



The relationship between vitamin D deficiency and diabetes Type 1,2: a review

Hawraa Aqel Abdulmonem and Hanaa Ali Aziz

College of Science, Al-Muthanna University, Iraq

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(✉) Corresponding Author: hanabio-1983@mu.edu.iq

Abstract

Types 1 and 2 diabetes are predisposed to people with vitamin D deficiency, and immune cells and beta cells were found to include receptors for vitamin D's activated form, 1,25-dihydroxyvitamin D₃. Type II diabetes was linked to vitamin D deficiency, which was proven to affect insulin synthesis and secretion in people and diabetes-prone animals. In addition, epidemiological research suggests a connection of the deficiency of vitamin D in adolescence with type I diabetes onset later in life. Various polymorphisms in vitamin D receptor genes have been linked to type I diabetes in certain groups. Pharmacological dosages of 1,25-dihydroxyvitamin D₃, or its structural counterparts were proven in tests on nonobese diabetic mice to postpone the onset of diabetes, mostly by modulating the immune system. Thus, vitamin D deficiency could have an influence upon etiology of both types of diabetes, and a deeper comprehension of the underlying mechanisms might help create preventative measures.

Keywords: 1,25(OH)₂D₃, Vitamin D deficiency, Beta cell, Diabetes Type 1,2

Introduction

Our role of physiological role regarding such molecules was expanded as a result of the discovery of receptors for 1,25(OH)₂D₃, activated vitamin D form, in the tissues other than the ones that are directly involved in the calcium and bones' metabolism, such as immune system cells and pancreatic beta cells (Holick, 2003, Haussler et al., 1998). Vitamin D deficiency has been associated with an increase in the risks of diabetes of type II (Boucher et al., 1995, Chiu et al., 2004), and beta cells from animals with vitamin D-deficiency have been found to have impaired insulin production and secretion. In a case where levels of vitamin D are back to normal, glucose tolerance is re-established. In investigations using animal models of type I diabetes, the discovery of 1,25(OH)₂D₃ receptors in immune system cells resulted in the discovery that high dosages of 1,25(OH)₂D₃ can prevent type I diabetes, mostly via regulating the immune system. 1,25(OH)₂D₃ was shown to be one of the most effective inhibitors of dendritic cell development and to directly inhibit IL12 secretion (Mathieu et al., 1994; D'Ambrosio et al., 1998). The

formation of regulatory cells is boosted while lymphocyte proliferation is suppressed (Van Halteren et al., 2002). In addition to discussing potential uses for the molecule or the synthetic analogs (Bouillon et al., 2003; Bouillon et al., 1995) in clinical illness, this review gives a summary of the information that is currently known on vitamin D role in types 1 and 2 diabetes. It is difficult to understand and analyze data because of the ambiguous terminology utilized in various articles to discuss vitamin D as well as vitamin D metabolites. The word "vitamin D" in this review indicates products found in the foods (vitamin D₃ and vitamin D₂) and produced by the skin under the UVB light effect (vitamin D₃), while "1,25(OH)₂D₃" indicates metabolically active molecules. Numerous studies (Luong et al., 2005; Mathieu et al., 2005) have discussed a potential relation between T1DM and vitamin D deficiency. In humans (EURODIAB, 1999; Stene et al., 2000) as well as animal models (Mathieu et al., 1992, Gregori et al., 2002), the administration of vitamin D was found to ameliorate and even prevent T1DM. These outcomes have mostly been linked to vitamin D's immunomodulating properties (Mathieu et al., 2005). The link between

T2DM and vitamin D is less well understood. In both rats and humans, a deficiency of vitamin D leads to a decrease of secretion of insulin, and vitamin D supplementation enhances b-cell function and glucose tolerance (Norman et al., 1980, Boucher et al., 1995). Additionally, some allelic variants in vitamin D-binding protein (DBP) and vitamin D receptor (VDR) could impact insulin secretion and glucose tolerance (Iyengar et al., 1980, Pratley et al., 1998), adding to hereditary risk for type II diabetes. Vitamin D has been considered as an intriguing environmental candidate for the secretion and pathogenesis of T2DM because it regulates insulin secretion and insulin receptor gene expression (Ortlepp et al., 2003). This notion is already supported by circumstantial evidence. Impact of vitamin D as hereditary and environmental component in the T2DM will be the subject of this study. It will pay particular attention to its hypothesized protective role and potential mechanisms by which that protection could take place.

Metabolism and Biological Functions of Vitamin D

Vitamin D promotes calcium reabsorption through the kidney and increases gut uptake of the ingested phosphorus and calcium, which elevates those two mineral components in the plasma (Deluca and Cantorna, 2001). Which is why, major biological effects regarding such vitamin include regulation of bone remodeling and maintenance of mineral homeostasis (Ogunkolade et al., 2002; Zittermann, 2003). Since some foods naturally contain vitamin D, just a small percentage (30%) could be gained from diet. The photochemical conversion of 7-dehydrocholesterol caused by sunshine therefore meets all vitamin D requirements (Holick, 2004; Zella and DeLuca, 2003; Fig.1). Since industrialization decreased our exposure to the sun-light, the reliance on vitamin D food sources had increased. In order to produce 1,25(OH)₂D₃, the physiologically active vitamin D form, it's necessary to hydroxylate vitamin D twice (Deluca and Cantorna, 2001; Fig. 1). While 2nd hydroxylation phase occurs outside of the liver, the first hydroxylation process creates 5(OH)D₃. Which primarily happens in kidney and produces the final active metabolite (Deluca and Cantorna, 2001). The 25-hydroxylase in the liver and the 1 α -hydroxylase in the kidney, which are all members of cytochrome P-450-dependent steroid hydroxylases, are responsible for such processes (Haussler et al., 1998). Since 1,25(OH)₂D₃ clears more slowly compared to the serum 25(OH)D₃, the level of this serum is a superior predictor of the status of vitamin D (Zittermann, 2003). Additionally, secondary hyperparathyroidism might lead to elevated levels of serum 1,25(OH)₂D₃, making it as an unreliable indicator in those circumstances (Zittermann, 2003). "Vitamin D" must hereafter include only the active vitamin D form, 1,25(OH)₂D₃, and shall not include any other forms. During development, vitamin D deficiency could result in the bone-deforming disease rickets; in grown-ups, it can lead to osteomalacia and altered metabolism of the muscle due to a problem with the calcium balance (Holick, 2004). Patients who have type 2 diabetes could have problems in vitamin D and mineral

metabolism which might eventually result in osteopenia, and such effects were seen in these patients (van Daele et al., 1995; Inaba et al., 1999). Yet, the topic of vitamin D and bone damage in T2DM will not be covered in this review. The stomach, heart, brain, liver, pancreatic islets (i.e. beta cells), skin, thyroid, adrenal and parathyroid glands, as well as immune cells, have all been mentioned as additional vitamin D targets (Bikle, 1992). Surprisingly, a few of such cell and tissue types, such as the activated lymphocytes (B and T cells), brain, skin, and macrophages, possess both nuclear VDR and enzymes that are necessary for its synthesis, pointing to potential non-classical activities (Holick, 2002, Chiu et al., 2004).

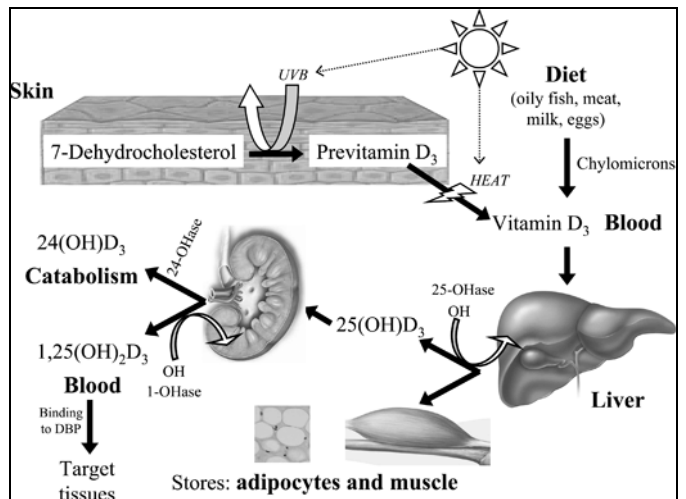


Fig. 1

Photo-chemical conversion regarding 7-dehydrocholesterol to pre-vitamin D₃ caused by sunshine or through direct dietary consumption are both ways to get vitamin D₃. Pre-vitamin D₃ goes through thermally induced conversion into Vitamin D₃ while being thermodynamically unstable. The biologically active vitamin D₃ form requires two hydroxylations, twice the source. Therefore, vitamin D₂₅-hydroxylase (25-OHase) catalyzes the initial hydroxylation process that creates 25(OH)D₃ in the liver. 25-hydroxy-vitamin D₃ 1 α -hydroxylase (1-OHase) mediates the 2nd step of the hydroxylation that results in the final active metabolite of the vitamin D₃ (1,25(OH)₂D₃). This phase primarily takes place in the kidneys (Boucher et al., 1995). After that, 1,25(OH)₂D₃ is released in circulation, where it attaches to DBP (i.e. vitamin D-binding protein), to the point where it travels through the VDR to the intended target tissue. The enzyme responsible for catalyzing the hormone's catabolism in the kidney is vitamin D 24-hydroxylase (24-OHase). In development, vitamin D deficiency may lead to bone-deforming illness rickets; in adults, it can lead to osteomalacia and altered metabolism of the muscles due to a problem with the calcium balance. Individuals with type 2 diabetes might have problems in vitamin D and mineral metabolism which could eventually result in osteopenia, and such effects have also been seen in these patients (Deluca and Cantorna, 2001). Yet, the topic of vitamin D and bone damage in

T2DM will not be covered in this study. The stomach, heart, brain, liver, pancreatic islets (i.e cells), skin, thyroid, adrenal and parathyroid glands, as well as the immune cells, have all been mentioned as additional vitamin D targets (Ogunkolade et al., 2002). A few of such cell types and tissues, such as the brain, activated lymphocytes (B & T cells), skin, and macrophages, possess both nuclear VDR and enzymes which are necessary for its syntheses, pointing to potential non-classical activities (Zittermann, 2003).

β-cell and Vitamin D Functions

Numerous pieces of evidence, such as the existence of VDR in the β-cells and the DBP in pancreatic tissue, point to role of vitamin D in the secretion of the insulin (Morrissey et al., 1975, Johnson et al., 1994). Vitamin D was necessary for adequate release of insulin in a response to the glucose and for glucose tolerance maintenance in both in vivo and in vitro models. For example, insulin sensitivity is changed in rats with diet-induced deficiency of vitamin D due to impaired glucose tolerance and hyporesponsiveness to the exogenous insulin (Inomata et al., 1986; Ismail and Namala, 2000). Additionally, a deficiency of vitamin D reduces the pancreatic insulin secretion while leaving the glucagon secretion unaffected (Kadowaki and Norman, 1984; Gedik and Akalin, 1986). It's significant to note that vitamin D repletion enhances glucose tolerance and corrects the secretion of the insulin in a response to the glucose in animals who have vitamin D deficiency (Boucher, 1998) or in early phases of experimental dietary deficiency of vitamin D (Chertov et al., 1983). Levels of plasma calcium, circulating vitamin D, DBP, and the value of the bone mass are all decreased in streptozotocin-induced diabetic rats (Shires et al., 1981; Ishida et al., 1985). As a result of inhibitory effects of the insulin deficiency on renal 25(OH)D₃ 1α-hydroxylase activities, these abnormalities were linked to altered vitamin D metabolism (Zeit et al., 2003). In an effort to better comprehend how vitamin D affects b-cell activity.

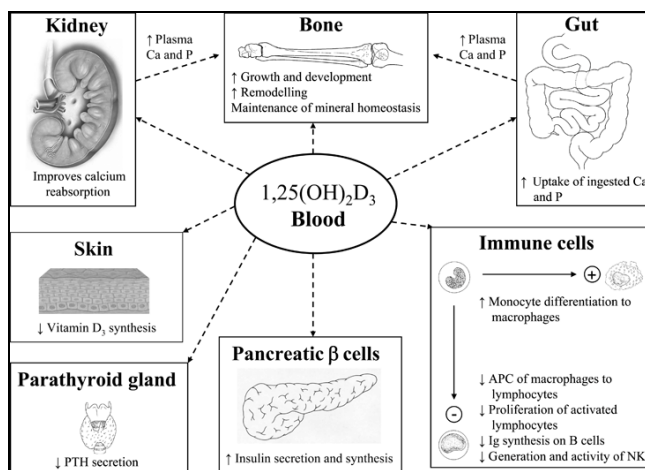


Fig. 2

There are transgenic VDR knockout mice available. Yet, in that model, some groups found no impact on glucose tolerance

whereas others have reported altered glucose tolerance (Mathieu et al., 2001; Isaia et al., 2001). The disparate genetic backgrounds of strains that are utilized in order to produce transgenic mice have been blamed for these inconsistent results (Haussler et al., 1998). In humans, supplementation of vitamin D increases the stimulated secretion of insulin in a response to oral glucose loads in patients who have a mild T2DM (i.e normal levels of the fasting serum glucose), in healthy subjects who do not have diabetes, and in patients who have vitamin D deficiency, yet not in individuals with T2DM that has already developed (Johnson et al., 1994). This is followed by a marked decrease in serum free fatty acid levels and an increase in the levels of serum calcium (Bikle, 1992). Additionally, restoring vitamin D levels was demonstrated to increase insulin responses in female patients who have type II diabetes (Borissova et al., 2003; Taylor and Wise, 1998) and enhance the tolerance of glucose in patients that have vitamin D deficiency. It was observed that vitamin D supplementation in Asian cultures who have got T2DM and vitamin D deficiency led to increasing insulin resistance and a decline in glycemic regulation (Sergeev and Rhoten, 1995). Yet, contrasting results have also been attained in other populations. The effects of vitamin D on the secretion of the insulin could occur via a number of different routes. There is evidence that vitamin D results in an increase of the intra-cellular calcium concentrations through voltage-dependent non-selective channels of the calcium, which in turn affects b-cell insulin secretion (Lee et al., 1994). As a result, the β-cell calciumdependent endopeptidases, producing cleavage which helps proinsulin conversion into insulin, will potentially have an important impact on the vitamin D action mechanism on synthesis and secretion of insulin (Holick, 2004).

Additionally, calcium is required for the glycolysis of the β-cells, which aids in signaling the role of circulating glucose, in addition to insulin exocytosis (Ismail and Namala, 2000). Through the activations of the protein bio-synthesis in the pancreatic islets, vitamin D affects secretion of insulin as well through promoting its syntheses (Zeit et al., 2003). The augmentation of secretion of insulin by treatment with the use of vitamin D was a result of several additional factors, which include serum phosphorus or direct effects of vitamin D on pancreatic beta cells (Bikle, 1992). Vitamin D has been responsible for the enhanced secretion of the insulin through other pathways, like direct modulations of the β-cell growth, as serum phosphorus isn't changed by the supplementations of vitamin D (Lee et al., 1994).

Vitamin D and type I diabetes

Numerous epidemiological research had noted some interesting correlations of latitude with type I diabetes incidence as well as the intriguing association between the number of sunshine hours per month and diabetes incidence. For type I diabetes, a seasonal pattern of onset of the illness was reported as well (Karvonen et al., 1998; Hanaa and Dhay, 2020), again pointing to an inverse correlation between the

sunshine and the condition. An apparent option for mediating this solar impact is vitamin D. For children and pregnant women, dietary vitamin D supplementation is frequently advised for the prevention of the deficiency of vitamin D. A multicenter case-control study had revealed as well that there is a link between the supplementation vitamin D in period of infancy and decreased risks of type I diabetes (The EURODIAB, 1999, Hanaa and Dhay, 2020), and it has been reported that taking oil of the cod liver throughout the 1st year of life results in lowering risks of the childhood-onset type I diabetes (Stene and Joner, 2003). Another research revealed that consuming 2,000IU of vitamin D throughout first year of the life reduced risks of type I diabetes and had revealed the fact that the participants with suspected rickets had a threefold greater chance of childhood diabetes (Hyponen et al., 2001). More recently, the Diabetes Autoimmunity Study in the Young (DAISY) found that mother dietary intake of vitamin D throughout the period of the pregnancy has been negatively linked to the existence of islet auto-antibodies in the children (Fronczak et al., 2003). It is still unclear whether such observations are the result of supplementation of vitamin D at supra-physiological levels or are simply due to vitamin D deficiency prevention. Regular vitamin D supplements that are given to the Bio Breeding (BB) rats and non-obese diabetic (NOD) mice during fetal and early life did not protect against type I diabetes, according to observations in animal models, while diabetes prevalence is doubled in the NOD mice that were born with vitamin D deficiency (Giulietti et al., 2004; Zella et al., 2003). Results of the genetic studies looking into some potential connection between the VDR polymorphisms and the type I diabetes had been found extremely ambiguous: In certain populations (McDermott et al., 1997; Motohashi et al., 2003), there is a clear correlation, but in others, there is no correlation (Nejentsev et al., 2004).

Vitamin D status and T2DM

Even though the exact aetiopathogenesis of T2DM is uncertain, it has been characterized via insulin resistance and reduced levels of the secretion of insulin. Environmental elements play a crucial role in this process, acting not just as triggers but also as accelerators or protectors. Long thought to be one of the risk factors for glucose intolerance, hypovitaminosis D caused by the depletion or relative resistance of vitamin D. For example, long-term treatment with vitamin D for osteomalacia enhances glucose tolerance and enhances insulin secretion (Ismail and Namala, 2000). Also, it was hypothesized that both those without and with diabetes may have hyperinsulinaemia, which has been linked to higher BMD. At the same time, diabetic patients who get one large dosage of vitamin D had higher amounts of the blood glucose (Boucher et al., 1995). Furthermore, the supplementation of vitamin D in the participants that did not have a vitamin D deficiency did not improve glucose tolerance (Ismail and Namala, 2000). According to data from numerous research, hypovitaminosis D could be one of the significant factors in role of type II diabetes in humans. The epidemiological information had revealed that persons at risk

of getting T2DM had lower serum vitamin D concentrations than subjects who were not at risk (Hanaa and Dhay, 2020) in a London-based Bangladeshi community. When compared to the British Caucasian population, such patients had a higher prevalence of T2DM, which may indicate that vitamin D status affects disease's development (Boucher et al., 1995). While extended vitamin D treatment likewise reduced glucose levels, short-term replenishment of vitamin D in Bangladesh Asian population had boosted the secretion of the insulin without changing the glycaemia (Boucher et al., 1995). Additionally, the treatment with vitamin D was exhibited to partially restore secretion of insulin and action in a Bulgarian community of type II diabetic female patients with a high hypovitaminosis D prevalence (Zeit et al., 2003).

Additionally, research from New Zealand found that compared to matched control people, the patients who have been newly diagnosed with type II diabetes or impairment in the tolerance of glucose had lower 25(OH)D3 levels. Additionally, glucose tolerance and insulin secretion were negatively associated with vitamin D levels in older Dutch men (Baynes et al., 1997). Inverse relationships between vitamin D level and rate of diabetes were seen as well in non-Hispanic white as well as Mexican Americans, yet not in non-Hispanic black persons, based on the data from 3rd National Health and Nutrition Examination Survey (Scragg et al., 2004). Additionally, in an English population (Wareham et al., 1997), levels of serum 25(OH)D3 had been unrelated to glucose status. All of these data imply that, although not in all groups, hypovitaminosis D could be one of the important factors of risk for the glucose intolerance. It is startling that non-Hispanic black individuals do not exhibit inverse correlation of vitamin D status with diabetes, especially given their low level of serum vitamin D. Absence of correlation might be explained by the possibility that various ethnic groups have distinct threshold effects (Scragg et al., 2004). Additionally, non-Hispanic Blacks may have been less sensitive to vitamin D or hormones connected to it, like parathyroid hormone (PTH) (Bell et al., 1985). In this regard, non-Hispanic black persons have been found to be less sensitive to the effects of PTH than Caucasians (Cosman et al., 1997).

The frequency of metabolic syndrome was higher in healthy normoglycaemic subjects with hypovitaminosis D compared to those without it, according to Chiu et al., research (Chiu, 2005). Additionally, they discovered a correlation between insulin sensitivity and the levels of 25(OH)D3, as well as a variation in beta-cell function that is linked to the hypovitaminosis D, which raises the possibility that hypovitaminosis D could act as a standalone factor of risk for the resistance to insulin, type II diabetes, and metabolic syndrome. Potential Coronary Artery Risk Development in the Young Adults Study (Hanaa and Dhay, 2020) has also raised the potential that vitamin D could have some role in metabolic syndrome. In that trial, treatment with vitamin D has been more effective at increasing insulin sensitivity compared to metformin or troglitazone treatment (Holick, 2004). Obesity,

which is frequently linked to hypovitaminosis D, increases prevalence of type II diabetes. A considerable fraction of obese people likely chronic vitamin D deficiency because it is effectively stored in stores of the body fat where it's not accessible anymore (Hanaa and Dhay, 2020). Additionally linked to functional changes like higher PTH levels are vitamin D deficiencies in obese people (Boucher et al., 1995). Productions of glucose intolerance and CVD, both linked to obesity, might be facilitated by this secondary hyperparathyroidism. As previously mentioned, vitamin D increases the secretion of by pancreatic beta cells while decreasing the syntheses of PTH (Ogunkolade et al., 2002). The acute deficiency of the insulin in the DM could reduce the production of vitamin D because PTH and insulin boost the production of vitamin D (Ogunkolade et al., 2002). Which has been supported by the support that patients who have hyperparathyroidism are more likely to have diabetes and insulin resistance (Stene and Joner, 2003). Also, abnormal glucose intolerance and insulin resistance are corrected after parathyroidectomy. Decreased insulin secretion, type 2 diabetes, and hypovitaminosis D are all linked by a number of similar metabolic consequences. Obesity, which is frequently linked to hypovitaminosis D, increases the prevalence of type II diabetes. A considerable number of the people who have obesity likely have chronic vitamin D deficiency because vitamin D is effectively stored in body fat stores where it is not bio-available any longer (Hanaa and Dhay, 2020). Additionally linked to functional changes like higher PTH levels are vitamin D deficiencies in obese subjects (Boucher et al., 1995). Production of the glucose intolerance and CVD, both linked to obesity, could be facilitated by this secondary hyperparathyroidism. As previously mentioned, vitamin D stimulates pancreatic β cells to secrete insulin but inhibits the secretion of PTH (Ogunkolade et al., 2002). Acute insulin deficiency in diabetes mellitus could reduce the production of vitamin D because PTH and insulin boost vitamin D synthesis (Ogunkolade et al., 2002). It's generally known that the patients who have the hyperparathyroidism have higher rates of insulin resistance and diabetes (Scragg et al., 2004) as support for this. In addition, abnormal resistance of the insulin and glucose intolerance are corrected after para-thyroidectomy. As a result, a number of linked metabolic processes may be responsible for the correlation between type 2 diabetes, decreased insulin secretion, and hypovitaminosis D.

Conclusions

There's strong evidence that deficiency of vitamin D predisposes b-cell functions, causes the glucose intolerance in human as well as animal models, and increases risks of type II diabetes. Early-life vitamin D deficiency results in predisposing the NOD mice and humans to later onset of the autoimmune type of the diabetes. The research on vitamin D and diabetes that had been done up to this point show that a vitamin D deficiency isn't only bad for bone and calcium, yet for the glucose metabolism as well. In animal models of type I diabetes, high dosages of activated vitamin D form,

1,25(OH)₂ D₃, have immune-modulating actions that prevent diabetes. The availability of 1,25(OH)₂ D₃ structural counterparts offers up new avenues for the application of these intriguing characteristics in humans. The answer to the question of such analogs' therapeutic promise in the prevention of diabetes will yield from carefully planned intervention research utilizing them, either alone or combined with other immune modulators.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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