DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2009; **25**: 417–419.
Published online in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.927

COMMENTARY

Vitamin D in diabetes mellitus – a new field of knowledge poised for D-velopment

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Received: 18 July 2008
Revised: 3 March 2009
Accepted: 9 March 2009

Abstract

This commentary reviews the current state of knowledge regarding the role of vitamin D in the pathogenesis of diabetes mellitus. In type 1 diabetes mellitus or in adult onset latent autoimmune diabetes (LADA), vitamin D exhibits immunomodulatory actions, influencing the activity of lymphocytes and interleukins. In type 2 diabetes mellitus vitamin D appears to act through different mechanisms, affecting insulin secretion and insulin sensitivity through its effects on the β cells, mediators of inflammation and parathyroid hormone. Much work remains to be done in this new field of knowledge before the role of vitamin D in the pathogenesis of diabetes mellitus is completely understood. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords vitamin D; type 1 diabetes mellitus; type 2 diabetes mellitus; adult onset latent autoimmune diabetes (LADA)

Vitamins are essential substances derived from the diet that cannot be synthesized by the human body. Hormones, on the other hand, are naturally occurring substances synthesized in the human body by specialized cells and affecting the function of other cells possessing receptors for the hormone.

Vitamin D is obtained from diet but is also synthesized in the skin. Vitamin D is synthesized in the skin under the effect of ultraviolet radiation. This form of vitamin D is more specifically named vitamin D3 or cholecalciferol. Vitamin D obtained from diet can be of animal (vitamin D3) or of plant (vitamin D2 or ergocalciferol) origin. Both vitamin D2 and vitamin D3 are then converted to the active metabolite 1,25 $(OH)_2$ vitamin D (calcitriol) after a two-step hydroxylation process in the liver and kidney. 1,25$(OH)_2$ vitamin D3 exerts its actions by binding to the vitamin D receptor (VDR), a nuclear receptor that regulates gene transcription in the promoter region of vitamin D target genes.

So, is vitamin D a vitamin or a hormone? The answer is obvious – it is both. Structure of vitamin D and its receptor activity resemble those of steroid hormones. Therefore, vitamin D can be expected to possess some functional characteristics of steroid hormones, including, perhaps, capacity for immunomodulation.

In this issue of *Diabetes/Metabolism Research and Reviews* Li *et al*. [1] report the results of a pilot study in which adult onset latent autoimmune diabetes (LADA) patients were given 1-alpha-hydroxy vitamin D3 in addition to insulin treatment and were then compared to a control group of LADA patients who were treated with insulin alone (1-alpha-hydroxy vitamin D3 is a synthetic vitamin D3 analogue which undergoes hepatic conversion to the active 1,25$[OH]_2$ vitamin D3). The patients who received 1-alpha-hydroxy vitamin D3 exhibited a better ability to preserve the beta-cell function, assessed by C-peptide levels, when compared to the patients treated with insulin alone. The study by Li *et al*. is added to already significant

literature indicating that vitamin D may play a role in modifying the course of type 1 diabetes mellitus. What could be the mechanism of this effect?

There is evidence that autoimmune diabetes presents a continuum of genetic susceptibility, which extends from a strong effect in childhood-onset type 1 diabetes to the relatively limited effect in LADA. These forms of autoimmune diabetes have specific genetic and non-genetic characteristics, environmental influences, diabetes-associated immune responses and metabolic changes. The potential for even better results of immunomodulation in LADA than in type 1 diabetes is based on evidence that the natural history of pre- and post-clinical type 1 diabetes is age-dependent, with the rate of beta-cell destruction inversely related to age. LADA is considered to be a subtype of type 1 diabetes, in which the clinical manifestations begin and progress slowly in adulthood. Like in type 1 diabetes mellitus, patients with LADA exhibit presence of autoantibodies to the islet cells and/or the glutamic acid decarboxylase [2].

There are several theories which attempt to explain the pathogenesis of both LADA and type 1 diabetes mellitus. One of these hypotheses describes the initiation of the pathogenic process by a release of self-reactive T cells in the periphery, positive selection of self-antigen-specific T cells, loss of peripheral tolerance and the loss of regulatory T-cell activation [3]. The progression of the disease involves infiltration of the pancreas with dendritic cells, macrophages, T cells and B cells [4]. A major mechanism appears to involve disruption of the T helper 1 (Th1)/T helper 2 (Th2) balance, with a predominant production of Th1 cells that are destructive to the pancreatic beta cells. After antigenic stimulation, the mature dendritic cells produce interleukin 12 (IL-12), which induces the formation of Th1 cells preferentially over Th2 cells from the T helper precursor cells, Th0. These IL-12-dependent Th1 cells are thought to be the primary initiators of the cell-mediated immune attack.

Although there is no clear understanding how vitamin D may alter this process, recent research has suggested some possible mechanisms. $1,25(OH)_2$ vitamin D3 has been shown to inhibit the production of interferon-gamma (IFN-γ), IL-2 and IL-12 [5], therefore potentially disrupting initiation and progression of the Th1-mediated pathogenesis of autoimmune diabetes. $1,25(OH)_2$ vitamin D3 also inhibits the differentiation and maturation of dendritic cells into potent antigen-presenting cells, so the dendritic cells are no longer capable of stimulating T cells and unable to produce IL-12 [6]. Lack of production of IL-12 could potentially prevent the imbalance of Th1 to Th2 cells. In addition, $1,25(OH)_2$ vitamin D3 and its analogues enhance the presence and function of suppressor T cells, which are known to inhibit T-cell-mediated immunity [7].

Further, it appears that the VDR (which is present in multiple organs and is likely responsible for multiple effects of vitamin D) is related to the risk of development of type 1 diabetes mellitus. The gene encoding the VDR is located on the 12q chromosome and there are four common allelic variations that translate into functional VDR proteins. There are several reports of certain allelic variations in the VDR gene that might carry a genetic risk for insulin-dependent diabetes [8–11]. In addition, several animal studies in non-obese diabetic mice demonstrated that vitamin D and its analogues reduce the incidence of both insulitis and diabetes in these animal models of type 1 diabetes mellitus. [7,12,13].

In humans, epidemiological studies provide evidence that vitamin D supplementation can prevent type 1 diabetes mellitus. Hypponen *et al*. found a significantly reduced risk for type 1 diabetes in a birth-cohort study when high-dose vitamin D supplementation (2000 U daily) was given during infancy. By contrast, the children with suspected rickets during the first year of life had a three-fold increased risk of developing diabetes later in life [14]. Stene *et al*. reported that the use of cod liver oil, rich in Vitamin D, during pregnancy or during the first year of life was associated with a lower incidence of type 1 diabetes [15]. The EURODIAB Substudy 2 Study Group found that vitamin D supplementation during childhood significantly reduced the risks for type 1 diabetes [16].

Some studies, however, were not able to demonstrate a beneficial influence of vitamin D on the beta-cell preservation. Pitocco *et al*. published the results of an interventional study where children with new onset type 1 diabetes were given 0.25 μg calcitriol or nicotinamide in addition to the insulin treatment in order to preserve beta-cell function. They found no significant difference between the treatment group and the control group with respect to the C-peptide levels or HbA_{1c} at 1 year after the diagnosis. The authors noted, however, that insulin requirements decreased significantly in the calcitriol group at 3 and 6 months [17].

Thus, even though there is evidence suggesting the new role for vitamin D in the pathogenesis of type 1 diabetes mellitus, the clinical trials yielded conflicting results so far. More interventional clinical trials in patients with autoimmune diabetes need to be completed before we have a clear understanding of the practical applications of vitamin D in type 1 diabetes mellitus or in LADA.

The role of vitamin D in diabetes may not be limited to the autoimmune forms of diabetes, such as type 1 diabetes or LADA. Type 2 diabetes appears to be influenced by vitamin D as well, although probably through very different mechanisms. Unlike in type 1 diabetes, the association between vitamin D and type 2 diabetes is less clear. Human observational studies report higher rates of metabolic syndrome, its components (hypertension, hypertriglyceridemia, obesity), and type 2 diabetes in patients with hypovitaminosis D. While the mechanism of vitamin D action in type 1 diabetes appears to involve primarily immunomodulatory actions, the role of vitamin D in type 2 diabetes and insulin resistance syndrome involves different mechanisms. One of these mechanisms includes stimulation of insulin secretion and synthesis by vitamin D via its role in regulation of intracellular calcium concentrations [18]. Further, secondary hyperparathyroidism of vitamin D deficiency may contribute to insulin resistance [19]. Finally, vitamin D may

DOI: 10.1002/dmrr

improve insulin sensitivity and promote beta-cell survival via down-regulation of inflammatory mediators that are associated with insulin resistance and beta-cell failure.

Human interventional studies, however, showed either little or no effect of vitamin D supplementation on glycemia or insulin resistance, but definite conclusions are difficult to draw because many of these studies were short in duration, enrolled small numbers of subjects, involved various doses and formulations of vitamin D, and used *post hoc* analyses [20]. In a trial of patients with type 2 diabetes and vitamin D deficiency, there was a trend towards reduced insulin requirements and lower serum triglycerides, which did not reach statistical significance, in subjects who were supplemented with vitamin D3 [21]. Studies showing benefit with vitamin D supplementation involved subjects with relatively new diabetes or patients at risk for diabetes (i.e. glucose intolerance) [20].

In addition, several VDR gene polymorphisms are associated with reduced insulin secretion or elevated glucose [18]. VDRs are expressed in beta cells and muscle [18]. Alterations in the VDR gene may predispose to diabetes by affecting insulin signaling and secretion, calcium metabolism and inhibition of vitamin D action. Thus, there may be coexisting risk for both hypovitaminosis D and diabetes.

It appears, therefore, that the relationship between vitamin D and insulin as well as the role of vitamin D in the pathogenesis of type 2 diabetes are complicated, involving various mechanisms that are not yet fully elucidated. Prospective studies are required to identify individuals with or at risk for type 2 diabetes mellitus that will most benefit from vitamin D supplementation, and the dose and formulation which would be most effective.

In summary, a new field of knowledge dealing with the interaction of vitamin D and two most common forms of diabetes is emerging.

The article of Li *et al*. is a welcome contribution to this emerging new field, but much more work remains to be done.

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DOI: 10.1002/dmrr