

# Baseline serum 25-hydroxy vitamin D in predicting glycemic status and insulin levels

H Michiel J Krans<sup>1,2</sup>

Addresses: <sup>1</sup>Vlietpark 2, 2355CT Hoogmade, The Netherlands; <sup>2</sup>Department of Endocrinology, Leiden University Medical Center (LUMC), Postbus 9600, 2300 RC Leiden, The Netherlands

Email: [hmjkrans@wanadoo.nl](mailto:hmjkrans@wanadoo.nl)

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## Abstract

Vitamin D may have a protective role in insulin secretion and an effect on insulin resistance. Low levels of vitamin D are indicated as a risk factor for both type 1 and type 2 diabetes, however, clinical evidence that increased vitamin D levels benefit diabetic patients has not yet been established.

## Introduction and context

Low levels of vitamin D may be a risk factor for the development of both type 2 [1] and type 1 [2] diabetes. The role of vitamin D in insulin secretion and transfer of the insulin message in insulin sensitive tissues is discussed. Some clinical studies on the relationship between vitamin D levels and development of diabetes are included.

### Vitamin D and calcium

Vitamin D<sub>3</sub>, or cholecalciferol, is formed in the skin by ultraviolet radiation. External supplementation of vitamin D is necessary when low levels of vitamin D are found, such as during periods with little sun, and when the body is totally covered and the intake of vitamin D in the diet is low. The vitamin D<sub>3</sub> generated in the skin is biologically not very active and has to be activated via two enzymatic steps. First, vitamin D<sub>3</sub> is hydroxylated to 25-hydroxycholecalciferol (25(OH)D<sub>3</sub>) in the liver by the enzyme 25-hydroxylase. Next, 1-alpha-hydroxylase, present primarily in the kidneys but also in other tissues, hydroxylates 25(OH)D<sub>3</sub> into 1,25-dihydroxycholecalciferol (1,25-(OH)2D<sub>3</sub>), the hormonally active form [3]. 1,25-(OH)2D<sub>3</sub> and parathyroid hormone regulate calcium homeostasis. Levels of 25(OH)D<sub>3</sub> over 50 nmol/l (in Europe [4]) or 70 nmol/l (in the US) are considered sufficient; levels under 25 nmol/l are clearly deficient.

Vitamin D has two intracellular effects: it binds to the intranuclear vitamin D receptor, which modulates gene expression, and it has an effect through the regulation of extracellular and intracellular calcium [5]. Moreover, vitamin D may also reduce apoptosis of  $\beta$  cells in type 2 diabetes by inhibiting inflammatory reactions [6] and increasing calbindin, a cytosolic calcium binding protein [7].

Calcium is important for many cellular processes and its levels are regulated by parathyroid hormone and vitamin D. Vitamin D increases calcium resorption in the gut and stimulates the uptake of calcium in many tissues, including the islets of Langerhans. Calcium has an essential role in glucose-induced insulin secretion [8,9].

### Insulin secretion from the $\beta$ cell

When glucose enters a  $\beta$  cell, ATP production is increased and the resulting high levels of ATP/ADP lead to closure of the potassium channels in the membrane. This increases the influx of calcium, which stimulates insulin secretion from the  $\beta$  cell. Vitamin D stimulates this glucose-stimulated insulin secretion [10]. The  $\beta$  cell has a vitamin D receptor that binds 1,25-(OH)2D<sub>3</sub>. 1-alpha-hydroxylase is also found inside the  $\beta$  cell [11]. It is not clear whether the effect of vitamin D is a consequence of increased availability of intracellular calcium.

### **Insulin resistance**

Insulin resistance is frequently seen in type 2 diabetes and insulin resistance in diabetes is always combined with cellular changes in the islet cells. An important factor for insulin resistance is obesity, in which fat metabolism is more prominent and higher levels of free fatty acids are seen. Mitochondria are essential for the metabolism of fatty acids and high amounts of fatty acids in the cell reduce the formation of ATP, which decreases insulin secretion in the  $\beta$  cell [12]. When insulin resistance is increased in non-diabetics the  $\beta$  cell produces more insulin to prevent hyperglycemia and no increase in glucose levels is seen. In impaired glucose tolerance the  $\beta$  cell cannot produce sufficient amounts of insulin to keep blood glucose within normal limits. When (genetic) factors favoring diabetes are present, insulin resistance leads to the expression of type 2 diabetes. Insulin resistance is always combined with cellular changes in the islet cells.

An increased extracellular supply of calcium increases the availability of intracellular calcium, which is necessary for insulin-mediated processes in insulin-sensitive cells such as those of fat and muscle [13]. Vitamin D increases the expression of insulin receptors in human-derived cells [14]. Whether vitamin D reduces insulin resistance directly through improvement of the insulin signaling pathway in the cell or whether it primarily stimulates insulin secretion is not clear. The major role of vitamin D in insulin resistance is protection of the insulin secreting capacity of the  $\beta$  cell and suppression of peripheral inflammation.

### **Metabolic syndrome**

Insulin resistance is an important feature of metabolic syndrome and obesity is an important factor for the emergence of type 2 diabetes. Although vitamin D facilitates insulin secretion, a causal relationship between low vitamin D levels and the presence of metabolic syndrome is unclear. Hypertension and vascular disease are associated with metabolic syndrome, and vitamin D deficiency in those with metabolic syndrome may increase the development of cardiovascular disease and increase inflammatory reactions in the  $\beta$  cell and adipose tissue.

### **Diabetes mellitus**

In type 1 diabetes vitamin D may reduce the immunological effect on islet cell destruction and in type 2 diabetes it may improve the cellular transfer of the insulin message. Vitamin D may also contribute to the survival of the islets and inhibit inflammatory processes. Some authors [15] report a relationship between low vitamin D levels in humans and reduced glucose-

stimulated insulin secretion. In some trials improvement of (glucose-stimulated) insulin release after vitamin D supplementation has been found but other studies have not confirmed this [16,17]. Most prospective studies are short term and give variable outcomes about the relationship between vitamin D levels and the development of diabetes (for recent reviews on various aspects of vitamin D and diabetes see [1,18]).

### **Recent advances**

Associations between low vitamin D levels and metabolic syndrome have been reported in British [19], American [20,21], and Chinese patients [22]. However, these associations do not answer the question of whether vitamin D deficiency contributes to the emergence of the metabolic syndrome; long-term prospective studies are necessary to determine a potential role of vitamin D in this syndrome.

Four studies looking at the effects of vitamin D supplementation on glycemic status and insulin resistance have been reported recently. In a 3-year study, Pittas *et al.* [23] found that supplementation of calcium and vitamin D in older people with impaired glucose tolerance reduced the rise of fasting glucose and insulin resistance when compared with non-supplemented patients. A long-term prospective study over 10 years found inverse relations between baseline 25(OH) vitamin D and future hyperglycemia and insulin resistance [24]. However, when serum 25(OH) vitamin D was increased from  $39.9 \pm 1.5$  (standard error of the mean) to  $90.3 \pm 4.3$  nmol/l ( $P < 0.0001$ ) by administration of more vitamin D, no change was observed in mean blood glucose or insulin levels 0-120 minutes after glucose was given, and no change in insulin sensitivity was seen [25]. Half of 33,951 postmenopausal women in the Women's Health Initiative received 400 IE (10  $\mu$ g) vitamin D per day for 7 years. Although this treatment did not reduce the development of diabetes [26], 10  $\mu$ g daily is a low supplementary dose.

As mentioned above, hypertension and vascular disease are associated with metabolic syndrome. In the Framingham Offspring Study, 28% of 1,739 participants with no cardiovascular disease had a 25(OH)D<sub>3</sub> level under 15 ng/ml (39 nmol/l) and after 5.4 years 120 participants developed cardiovascular disease. Those with low 25(OH)D<sub>3</sub> levels were 1.62 times more likely to develop vascular disease and when a low 25(OH)D<sub>3</sub> level was combined with high blood pressure, the chance increased to 2.13; this difference was significant [27].

No direct clinical data are available on the relationship between vitamin D deficiency and the emergence of type

1 diabetes, but the observation that 1,25-(OH)<sub>2</sub>D<sub>3</sub> prevents diabetes mellitus in animal models highlights a potential association. Vitamin D deficiency modifies T cell differentiation and induces cytokine secretion and stimulates dendritic cells, which facilitate the autoimmune destruction of β cells. Therefore, low levels of vitamin D could make people more susceptible to type 1 diabetes [2]. Also, low vitamin D levels during pregnancy may increase the incidence of autoimmune diseases such as type 1 diabetes in children [2].

In type 2 diabetes, insulin resistance plays an important role (see above). In islet cells of persons with type 2 diabetes, signs of inflammation can be seen. Adipose tissue in (obese) persons with type 2 diabetes also displays signs of inflammation, contributing to insulin resistance [28]. Vitamin D inhibits the release and down-regulates increased levels of inflammatory markers such as interleukin (IL)-6, IL-1, and IL-8, intracellular adhesion molecule-1, and cyclo-oxygenase-2 [6]. This may contribute both to the positive effect of vitamin D on islet cells and the reduction of elevated C-protein levels, an indication of (vascular) inflammatory processes in type 2 diabetes.

### Implications for clinical practice

Vitamin D improves insulin secretion and reduces insulin resistance. Low vitamin D levels contribute to the manifestation of diabetes mellitus and a more rapid increase of insulin deficiency. Moreover, increased vitamin D levels may prevent the immunological process that destroys β cells in type 1 diabetes and may reduce the inflammatory processes in the β cell and the periphery and contribute to improved insulin signal transfer in type 2 diabetes.

It is not clear what levels of vitamin D are sufficient. It may be that levels of vitamin D within the normal range for an effect on bone formation and calcium metabolism are too low to reduce the emergence of diabetes mellitus and to improve glucose homeostasis, but a clear minimum level of 25(OH)D<sub>3</sub> needed for slowing the development of diabetes mellitus has not been established. The prescription of extra vitamin D during the early phase of diabetes is still experimental and more long-term clinical studies are necessary to gain better insight into the role of vitamin D and to establish what levels of vitamin D are optimal to reduce the emergence of diabetes. Currently, it has not been established whether it is useful to estimate vitamin D levels or prescribe vitamin D when diabetes mellitus is diagnosed except for investigational purposes. In conclusion, there is not yet sufficient evidence that administration of vitamin D will improve diabetes.

### Abbreviations

1,25-(OH)<sub>2</sub>D<sub>3</sub>, 1,25-dihydroxycholecalciferol; 25(OH)D<sub>3</sub>, 25-hydroxycholecalciferol; IL, interleukin.

### Competing interests

The author declares that he has no competing interests.

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