The role of vitamin D in protecting type 1 diabetes mellitus

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Summary

The relationship between autoimmune diabetes or type 1 diabetes mellitus and vitamin D has been reported in the literature. Many factors, environmental and genetic, have been known, as risk factors, to cause both type 1 diabetes and vitamin D deficiency. Vitamin D treatment has improved or prevented type 1 diabetes mellitus in animals and humans. Vitamin D also has been known to protect from autoimmune diseases in animal models. Therefore, it would be interesting to review the role of vitamin D in type 1 diabetes mellitus. Copyright © 2005 John Wiley & Sons, Ltd.

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Introduction

Vitamin D has been known as a regulator of bone and mineral metabolism by regulation of calcium absorption in the gut and reabsorption by the kidney. In addition, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] is also recognized in the regulating of the immune system. Vitamin D receptor (VDR) is presented in peripheral blood monocytes and activated T cells [1,2]. In the animal models, 1,25(OH)2D3 protects against autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) [3] and collagen-induced arthritis [4]. Recently, Zella and Deluca [5] suggested the effectiveness of vitamin D in diabetes. Therefore, it would be interesting to further review the role of vitamin D in protecting autoimmune diabetes, also known as type 1 diabetes mellitus.

Risk factors for type 1 diabetes mellitus

Many risk factors, environmental and genetic, have been known to contribute in the development of both vitamin D deficiency and type 1 diabetes (Table 1).

Environmental factors

Seasonal and geographical factors have been known, as risk factors, to cause both type 1 diabetes and vitamin D deficiency. There was a suggestion of geographic and seasonal variations for the prevalence of type 1 diabetes. Keen and Ekoe [6] reported that type 1 diabetes is more prevalent in higher latitudes of the tropics and subtropics. In addition, there is a seasonal variation in type 1 diabetes with the largest proportion of cases diagnosed during fall and winter and the lowest during the summer. In 1988, the Diabetes Epidemiology Research International Group [7] studied geographical patterns on risk of type 1 diabetes. This report was compiled from age- and sex-specific cases...
of type 1 diabetes from 1978 to 1980, representing approximately 50 million children younger than 15 years of age from 15 countries of 4 continents. They found that the risk for type 1 diabetes is determined by factor(s) correlated to the average yearly temperature of environment that was strongly associated with latitudes increasing in distance from the equator. Tuomilehto et al. [8] analyzed the age/calendar time/birth cohort effects on the increasing trend of type 1 diabetes between 1965 and 1984. They noted that the increase was mainly related to calendar time and that all age groups were similarly affected. Padaiga et al. [9] examined seasonal patterns of incidence of type 1 diabetes in children aged 0 to 14 years in the countries around the Baltic Sea (Finland, Sweden, Estonia, Latvia, and Lithuania) during 1983 to 1992 (1987–1992 for Finland). They found that the pattern among younger children (0–9 or 5–9 years) had one cycle with a decreased incidence of type 1 diabetes in May and June. Ishii et al. [10] reported a seasonal variation of glycemic control in their diabetic patients. They noted that mean HbA1C levels were elevated by average 0.5% in subgroups with better glycemic control in their diabetic patients. They noted that the increase was mainly related to calendar time and that all age groups were similarly affected.

Table 1. Similar risk factors for contributing in both vitamin D deficiency and type 1 diabetes

| Environmental: | Geographic: Latitudes distance from the equator |
| Foods: Cereal and gluten-containing foods | Genetic: Certain allelic variations in the vitamin D receptor may be of genetic risk for type 1 diabetes |

supplements taken either by the mother during pregnancy or by the child in the first year of life is associated with lower risk of type 1 diabetes in children. They found a lower risk of diabetes in children when mothers took cod liver oil during pregnancy. It was noted that newborn children of mothers who had taken cod liver oil during pregnancy had higher concentrations of 25OHD3 in the cord blood than children of mothers who had taken other vitamin D supplements during pregnancy [29]. However, there was no significant protection from type 1 diabetes risks when infants were fed either cod liver oil or vitamin D supplements. They suggested that exposure in utero could be relevant for the development of type 1 diabetes. In addition, Hypponen et al. [30] assessed the risk of type 1 diabetes and vitamin intake during infancy of 10,821 children in Oulu and Lappland of northern Finland. They reported that dietary vitamin supplementation is also associated with reduced risk of type 1 diabetes.

**Genetic factors**

Certain allelic variations in the VDR may also be of genetic risk for type 1 diabetes. Several reports now indicate that type 1 diabetes may be included among the list of diseases genetically determined, at least in part, by VDR gene polymorphisms. 1,25(OH)2D3 has been shown to inhibit β-cell growth by upregulation of vitamin D receptors, suggesting an alternative mechanism whereby VDR variants might alter insulin responses through early β-cell differentiation [31]. Ortlepp et al. [32] tested the influence of the VDR polymorphism on fasting glucose in healthy young men. They found that the VDR genotype is associated with altered fasting glucose levels in young men with low physical activity. McDermott et al. [33] found evidence of an association of one particular vitamin D receptor allele with type 1 diabetes susceptibility in Indian Asians. These allelic variations in VDR gene that influence genetic susceptibility to type 1 diabetes have also been reported in other ethnic groups: Brazilian [34], Taiwanese [35], German [36], Japanese [37], Bangladeshi Asians [38], Romanian [39], and Dalmatian population of South Croatia [40]. In addition, Taverna et al. [41] demonstrated an association between risk of French type 1 (insulin-dependent) diabetic retinopathy patients and polymorphism of the vitamin D receptor.

Furthermore, Yokota et al. [42] reported an association between vitamin D receptor genotype and age of onset in juvenile Japanese patients with type 1 diabetes. Recently, Motohashi et al. [43] found an association between a VDR gene polymorphism and acute onset of type 1 diabetes, regardless of the presence or absence of islet-associated autoantibody. However, VDR gene polymorphisms in patients with type 1 diabetes do not have an effect on biochemical parameters of bone metabolism [44].

Vitamin D–binding protein (DBP) is essential for vitamin D cellular endocytosis and metabolism [45], thus variants of the DBP protein may affect the amount of active vitamin D on β cells and, subsequently, insulin secretion. It has been found that the locus of the DBP gene was linked to plasma glucose and insulin concentrations in nondiabetic Pima Indians [46]. In a Hispanic-American/Anglo population of the San Luis Valley in Colorado, a variation in DBP is associated with elevated plasma glucose [47]. Genetic variants of the DBP have been reported to be associated with type 1 diabetes [48,49].

Vitamin D 1α-hydroxylase (CYP1αα) is the key enzyme for both systemic and tissue levels of 1,25(OH)2D3 [50,51]. Induction of CYP1α expression was found to be defective in macrophages of diabetic NOD mice [52]. Malecki et al. [53] reported the association of CYP 1α gene and type 2 diabetes in a Polish population.

CYP27B1 (25-hydroxy-vitamin D3-1α-hydroxylase) enzyme catalyzes the 1α-hydroxylation of the 25-hydroxy-vitamin D3 to 1,25(OH)2D3, the most active form of vitamin D3 metabolite. Interestingly, CYP27B1 polymorphisms variants have been reported to associate with type 1 diabetes mellitus in Germans [54].

**Role of vitamin D in diabetes**

Several studies in rats and humans [55,56] have demonstrated that vitamin D deficiency causes reduced insulin secretion, and that 1,25(OH)2D3 improves in β-cell function and consequently in glucose tolerance [57]. In vitamin D–deficient rats, glucose tolerance and insulin secretion were improved with 1,25(OH)2D3 treatment [58]. In gestational diabetes mellitus, Rudnicky and Molsted-Petersen [59] reported that the glucose level decreased from 5.6 to 4.8 mmol/L after intravenous treatment with 1,25(OH)2D3. This vitamin D also corrects glucose intolerance and normalizes insulin sensitivity in uremic patients [60,61].

The NOD mouse has been known as a model of human type 1 diabetes. Similar to the human disease, NOD mouse strain developed hyperglycemia as a result of a T-cell mediated autoimmune reaction against the insulin-producing β cells of the islets of Langerhans in the pancreas. Clinical disease is preceded by insulitis, which is a basic histological lesion in the islet of Langerhans of the pancreas. Islets are invaded mainly by CD4+ and CD8+ T cells and also by monocytes [62]. The onset of insulitis is observed at 20 to 40 days of age. The loss of glycemic control results in polydipsia, polyuria, and excessive weight loss if not treated with exogenous insulin, becoming 100% by 200 days. Mathieu et al. [63] reported that 1,25(OH)2D3 has been shown to reduce type 1 diabetes onset in NOD mice. No mouse (100%) showed insulitis at 21 days of age. 1,25(OH)2D3 has shown partial protection, reduction to 42%, against insulitis by 100 days of age. When 1,25(OH)2D3 treatment (on alternate days) was started at the age of 21 days and terminated at the age of 200 days or on the day of diabetes diagnosis [64], it reduced insulitis incidence from 81% in the control group to 58% in the treated group. Diabetes incidence in female NOD mice at 200 days
was reduced to 8% in the 1,25(OH)2D3-treated group versus 56% in the control group. Both 1,25(OH)2D3 and its nonhypercalcemic analogs, 1α,25(OH)2-20-epi-22-oxa-24,26,27-trishomo-vitamin D (KH1060), have been shown to reduce type 1 diabetes onset in NOD mice [65]. However, Zella and DeLuca [5] found that 1,25(OH)2D3 does not offer complete protection against type 1 diabetes onset in NOD mice when administered every other day. They also showed that all NOD mice are completely resistant to type 1 diabetes by 200 days of age when a daily dose of 50-ng 1,25(OH)2D3 is administered orally through the diet from weaning. They suggested that oral administration of 1,25(OH)2D3 or preferably a nonhypercalcemia analog would be more clinically relevant for the prevention of type 1 diabetes in humans.

Recently, Giulietti et al. [66] reported that vitamin D deficiency in early life might increase type 1 diabetes in NOD mice. They found, at 250 days, that 35% male and 66% female vitamin D–deficient mice were diabetic compared to 15 and 45% of the control mice. In the vitamin D–deficient mice, higher IL-1 expression was detected in islets. Thymus and lymph nodes also contained less CD4CD62L+ cells; a defect in this cytokine profile might trigger the diabetes.

In addition, Casteels et al. [67] reported that nonhypercalcemic analogs of 1,25(OH)2D3 administered to NOD mice when the autoimmune disease is already active can prevent clinical diabetes when this therapy is combined with a short induction course of an immunosuppressant such as Cyclosporin A (CsA).

**Mechanism of vitamin D in type 1 diabetes mellitus**

**At the molecular level**

To clarify the role of vitamin D in the regulation of the endocrine pancreas, some studies [68,69] suggested that vitamin and its metabolites act not only via the plasma calcium levels but also directly on the β cells. 1,25(OH)2D3 may influence both endocrine and exocrine pancreatic function [70]. The effects of 1,25(OH)2D3, a biologically active metabolite of vitamin D, and its analogs have been examined regarding binding to nuclear VDR (nVDR) and membrane VDR (mVDR), through which they might induce genomic and nongenomic responses respectively.

Kajikawa et al. [71] studied the effect of 1,25-dihydroxylumisterol1,25(OH)2lumisterol3 – an analog of 1,25(OH)2D3 that is preferred for its nongenomic action through putative signal transduction by binding to mVDR [72] – on insulin release from rat pancreatic β cells. They found an insulinotropic effect of this vitamin analog with increasing intracellular Ca2+ concentration in pancreatic β cells through nongenomic signal transduction. There is also evidence that 1,25(OH)2D3 directly influences insulin secretion in the β cell through a rise in intracellular-free calcium concentration via the nonselective calcium channel, rather than the calcium-dependent inositol 1,4,5-triphosphate receptor-mediated pathway [73,74]. 1,25(OH)2D3 also exerted a stimulating effect on insulin release via protein kinase A activation, but reduced the supranormal cyclic adenosine monophosphate (AMP) synthesis [75]. 1,25(OH)2D3 may provide supplementary calcium to the β cell by regulating the intracellular signaling processes involving phospholipids metabolism, protein kinase C induction, Ca2+ mobilization, and Ca2+ entry by Ca2+ channels [76] (Figure 1).

Norman et al. [55] reported the presence in the pancreas of a vitamin D–dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D, 1,25-dihydroxyvitamin D3, suggesting an important role of vitamin D in the endocrine functioning of the pancreas. Vitamin D–deficient rats were unable to respond to a glucose challenge by secreting appropriate amounts of insulin [55] since insulin release in vitro is dependent on acute change in plasma calcium [77]. Glucagon secretion is also calcium-dependent [78], but secretion of this hormone was unaffected by 1,25(OH)2D3 treatment [55]. The genomic actions of 1,25(OH)2D3 on β-cells of the endocrine pancreas have been reported. Calbindin-D28K, a calcium-binding protein that is thought to act as a facilitator of calcium diffusion in intestine and kidney [79], is known to be regulated by vitamin D in these tissues. In cells transfected with Calbindin-D28K [80], there was a marked increase in the expression of insulin mRNA. In addition, Calbindin-D28K overexpression was also associated with an increase in insulin content and

**Figure 1. Schematic nongenomic model for 1,25(OH)2D3 effects on insulin secretion in β cells**
Vitamin D₃ and the immune system

The presence of the VDR in peripheral blood monocytes and activated T cells [1,2] has suggested a relationship between vitamin D and the immune system.

There were many reports on the immunological events that might trigger self-destruction of the pancreatic β-cells in type 1 diabetes. Progression of type 1 diabetes has been shown to involve infiltration into pancreatic islet cells by several types of immune cells including antigen-presenting cells (APCs – such as macrophages and dendritic cells), CD4⁺, and CD8⁺ T B cells, and B cells [93] (Figure 3).

Upon antigen stimulation, CD4⁺ cells differentiate into two distinct effectors populations, T helper 1 (Th1) and T helper 2 (Th2) cells. Their functions correlate well with their distinctive cytokines. Th1-type cytokines interleukin 2 (IL-2), interferon γ (IFN-γ), and tumor necrosis factor β (TNF-β), which activate cell-mediated immunity, that is, cytotoxic and inflammatory responses mediated by T cells, natural killer (NK) cells, and macrophages. Th2-type cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, IL-13) activate humoral immunity, that is, antibody production by β-cells [94]. Insulitis lesion is β-cell destructive when

Th1 cytokines produced by islet-infiltrating leukocytes dominate over Th2, and that insulitis is benign when Th2 dominate and downregulate (suppress) Th1 cytokine production, thereby preventing β-cell destruction [94].

1,25(OH)₂D₃ treatment induces an autoantigen-specific ‘protective’ Th2 cell population not only at the site of the β-cell attack but also in the peripheral immune system [95]. This vitamin D also has a direct effect on naïve CD4⁺ T cells to enhance the development of Th2 cells [96] in the absence of APC.

Dendritic cells (DCs) play a central role in regulating immune activation and response to self. DC maturation is central to the outcome of antigen presentation to T cells. Differentiation and maturation of DCs into potent APC are inhibited by physiological levels of 1,25(OH)₂D₃ and its analogs [97,98]. In NOD mice, 1,25(OH)₂D₃ analog treatment prevents DCs maturation, decreases liposaccharide-induced IL-12 and α-interferon production, enhances CD4⁺ CD25⁺ regulatory cells, arrests Th1 infiltration and progression of insulitis, and
suppressor cell activity of 1,25(OH)\textsubscript{2}D\textsubscript{3} and its analogs.

The treatment of adult NOD mice with an analog inhibited diabetes development at nonhypercalcemic dose [25].

1,25(OH)\textsubscript{2}D\textsubscript{3} treatment induced inhibition of peripheral blood mononuclear cells (PBM) proliferation mediated through selective inhibition of IL-2 production [99]. Mathieu et al. [63,64] demonstrated a restoration of suppressor cell activity of 1,25(OH)\textsubscript{2}D\textsubscript{3} and its analogs in vitro and in vivo.

Fujihira et al. [100] suggested that IL-12 may be an important regulator of effector cell development and activation in type 1 diabetes by neutralization of endogenous IL-12 with anti-IL-12 antibody that has been shown to ameliorate both insulin and diabetes in NOD mice. Since 1,25(OH)\textsubscript{2}D\textsubscript{3} has been known to inhibit the production of IFN-\gamma, IL-2, and IL-12 [101], short-term treatment of adult NOD mice with an analog of 1,25(OH)\textsubscript{2}D\textsubscript{3} inhibited IL-12 production, blocked pancreatic infiltration of Th1 cells, and arrested the progression of type 1 diabetes [102]. Therefore, vitamin D may be able to disrupt both the initiation and progression of the Th1-mediated pathogenesis of type 1 diabetes [65].

To investigate whether the restoration of the defective immune regulator system of the NOD mice is the only mechanism in the prevention of diabetes by 1,25(OH)\textsubscript{2}D\textsubscript{3}, Casteels et al. [103] tested if 1,25(OH)\textsubscript{2}D\textsubscript{3} could prevent cyclophosphamide-induced diabetes, since diabetes occurring after cyclophosphamide injection is believed to be because of the elimination of suppressor cell. They found that NOD mice treated with 1,25(OH)\textsubscript{2}D\textsubscript{3} from the time of weaning were clearly protected against diabetes induced by cyclophosphamide. They suggested that the protection against diabetes offered by 1,25(OH)\textsubscript{2}D\textsubscript{3} may be independent of the presence of suppressor cells, and may involve increased apoptosis of Th1 autoimmune effector. In addition, Gysemans et al. [104] reported that vitamin D\textsubscript{3} analogs (TX527) might have a role in preventing autoimmune diabetes recurrence after islet transplantation in spontaneously diabetic NOD mice. Mice treated with a combination of Interferon-\beta (IFN) and CsA showed no delay in autoimmune diabetes recurrence. However, 67% of mice treated with CsA combined with TX527 demonstrated normoglycemic blood levels. Interestingly, INF-\beta in combination with TX527 is effective (100%) in inhibiting autoimmune diabetes recurrence.

**Summary**

The relationship between vitamin D and diabetes has been discussed in the literature. The potential for vitamin D supplement in the type 1 diabetes would be interesting. However, 1,25(OH)\textsubscript{2}D\textsubscript{3} enhances the insulin secretion. It does not participate in generating the new \(\beta\)-cells. Therefore, 1,25(OH)\textsubscript{2}D\textsubscript{3} seems to have a role in the prevention of diabetes in early age and/or improving of diabetes rather than treating the disease. In addition, hypercalcemia is the most serious side effect of vitamin treatment, which may be lethal. Further investigation with nonhypercalcemic analogs of 1,25(OH)\textsubscript{2}D\textsubscript{3} would be needed.

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