feet, a risk factor for limb amputation.
Recently, diabetic neuropathy has been linked with low levels of 25(OH)D.\textsuperscript{202} In this study, a total of (only) 51 patients with T2D (all vitamin D insufficient) with typical neuropathic pain were included and given vitamin D\textsubscript{3} treatment (mean dose, approximately 2000 IU). Serum concentrations of 25(OH)D increased from 18 to 30 ng/mL, and the intervention was associated with significant pain reduction. Whether vitamin D can be useful as therapeutic application for neuropathic pain needs to be elucidated in adequately powered prospective clinical studies.

Diabetes also increases the risk of Alzheimer disease and vascular dementia.\textsuperscript{203} There is ample biologic evidence to support a role for vitamin D in neuroprotection and reducing inflammation, and moreover to put forward a role for vitamin D in brain development and function.\textsuperscript{30} Whether vitamin D can reduce the risk of diseases linked to dementia, such as vascular and metabolic diseases like diabetes, needs further investigation.

### Bone Fractures

Large cross-sectional studies have indicated that patients with T2D have significantly increased risk of bone fractures, predominantly hip fractures.\textsuperscript{204} This group of patients frequently displayed loss of vision caused by diabetic eye disease, peripheral neuropathy, arterial hypertension, orthostatic hypotonia, and ischemic disease of the brain, heart, and lower extremities—conditions that predispose to falls. Lately, frequently used drugs in T2D (thiazolidinediones) have been implicated in an increase in bone fractures. Implication of the vitamin D system in this issue is unlikely, but data are scarce. The ADOPT (A Diabetes Outcome Progression Trial) group recently reported slightly reduced vitamin D levels in rosiglitazone-treated patients compared with metformin-treated patients.\textsuperscript{205} Moreover, as vitamin D exerts a direct action on skeletal muscle function,\textsuperscript{206} it was suggested that T2D patients might benefit from eliminating unfavorable diet and environmental factors, such as low physical action and low vitamin D intake. Several meta-analyses of randomized controlled trials showed that vitamin D supplementation (>400 IU/d) reduces the risk of nonvertebral fractures by 20\% and hip fractures by 18\%.\textsuperscript{207,208} These studies also pointed out that vitamin D deficiency is common in patients with hip fractures, and truly contributes to the risk of fracture.

### SUMMARY

There is no doubt that vitamin D deficiency is the cause of several metabolic bone diseases, but vitamin D status is also linked to many major human diseases including immune disorders. Mounting data strengthen the link between vitamin D and diabetes, in particular T1D and T2D. Despite some inconsistencies between studies that associate serum 25(OH)D levels with the risk of developing T1D or T2D, there seems to be an overall trend for an inverse correlation between levels of 25(OH)D and both disorders. There is also compelling evidence that 1,25(OH)\textsubscript{2}D regulates β-cell function by different mechanisms, such as influencing insulin secretion by regulating intracellular levels of Ca\textsuperscript{2+}, increasing β-cell resistance to apoptosis, and perhaps also increasing β-cell replication.

The capacity of vitamin D, more specifically 1,25(OH)\textsubscript{2}D, to modulate immune responses is of particular interest for both the therapy and prevention of diabetes. In the case of T1D, vitamin D supplementation in prediabetic individuals could help prevent or reduce the initiation of autoimmune processes possibly by regulating thymic selection of the T-cell repertoire, decreasing the numbers of autoreactive T cells, and inducing Treg cells. Although immune modulation is generally discussed
for the treatment of T1D, it is also relevant for T2D. Indeed, recent studies have shown that T2D patients have increased systemic inflammation and that this state can induce β-cell dysfunction and death.

Supplementation trials with regular vitamin D for the protection against the development of T1D and T2D have generated some contradictory data, but many weaknesses can be identified in these trials as most were underpowered or open-labeled. However, the overwhelming strength of preclinical data and of the observational studies make vitamin D or its analogues strong candidates for the prevention or treatment of diabetes or its complications. However, proof of causality needs well-designed clinical trials and if positive, adequate dosing, regimen, and compound studies are needed to define the contribution of vitamin D status and therapy in the global diabetes problem. There are many confounding factors that need to be taken into consideration when translating successful vitamin D therapies in animal models into humans, for example, gender, age, lifestyle, and genetic background. To come to solid conclusions on the potential of vitamin D or its analogues in the prevention of or therapy for all forms of diabetes, it is clear that large prospective trials with carefully selected populations and end points will be needed, but should also receive high priority.

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