

## Editorial

## Let the Sunshine In: Therapeutic Prospects of Vitamin D in Diabetology

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### Description

Deficiency of sunshine vitamin 'Vitamin D' and diabetes mellitus are two common conditions encountered during clinical practice and they are widely prevalent across all ages, races, geographical regions and socioeconomic conditions [1]. More than one billion people worldwide are likely to have vitamin D deficiency due to a lack of sunshine exposure. Vitamin D (Calciferol) which comprises a group of fat soluble seco-sterols photosynthesized in the skin of vertebrates by the action of solar ultraviolet B radiation. During sun exposure, the ultraviolet B photons with energies between 290 and 315 nm are absorbed by the cutaneous 7-dehydrocholesterol to form the split sterol previtamin D<sub>3</sub>. Latitude, time of day and season of the year have a dramatic influence on the cutaneous production of vitamin D<sub>3</sub>. An increase in skin melanin pigmentation or the topical application of a sunscreen will absorb solar ultraviolet B photons and thereby significantly reduce the production of vitamin D<sub>3</sub> in the skin. Depending on seasonal variation, it is estimated that 5 to 30 minutes of sun exposure to arms and legs during mid-day is adequate to gain D<sub>3</sub> activity [2]. For those with fat malabsorption, which may decrease vitamin D availability, safe exposure to UVB with adherence to therapeutic protocols has been recommended to treat vitamin D deficiency [3-4]. In nature, very few foods contain vitamin D like some fish liver oils, the flesh of fatty fish, the liver and fat from aquatic mammals such as seals, polar bears and eggs from hens.

Vitamin D comes in many forms, but the two major physiologically relevant ones are vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). Vitamin D<sub>2</sub> is plant derived, produced exogenously by irradiation of ergosterol and enters the circulation through diet. Vitamin D<sub>3</sub> originates from 7-dehydrocholesterol, a precursor of cholesterol, when synthesized in the skin [3]. The biologically active form of Vitamin D is 1,25-dihydroxyvitamin

D (1,25(OH)<sub>2</sub>D). The characteristics of 1,25(OH)<sub>2</sub>D are those of a hormone and consequently vitamin D is a prohormone, rather than a true vitamin.

Vitamin D and its metabolites are transported in the circulation by vitamin D-binding protein and the complex enters the cell together with megalin and cubilin [4]. Vitamin D exerts its actions in a variety of cell types by binding to the nuclear vitamin D receptor (VDR), which shares its structure with many other nuclear steroid hormone receptors, such as the glucocorticoid, thyroid hormone and estrogen receptors. VDRs are present in pancreatic  $\beta$ -cells and vitamin D is essential for normal insulin secretion. Islet cell insulin secretion is reduced in vitamin D-deficient animals and can be corrected by vitamin D supplementation. Therapeutic effect of vitamin D in diabetology maybe due to its anti-inflammatory properties, its effects on calcium and phosphorus metabolism and regulation of the insulin receptor gene. Vitamin D also regulates nuclear PPAR (Peroxisome proliferative activated receptor) that has an important role in the insulin sensitivity [5]. In vivo studies have shown that vitamin D attenuates the expression of proinflammatory cytokines involved in insulin resistance such as interleukins, IL-1, IL-6, TNF- $\alpha$ , also down regulates NF- $\kappa$ B (Nuclear factor) activity [6-7]. There are evidences showing that vitamin D supplementation to offspring during infancy, as well as dietary exposure during pregnancy, was associated with a reduced risk of human type 1 diabetes [8].

Epidemiological studies suggests that an adequate intake of vitamin D may prevent or delay the onset of diabetes and its associated complication such as cardiovascular disease, renal insufficiency and peripheral neuropathies. Various clinical studies have also demonstrated that vitamin D may help with metabolic control, particularly as it relates to  $\beta$ -cell function [7-15]. Evidence suggests that lack of vitamin D may be associated with hyperglycemia, increased glycosylated hemoglobin, insulin resistance, progression of diabetes, as well as hypertension and cardiovascular disease. It appears that diet alone will not provide sufficient amounts of vitamin D and that treatment with supplements is probably necessary for most individuals with

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diabetes. However, given the possible benefit, it may be an easy and cost-effective therapy which could improve their long-term health outcomes as well as their quality of life. Treatment of low vitamin D by sun exposure, diet and oral supplements may be an easy and cost-effective method to improve metabolic control and prevent the serious complications associated with diabetes [14-16].

Numerous studies during last decade have shown a relationship between vitamin D deficiency and diabetes [4-15]. Studies have also shown that vitamin D may play a functional role on glucose tolerance through its effects on insulin secretion and insulin sensitivity. As vitamin D modulates insulin receptor gene expression and insulin secretion, it is an interesting environmental candidate for diabetologists. The challenge for diabetologists is to determine whether vitamin D deficiency actually causes or increases the incidence of diabetes or whether, instead, low levels of vitamin D are simply coincidental given that the majority of the general population, regardless of disease, is likely to have insufficient levels of vitamin D.

As vitamin D can improve diabetes control and it is recommended that vitamin D supplementation should be included in treatment by diabetologist. Studies have shown that vitamin D deficiency should be avoided in pregnancy, not only because of its effects on bone development, but also because it might increase the incidence of autoimmune diseases, such as type 1 diabetes in genetically at-risk individuals.[7] Various studies have demonstrated various mechanism for understanding the therapeutic effect of vitamin D i.e. presence of vitamin D receptors on pancreatic  $\beta$  cells, vitamin D activating  $1\alpha$  hydroxylase is expressed in pancreatic  $\beta$  cells, presence of vitamin D response element in the insulin gene, presence of vitamin D receptor in skeletal muscle and the fact that 1,25(OH)D increases transcription of insulin receptor genes and also suppresses the renin gene reducing hyperglycemic induced increases in renin levels in pancreatic  $\beta$  cells and blockade of renin-angiotensin activity has been proposed as a novel target for diabetes treatment. [9-17] Therefore, a major clinical lesson that can be drawn at this moment is that avoidance of vitamin D deficiency is essential for b-cell function and might contribute to protection against diabetes in later life.

In a nutshell, vitamin D deficiency leads to glucose intolerance and predisposes to type 2 diabetes mellitus, while the restoration of vitamin D levels may reduce the risk of type 1 diabetes mellitus. The information regarding vitamin D receptor activity as well as the genetic variations that may predispose individuals to problems with vitamin D synthesis and utilization will be important areas of clinical research. It would be useful for the researchers and diabetologist to undertake further studies to discover more about the optimum dose, mechanism and the effect of vitamin D on both alpha and islet beta-cell function and insulin resistance. Large long-term clinical trials are needed to clarify these issues and that will have a major impact on public health.

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