DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2005; **21**: 338–346.
Published online 26 April 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.557

REVIEW ARTICLE

The role of vitamin D in protecting type 1 diabetes mellitus

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Received: 3 March 2004
Revised: 15 July 2004
Accepted: 10 March 2005

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.

Keywords vitamin D; diabetes mellitus; 1,25-dihydroxyvitamin D3

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 D_3 [$1,25(OH)_2D_3$] 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, $1,25(OH)_2D_3$ 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 HbA_{1C} levels were elevated by average 0.5% in winter compared to the period between spring and fall. Muntoni *et al*. [11] compared the number of people with type 1 diabetes born in each month of 1974 to 1995 in Finland, where the incidence of type 1 diabetes in children aged <14 years is the highest in the world [7] and there is 2 h of sun every day in December, and Sardinia (an island with very high sunlight exposure). They reported that type 1 diabetes developed at an age younger than 15 years in Finland compared to such children in Sardinia.

Similar seasonal and geographic variations have also been suggested for the prevalence of serum 25-hydroxyvitamin D_3 ($25OHD_3$) levels. McKenna [12] studied vitamin D status between countries in young adults and in the elderly. He found vitamin D status varies with the season in young adults and in the elderly, and is lower during winter in Europe than in both North America and Scandinavia. Webb *et al*. [13] reported the influence of season and latitude on the cutaneous synthesis of vitamin D_3. In Boston, USA (42.2 °N), from November through February, human skin produced no previtamin D_3 when exposed to sunlight on cloudless days. In Edmonton, Canada (52 °N), this ineffective period extends from October through March. Further south (34 °N and 18 °N), sunlight effectively photoconverted dehydrocholesterol to previtamin D_3 in the middle of winter. Fairney *et al*. [14] measured circulating $25OHD_3$ levels of Caucasians in the Antarctic. Following a period of 3 months' complete darkness, there was a significant fall in the vitamin levels. Sunlight exposure and vitamin D status are highest in the summer and lowest during the fall and winter in the northern latitudes [15]. Seasonal variations of 25OHD levels were also reported in Ushuaia (Argentina)(latitude 55 °S), the southernmost city of the world [16]. Recently, Barger-Lux and Heaney [17] confirmed and quantified the relatively large seasonal fluctuations in circulating $25OHD_3$ levels in association with summer sun exposure among outdoor workers. Median serum $25OHD_3$ levels decreased from 122 nmol/L in late summer to 74 nmol/L in late winter.

Recently, there were two articles that investigated dietary exposures in infancy and the risk of developing islet autoantibodies. Norris *et al*. [18] found that the risk of developing islet autoantibodies was significantly higher among children initially exposed to cereal between ages 0 and 3 months or at 7 months than among infants exposed to cereals between ages 4 and 6 months. In the second study, Ziegler *et al*. [19] also reported that introduction of gluten-containing foods before age 3 months was significantly associated with increased risk of developing islet autoantibodies. However, these findings also might suggest a role of vitamin D in their studies. Pileggi *et al*. [20] reported the role of vitamin D in the prevention of rickets in rats on cereal diets. Review of the evidence of the Irish Nutrition Survey [21], concerning a marked rise in the incidence of rickets in Dublin in 1942, concluded that a rise in the extraction rate of the national flour, more phytate and total phosphorus, from 70 to 100% was principally responsible. This rise and, subsequently, decrease in incidence in the extraction rate of flour was reduced. Ford *et al*. [22] suggested a strong and possibly causal relationship between high-extraction cereal and rickets and osteomalacia. Corazza *et al*. [23] reported a change in bone mineral density (BMD), serum calcium, and serum 25-vitamin D_3 levels in gluten-sensitive patients. Gluten-free diet was able to normalize BMD and abnormal blood tests. In addition, the presence of islet cell antibodies has been reported in malnutrition patients [24,25], which is related to rickets. Two of the antigens for islet cell antibodies (ICAs) are glutamic acid decarboxylase (GAD) and a tyrosine phosphatase-like protein termed IA-2. Vitamin D analogs are able to inhibit the spontaneous T-cell response to the intracytoplasmic region of the tyrosine phosphatase-like protein (termed IA-2), an autoantigen associated with type 1 diabetes in both humans and the nonobese diabetic (NOD) mice [26].

The relationship between vitamin D and type 1 diabetes has been known in the past. Baumgartl *et al*. [27] reported that serum $25OHD_3$ levels measured at matched time points throughout the year are lower in patients newly diagnosed with type 1 diabetes than in healthy controls. In 1999, the EURODIAB Substudy 2 Study Group [28] studied the correlation between vitamin D supplements during the first year of life with the development of type 1 diabetes. They reported that vitamin D supplement during the first year of life is associated with a decreased risk of type 1 diabetes. In another study, Stene *et al*. [29] investigated whether cod liver oil or vitamin D

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

- Environmental:
  - Season: Fall & winter
  - 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 $25OHD_3$ 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. $1,25(OH)_2D_3$ 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 (*CYP*1α) is the key enzyme for both systemic and tissue levels of $1,25(OH)_2D_3$ [50,51]. Induction of *CYP*1α 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.

*CYP*27B1 (25-hydroxy-vitamin D_3-1α-hydroxylase) enzyme catalyzes the 1α-hydroxylation of the 25-hydroxy-vitamin D_3 to $1,25(OH)_2D_3$, the most active form of vitamin D_3 metabolite. Interestingly, *CYP*27B1 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 $1,25(OH)_2D_3$ improves in β-cell function and consequently in glucose tolerance [57]. In vitamin D–deficient rats, glucose tolerance and insulin secretion were improved with $1,25(OH)_2D_3$ treatment [58]. In gestational diabetes mellitus, Rudnicki and Molsted-Petersen [59] reported that the glucose level decreased from 5.6 to 4.8 mmol/L after intravenous treatment with $1,25(OH)_2D_3$. 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 $1,25(OH)_2D_3$ has been shown to reduce type 1 diabetes onset in NOD mice. No mouse (100%) showed insulitis at 21 days of age. $1,25(OH)_2D_3$ has shown partial protection, reduction to 42%, against insulitis by 100 days of age. When $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$-treated group versus 56% in the control group. Both $1,25(OH)_2D_3$ and its nonhypercalcemic analogs, $1\alpha,25(OH)_2$-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 $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ is administered orally through the diet from weaning. They suggested that oral administration of $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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. $1,25(OH)_2D_3$ may influence both endocrine and exocrine pancreatic function [70]. The effects of $1,25(OH)_2D_3$, 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-dihydroxyluminesterol$_3$ [$1,25(OH)_2$lumisterol$_3$] – an analog of $1,25(OH)_2D_3$ 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 Ca^{2+} concentration in pancreatic β cells through nongenomic signal transduction. There is also evidence that $1,25(OH)_2D_3$ 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]. $1,25(OH)_2D_3$ also exerted a stimulating effect on insulin release via protein kinase A activation, but reduced the supranormal cyclic adenosine monophosphate (AMP) synthesis [75]. $1,25(OH)_2D_3$ may provide supplementary calcium to the β cell by regulating the intracellular signaling processes involving phospholipids metabolism, protein kinase C induction, Ca^{2+} mobilization, and Ca^{2+} entry by Ca^{2+} 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 D_3, 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 $1,25(OH)_2D_3$ treatment [55]. The genomic actions of $1,25(OH)_2D_3$ on β-cells of the endocrine pancreas have been reported. Calbindin-D_{28K}, 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 D_{28K} [80], there was a marked increase in the expression of insulin mRNA. In addition, Calbindin D_{28K} overexpression was also associated with an increase in insulin content and

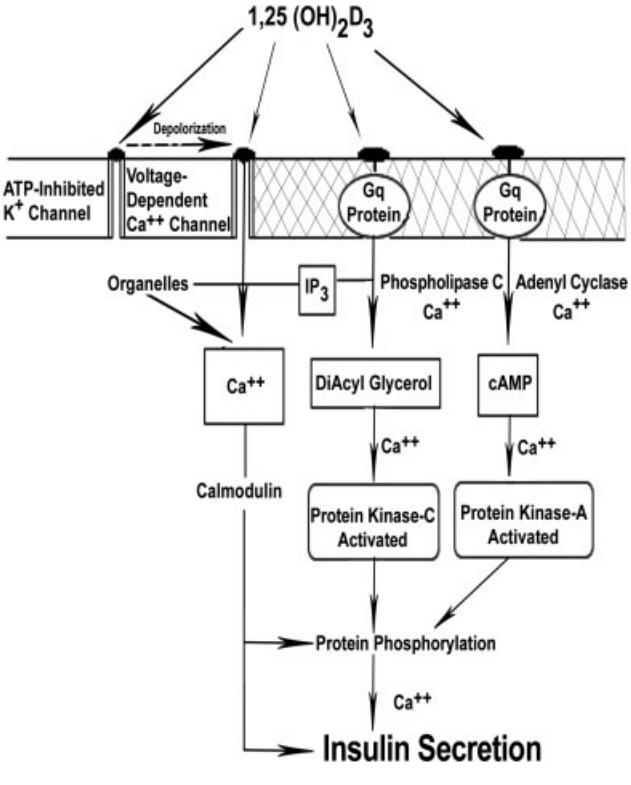

Figure 1. Schematic nongenomic model for $1,25(OH)_2D_3$ effects on insulin secretion in β cells

release. In chicken, pancreatic Calbindin D_{28K} is altered with variations in vitamin D and mineral status [81]. $1,25(OH)_2D_3$ activates the β cell insulin response to glucose *in vivo* after a delay of 3 to 20 h [57,82,83], or after 6-h *in vitro* [84], via an improvement of calcium handling occurring after a 4-h delay [84], increasing both Ca^{2+} entry by voltage-dependent channels and Ca^{2+} mobilization from Ca^{2+} stores [85,86]. Bourbon *et al*. [87] reported that *de novo* synthesis of numerous proteins is decreased during vitamin D_3 deficiency and is gradually restored by $1,25(OH)_2D_3$ repletion in the islets of Langerhans of rats. The existence of variable delays for the actions of $1,25(OH)_2D_3$ supports the hypothesis of a genomic action of the steroid on the biosynthesis of several β cell protein implicated in the different steps of the insulin excitation-secretion coupling. $1,25(OH)_2D_3$ causes transcriptional activation of the human insulin receptor gene in U-937 human promonocytic cells [88]. Treatment with $1,25(OH)_2D_3$ for 24 h increased, in a dose-dependent manner, the levels of the two major insulin receptor mRNA (11 and 8.5 Kb) present in U-937 human promonocytic cells [89], and preproinsulin (ppI) mRNA levels in $1,25(OH)_2D_3$-replete rats increased at 8 and 24 h [90]. However, binding assay also indicated that $1,25(OH)_2D_3$ increased the total insulin receptor number without altering receptor affinity [91].

Recently, Maestro *et al*. [92] reported vitamin D response elements (VDREs) in the insulin receptor (*hIR*) gene promoter that could account for the transcriptional induction of this gene by $1,25(OH)_2D_3$ detected in U-937 cells. This locus could mediate cross talk between vitamin D and insulin-signaling pathways in U-937 cells. (Figure 2)

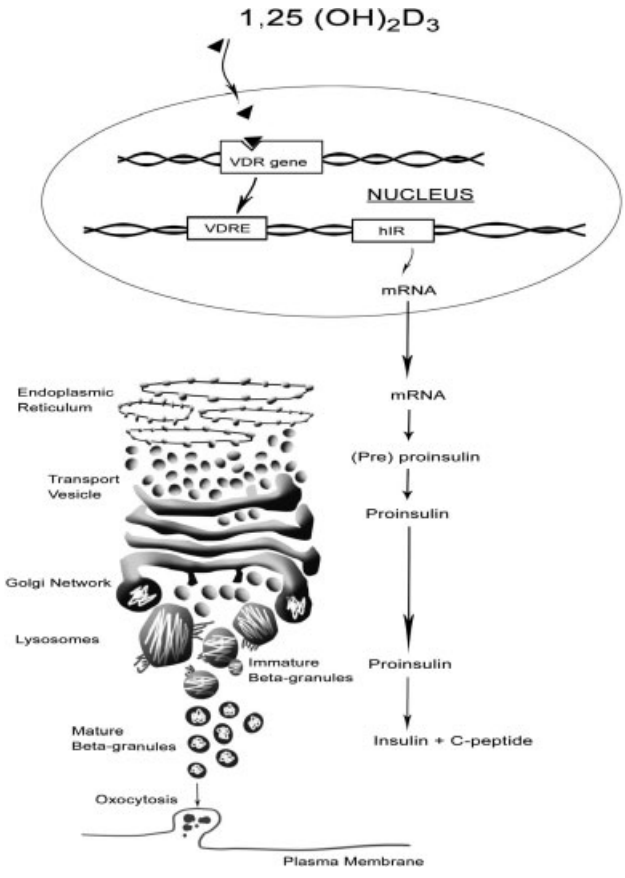

Figure 2. Schematic genomic model for $1,25(OH)_2D_3$ effects on insulin secretion in β cells. The occupied vitamin D receptor (VDR) binds to the transcriptional domain of the insulin receptor (*hIR*) gene promoter, which is composed of a vitamin D response element (VDRE). Transcription induction by the VDR-complex increases the new insulin mRNA and protein. Newly synthesized proinsulin is formed in the rough endoplasmic reticulum (RER), then it is transferred to the Golgi network, where immature β-granules form. Proinsulin is targeted to the β-granule compartment, where it undergoes proteolytic conversion to insulin and C-peptide

Vitamin D_3 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].

$1,25(OH)_2D_3$ 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 naive $CD4^+$ 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 $1,25(OH)_2D_3$ and its analogs [97,98]. In NOD mice, $1,25(OH)_2D_3$ 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

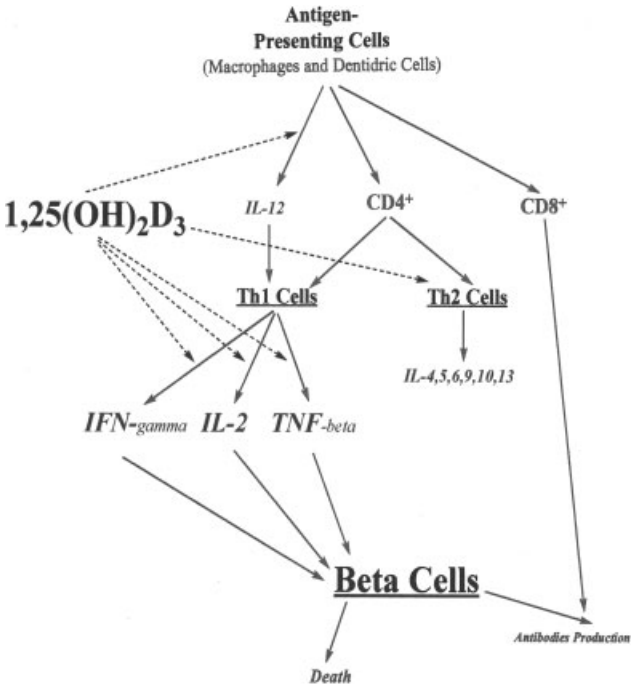

Figure 3. Role of $1,25(OH)_2D_3$ in protecting β cells

inhibits diabetes development at nonhypercalcemic dose [25].

$1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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 insulitis and diabetes in NOD mice. Since $1,25(OH)_2D_3$ has been known to inhibit the production of IFN-γ, IL-2, and IL-12 [101], short-term treatment of adult NOD mice with an analog of $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$, Casteels *et al*. [103] tested if $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ from the time of weaning were clearly protected against diabetes induced by cyclophosphamide. They suggested that the protection against diabetes offered by $1,25(OH)_2D_3$ 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_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-β (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-β 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 interested. However, $1,25(OH)_2D_3$ enhances the insulin secretion. It does not participate in generating the new β-cells. Therefore, $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ would be needed.

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