



DIABETES MELLITUS AND A NEW-FANGLED ROLE OF VITAMIN D - A REVIEW

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ABSTRACT

The newly discovered role of Vitamin D is now the current area of research as the ubiquitous presence of its receptor VDR and the presence of its activating enzymes like 1 alpha Hydroxylase implies its effect in various other metabolic processes other than bone growth and calcium metabolism. This review articles discusses about the role of Vitamin D deficiency and beneficial effect of its replenishment in Diabetes Mellitus particularly at molecular level affecting gene expression through various pathways. This new fangled role of Vitamin D in Diabetes Mellitus opens a new arena of research and prevention of Diabetes mellitus by its supplementation therapy.

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INTRODUCTION

Rickets was first described by Whistler in 1645 [1] and Glisson in 1650[2]. Later, scientists established that rachitic children were cured after exposure to sunlight [3,4]. The revelation by Goldblatt and Soames [5] showed that irradiation of 7-dehydro cholesterol in the skin could produce vitamin D. Windaus [6], a German chemist, elucidated the structures of vitamins D₂ and D₃.

Most of our vitamin D requirement is met by synthesis from 7-dehydrocholesterol (7 DHC) or provitamin D₃ present in the skin under the effect of sunlight therefore vitamin D in a strict sense is not a true vitamin. UV-B light (290-315 nm) breaks the B ring of 7DHC to form pre vitamin D₃. Previtmin D₃ is unstable and is rapidly isomerized to vitamin D₃ by thermal energy then transported with the help of vitamin D -binding protein to the liver for further metabolism.

7DHC is a precursor in the cholesterol biosynthetic pathway. The enzyme responsible for production of cholesterol from 7DHC is 7-Dehydrocholesterol reductase. Several feedback mechanisms facilitate the prevention of Vitamin D intoxication by excessive exposure to sunlight. Cutaneous vitamin D precursors are photosensitive and get degraded to inactive sterols like lumisterol, tachysterol before entering into the circulation. A maximum of 10% -15% of the provitamin D gets converted to vitamin D. Melanin pigment present in the skin provides an additional protection. Vitamin D requires two successive hydroxylations in the liver

(on C25) and kidney (on C1) using cytochrome P450 enzyme [7] to form its hormonally active metabolite, 1,25-dihydroxyvitamin D. An alternative hydroxylation of 25(OH) D on C24 by the enzyme 24 hydroxylase (CYP24A), mapped on human chromosome 20q13[8] forms, 24,25(OH)₂D ultimately leads to the formation of Calcitroic acid, the major end product of 1,25(OH)₂D.

Vitamin D is predominantly excreted in the bile, but some of its more polar metabolites like Calcitroic acid are excreted via the urine. Dietary vitamin D is transported by the lymphatic system by chylomicrons and stored in several tissues like fat and muscles.

With ageing, cutaneous stores of pro-vitamin D decreases, together with decreased production of vitamin D by UV rays [9].

Mechanism of action

The mode of action of vitamin D can be separated in three phases:

1. Endogenous activation of provitamin D by sequential hydroxylations at C25 and C1
2. The binding of 1,25 (OH)₂ D to a specific and quite ubiquitous nuclear transcription factor vitamin D receptor (VDR), a receptor now known to recruit a large number of proteins;
3. The regulation of expression of a very large number of genes (between 1% and 5% of the human genome) involved in either calcium homeostasis or related to cell proliferation or differentiation.

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The vitamin D receptor Protein

1,25(OH)₂D the active form of vitamin D, exerts its effects by activating the nuclear VDR, a member of the nuclear-receptor superfamily of ligand-activated transcription factors. Different functional domains are eminent in these nuclear-receptor proteins of various members of this family [10].

The human Vitamin D receptor gene (VDR gene), consists of 14 exons and spans more than 60kb on chromosome 12[11, 12]. The major transcript of the VDR gene is a 4.8 kb mRNA encoding a 427 amino acid protein. Binding of 1,25(OH)₂D to VDR leads to a conformational change of VDR followed by heterodimerization with unliganded RXR and binding to vitamin D target genes, with consequent release of corepressors and recruitment of coactivators and general transcription factors. This results in an assembly of an active transcriptional complex [13]. Corepressors bind to the unliganded steroid receptors, recruit histone deacetylases and silence the receptors thereby maintaining chromatin in a transcriptional repressive state [14]. A hexanucleotide direct repeat by three nucleotides (DR3) is the cognate vitamin D response element (VDRE) to which RXR and VDR bind to the 5' and 3' half-site, respectively[15].

Nongenomic actions

Various research groups have documented rapid effects by 1, 25(OH)₂D that are independent of transcription which are attributed to a membrane receptor for 1,25(OH)₂D or by the localization of the nuclear VDR near the membrane[16]. These supposedly nongenomic effects include the opening of calcium or chloride channels and the activation of second messenger signalling pathways (phosphoinositide turnover, activation of protein kinase C, and the Ras/Raf/ERK/MAPK pathway).

Classic target tissues

An intricate interaction between calcium and phosphate, 1,25(OH)₂D and PTH is the result of the effects of 1, 25(OH)₂D on bone, intestine, kidney, and parathyroid glands and its role in mineral metabolism. PTH mobilizes calcium from bone and stimulates the production of 1,25(OH)₂D while 1,25(OH)₂D inhibits the secretion of the parathyroid glands through negative feedback mechanism. 1, 25(OH)₂D also limits its own availability by inhibition of 1 α -hydroxylase and stimulation of 24 hydroxylase thus increasing the catabolism of 1,25(OH)₂D.

Effects on intestine: Owing to the abundance of vitamin D receptor in the duodenum, followed by jejunum and ileum, the efficiency of the small intestine to absorb dietary calcium is increased by 1, 25(OH)₂D. 1,25(OH)₂D increases the production and activity of several proteins in the small intestine like TRPV6 and V5, calbindin-D9K, alkaline phosphatase and low affinity calcium-ATPase. The active transport of Ca²⁺ from the cytoplasm to the extracellular space against concentration gradient is brought about by the plasma membrane calcium pump and a sodium-calcium exchanger. The stimulatory effect of 1,25(OH)₂D on the ATP dependant uptake of Ca²⁺ at the basolateral membrane involves an increase in PMCA gene expression[17].

Effects on kidney: - The kidney more specifically the proximal tubule plays a vital role in activation of Vitamin D through hydroxylation at C1 position by the enzyme 1 α

hydroxylase. Chronic renal failure reduces 1 α hydroxylase activity, which ultimately results in renal osteodystrophy or uremic bone disease. 1, 25(OH)₂D increases the distal tubular reabsorption of calcium mediated by TRP channels (TRPV5), calbindin-D9K and 28K, and the plasma membrane calcium ATPases. Contrary to intestine where active Ca absorption in the duodenum takes place before the less regulated diffusion process in the ileum, filtered Ca in the kidney is reabsorbed first by massive calcium-sodium reabsorption in the proximal convoluted tubule, followed by specific, actively regulated calcium reabsorption in the distal parts of the nephron.

Effects on bone: 1, 25(OH)₂D stimulates osteoclastogenesis as well as alter osteoblast function resulting in a complex interaction and modification of bone mineralization and resorption. From various studies and observations in man and animals, it is evident that vitamin D deficiency or intoxication impairs bone matrix mineralization. Bone mineralization and bone structure can be largely normalised in 1,25(OH)₂D deficient or resistant mice by sufficient supply of minerals like Calcium and Phosphorus which indicates that direct effects of vitamin D metabolites on chondrocytes and bone cells are redundant with a definite supply of minerals. However as most of the genes and proteins classically expressed in osteoblast and osteoclast cells are vitamin D regulated, it is likely that 1,25(OH)₂D fine tunes bone mineral homeostasis.

Nonclassic Actions of Vitamin D

The virtual ubiquitous expression of the VDR in all nucleated cells, the presence of functional 1 α -hydroxylase in various other tissues apart from the kidney, and the very large number of genes that are under direct or indirect control of 1,25(OH)₂D, all indicate toward a more universal role of vitamin D than just regulation of calcium, phosphate and bone metabolism. Documented evidences based on various studies carried on in cells, tissues, transgenic mice and observational studies in humans emphasizes on the finding that the functioning of nearly all major tissues or systems is modulated by vitamin D. Vitamin D is implicated in diverse settings such as glucose metabolism, cardiac diseases, cancers, and immunological regulation [18,19]. Hence, the role of Vitamin D in various diseases apart from bone health is now an active area of research and analysis.

Vitamin D and Diabetes Mellitus

Various studies have documented a suggested relationship between type 1 diabetes mellitus and vitamin D deficiency [20, 21]. Documented evidences shows that type 1 diabetes mellitus has improved and also prevented with Vitamin D supplementation. [22-25]. These effects have been primarily attributed to the immunomodulatory actions of vitamin D [25]. However, not much is known about the association between vitamin D and type 2 diabetes mellitus. Some literatures reveals that deficiency of Vitamin D leads to insulin insufficiency with its replenishment improving the β -cell function and insulin secretion.[26-30] Allelic variations in the vitamin D receptor (VDR) and vitamin D-binding protein (DBP) might influence glucose tolerance and insulin secretion thus contributing to the genetic risk for type 2 diabetes mellitus[31,32].

Type 2 diabetes mellitus is characterized by insulin resistance and altered insulin secretion. Hypovitaminosis D has long been suspected to be a risk factor for glucose intolerance.

Obesity often associated with hypovitaminosis D is a definitive risk factor for type 2 diabetes mellitus. Vitamin D is efficiently deposited in body fat stores where its bioavailability is decreased and as a consequence PTH levels are elevated. [33,34]. There is substantiation that patients with hyperparathyroidism have an diminished glucose tolerance and increased insulin resistance and post parathyroidectomy, there is a rectification of abnormal insulin resistance and glucose intolerance[35,36]. Thus, the relationship between obesity, hypovitaminosis D, altered insulin secretion and type 2 Diabetes may be the outcome of a number of interrelated metabolic effects.

Epidemiological data revealed a low serum vitamin D concentration in a population at risk for type 2 diabetes compared with subjects not at risk. These patients were London Bangladeshi population and showed a higher prevalence of type 2 diabetes mellitus than British Caucasian population, signifying that vitamin D status might contribute to the pathogenesis of the disease [37]. A New Zealand study reported that newly diagnosed patients with type 2 diabetes had lower Vitamin D levels than the control subjects [38]. Vitamin D replenishment study in a group of Bangladeshi Asian population showed improvement in secretion of Insulin and glucose levels, particularly on prolonged use. [26]. Vitamin D treatment in a Bulgarian population of type 2 diabetes female patients with high prevalence of hypovitaminosis D, showed beneficial effects on insulin secretion and action [27]. The Third National Health and Nutrition Examination Survey documented an inverse association between vitamin D status and diabetes in non-Hispanic white and Mexican American people but not in non-Hispanic black people [39]. A prospective study comprising of an English cohort with a total of 524 randomly selected non diabetic men and women, aged 40-69 years were assessed for serum 25(OH)D and IGF-1, had their glycaemic status, lipids, insulin, anthropometry, blood pressure and metabolic syndrome risk (metabolic syndrome z score) derived at baseline and at 10 years of follow-up. The study reported an inverse association between baseline serum 25(OH) D and future glycaemia and insulin resistance [40]. A study done by the authors also demonstrated an inverse relationship between Vitamin D levels and Fasting blood sugar levels in Type 2 Diabetes mellitus patients (41)

Gathered evidences suggest that hypovitaminosis D may be a significant risk factor but not universally i.e it may not be affecting glycaemic status in all populations. This was corroborated by the lack of an inverse correlation between vitamin D status and diabetes in non-Hispanic black people, even though their serum vitamin D level was very low. A possible explanation suggested for the lack of association was the existence of a variable threshold effect among different ethnic groups [39] and decreased sensitivity to vitamin D or related hormones, such as parathyroid hormone (PTH) [42]. Chiu *et al* [43] found that healthy normoglycaemic subjects with hypovitaminosis D had a greater prevalence of developing metabolic syndrome later, than subjects without hypovitaminosis D. They also found a positive correlation between Vitamin D concentration and

insulin sensitivity and an alteration in β -cell function associated with hypovitaminosis D.

Type 2 Diabetes Mellitus and Vitamin D-related Genetic Factors

Vitamin D Receptor Polymorphisms

Vitamin D Receptor or VDR, a member of the steroid/thyroid hormone receptor family is a nuclear/cytosolic receptor and functions as a transcriptional activator of many genes. Vitamin D exerts most of its actions on target tissues through its binding to this receptor. The VDR gene, located on chromosome 12q13.1, is expressed in a large number of tissues, including those involved in the regulation of glucose metabolism, such as muscle and pancreatic β cells [44,45]. The VDR undergoes a conformational change after binding with vitamin D that result in subsequent phosphorylation mediated by kinase cascades, thereby facilitating its binding to the retinoid X receptor. The resultant heterodimer then interacts with vitamin D-responsive elements in the target genes, thereby modifying their expression [46]. Vitamin D also demonstrates an array of effects that probably do not involve gene expression, such as a rise in intracellular calcium and cGMP levels and activation of protein kinase C [47]. The existence of a membrane VDR (mVDR) [16] is now projected to be responsible for these effects of vitamin D [48]. Ironically, pancreatic β cells express both the specific cytosolic/ nuclear VDR and the mVDR.

As vitamin D modulates insulin secretion, it is feasible that allelic variations of the VDR gene may contribute to the development of type 2 diabetes mellitus.

Four common allelic variants/polymorphisms of the VDR gene have been identified: FokI, BsmI, ApaI and TaqI. The role of these VDR polymorphisms has been thoroughly studied in patients with diabetes. Association between the ApaI polymorphism and lower insulin secretion was documented in a study on healthy Bangladeshi Asian population living in London with a high prevalence of vitamin D deficiency [49]. A correlation between ApaI polymorphism and fasting plasma glucose and glucose intolerance was also observed in a community based study of older adults without known diabetes [50]. Ogunkolade *et al* [51] corroborated these data and also showed a positive association between the TaqI and the BsmI polymorphisms with reduced insulin secretory capacity in the same population. Speer *et al* [52] reported that patients with diabetes and obesity with the BB genotype of the BsmI allele in the VDR gene presented higher levels of postprandial serum C-peptide which points to a possible role in the pathogenesis of type 2 diabetes.

A Study also showed that VDR B allele, which predisposes to altered calcium absorption, elevated PTH and type 2 diabetes mellitus, is associated with elevated fasting glucose in healthy young adults long before the onset of type 2 diabetes [31]. It has also been reported that TaqI polymorphism is a major determinant of insulin secretion in subjects with Vitamin D deficiency [53]. The FokI polymorphism in contrast to other VDR polymorphisms is located within the 5' end of the gene near the promoter region. The FokI polymorphism not only affects the translation product but also influences VDR interaction with the basal transcription factor IIB (TFIIB), a transcription factor that interacts with the VDR and modulates its

transcriptional activity [53]. The C-terminal hormone-binding domain of the VDR contains a consensus region for association with TFIIB [54].

The F variant of FokI polymorphism was reported to be more active than the f allele [44]. Subjects with the homozygous FF genotype showed increased insulin sensitivity compared to those with the f allele in an apparently healthy Caucasian population having a good glucose tolerance [54]. These data provide evidence for VDR as a candidate gene contributing to the susceptibility to type 2 diabetes mellitus.

Vitamin D-Binding Protein

The DBP/Calbindin-D28K functions as a specific transporter of circulating vitamin D metabolites [55] and is essential for vitamin D transport and functions. DBP, a highly polymorphic single-chain serum glycoprotein synthesized and secreted by the liver forms a complex with vitamin D and delivers the circulating vitamin D to target tissues [32]. Serum DBP concentration usually correspond to total concentration of vitamin D. Genetic variants of DBP have been known to be associated with diabetes and prediabetic traits in several populations. Two missense polymorphisms have been identified in sequence analysis of the Gc exons resulting in three electrophoretic variants of DBP: Gc1 fast (Gc1f), Gc1 slow (Gc1s) and Gc2. These DBP variants have been suggested to influence the availability of active vitamin D in β cells and subsequently affecting insulin secretion [56]. Study shows an association between the Gc1 allele of DBP with type 2 diabetes in Japanese subjects [57] In yet another study on non-diabetic Dogrib Indians from Canada, the lowest levels of fasting insulin was seen in Gc 1f-1f homozygous subjects [58].

Vitamin D and β -cell Function

The presence of the VDR in β cells and the vitamin D-dependent calcium-binding proteins (DBP) in pancreatic tissue gives clear evidences about the role of vitamin D in insulin secretion [59]. Both *in vitro* and *in vivo* studies reveal that vitamin D is vital for normal insulin release in response to glucose. In vitamin D-deficient rats, glucose intolerance was found to be associated with diminished response to exogenous insulin resulting in reduced insulin sensitivity. [28,29]. Moreover, vitamin D deficiency results in decreased pancreatic insulin secretion and repletion of vitamin D in the early stages of experimental dietary vitamin D deficiency leads to a partial improvement in glucose tolerance and correction of insulin secretion in response to glucose [60]. In streptozotocin-induced diabetic rats, plasma calcium levels, DBP, circulating vitamin D and bone mass are reduced These defects have been attributed to altered vitamin D metabolism owing to an inhibitory effect of insulin deficiency on the activity of the renal 25(OH) D31 α -hydroxylase [61].

Vitamin D can have an effect on the secretion of Insulin through multiple pathways. It can be through a rise in intracellular calcium concentration using a non-selective voltage-dependent calcium channel [62, 63]. This lays emphasis on a major mechanism of action of vitamin D on insulin secretion and synthesis involving the β -cell calcium dependent endopeptidases, which facilitates the conversion of proinsulin to insulin. Calcium is also necessary for insulin release and β -cell glycolysis that plays a significant role in representing the circulating glucose concentration.

Documented literatures show that vitamin D has a direct stimulatory effect on the growth of β cells of the pancreas resulting in the spur of insulin secretion seen during vitamin D replenishment [64].

Evidences and mechanisms to support a benefit for vitamin D and calcium in type 2 DM

Improvement in pancreatic β cell function

Direct effect of vitamin D on insulin secretion

Evidences in support are as follows:

- Presence of specific vitamin D receptor in pancreatic β cells [59]
- Expression of 1 α -hydroxylase enzyme in pancreatic β cells [65]
- Impaired insulin secretory response in mice lacking functional vitamin D receptors [66]
- Presence of the vitamin D response element in the human insulin gene promoter [67]
- Transcriptional activation of the human insulin gene by 1,25-OHD [68]
- Vitamin D deficiency impairs glucose-mediated insulin secretion from rat pancreatic β cells *in vitro* [30,69,70] and *in vivo* [71]
- Supplementation with vitamin D restores insulin secretion in animals [30,72]

Indirect effect of vitamin D on insulin secretion

- Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes and adequate [Ca²⁺] pool
- Regulation of calcium flux and [Ca²⁺] in the pancreatic β cell via regulation of calbindin, a cytosolic calcium-binding protein [62]

Calcium effect on insulin secretion

Evidences in support are as follows

- Alterations in calcium flux can have adverse effects on insulin secretion, a calcium-dependent process [73]
- Calcium repletion alone normalized glucose tolerance and insulin secretion in vitamin D-depleted rats [74]
- In diabetes patients, an oral calcium load augments glucose-induced insulin secretion [75]
- Patients with resistance to 1,25-OHD were found to have abnormal insulin secretion only if they were hypocalcemic [76]

Improvement on insulin action

Evidences in support are as follows:

- Presence of vitamin D receptor in skeletal muscle [77]
- Vitamin D stimulates the expression of insulin receptor and enhances insulin responsiveness for glucose transport *in vitro* [78]
- Vitamin D directly activates peroxisome proliferator activator receptor, a transcription factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue [79]

Calcium effect on insulin action

Evidences in support are as follows:

- Calcium is essential for insulin-mediated intracellular processes in insulin responsive tissues such as skeletal muscle and adipose tissue with a very narrow range of [Ca²⁺] needed for optimal insulin-mediated functions [80-82]
- Changes in [Ca²⁺] in primary insulin target tissues contributes to alterations in insulin action [83-86]
- Impairment of insulin receptor phosphorylation, a calcium-dependent process leading to impaired insulin signal transduction and decreased GLUT 4 activity [87]
- Changes in [Ca²⁺] modulate adipocyte metabolism, which may promote triglyceride accumulation via increased *de novo* lipogenesis and inability to suppress insulin-mediated lipolysis leading to fat accumulation [88]
- Patients with type 2 DM exhibit impaired cellular calcium homeostasis including defects in skeletal muscle, adipocytes, and liver [89]

Improvement in systemic inflammation

Effects of vitamin D on cytokines

Evidences in support are as follows:

- Vitamin D interacts with vitamin D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation and action [90]
- Vitamin D can down-regulate activation of nuclear factor- κ B which is an important regulator of genes encoding pro inflammatory cytokines implicated in insulin resistance [91,92]
- Vitamin D interferes with cytokine generation by up-regulating expression of calbindin a cytosolic calcium-binding protein found in many tissues including pancreatic β cells. Calbindin has been shown to protect against cytokine-induced apoptosis that may occur after a rise in cytosolic free calcium [Ca²⁺] [93].

CONCLUSION

From the facts that has evolved recently from various *in vitro*, *in vivo* and interventional studies it is now proved beyond doubt that Vitamin D has multiple actions and effects on various tissues extending beyond its well accepted and emphasized role on bone growth and calcium metabolism. Many studies also highlighted the beneficial effects of Vitamin D on diseases like epilepsy, infertility, cardio vascular diseases and cancer. Vitamin D acts through its receptors and the VDR seem to be a molecule expressed in a ubiquitous manner in various tissues and organs. Hence, more in depth studies on the detrimental and beneficial effects of its deficiency and replenishment can unearth new preventive methods of many diseases.

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