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Editorial

Impact of vitamin D on secretion and action on insulin: A glimmer of hope for the global burden of diabetes mellitus

Rahnuma Ahmad[1], Mainul Haque[2]

[1]Department of Physiology, Medical College for Women and Hospital, Dhaka, Bangladesh, [2]The Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia, Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia.

Vitamin D is referred to generally as ergocalciferol (vitamin D_2), found in plants, while vitamin D_3, also known as cholecalciferol, is found in animal sources. Vitamin D, in small amounts, is obtained from diet; however, the major portion of vitamin D in circulation is acquired from the skin when cholecalciferol is formed from 7-dehydrocholesterol upon exposure to sunlight rays.[1] Cholecalciferol is then biotransformed to 25-hydroxycholecalciferol in the hepatic cells and then, in the kidney, turns into 1,25-dihydroxycholecalciferol.[2,3] 25-hydroxycholecalciferol [25(OH)D] remains in the circulation and is a biomarker for the level of vitamin D.[4]

Vitamin D has its role in absorbing Ca^{2+}, growth, and remodeling of bone.[5] This vitamin also influences the immune system and biotransformation process. It has been noted in several research works that vitamin D affects the activity islets of Langerhans and resistance of insulin in type 2 diabetes mellitus (T2DM).[6–9] The increasing global trends in diabetes mellitus (DM) incidence are perhaps related to the pervasiveness of vitamin D insufficiency.[10–12]

VITAMIN D AND ISLETS OF LANGERHANS FUNCTIONING

T2DM is expected to rise globally in the decades to come. In T2DM, there is a characteristic decrease in the synthesis and release of insulin from pancreatic islets and the development of resistance to insulin. Such changes lead to hyperglycemia and intolerance to glucose.[10,13] The reduction in the function of β-cells and the mass of β-cells may be due to raised inflammation, lipotoxicity, and glucotoxicity.[13–15]

The expression of 1α-hydroxylase enzyme and vitamin D receptor transcript by the β-cells Islets of Langerhans promotes 25-hydroxycholecalciferol converting to 1,25-dihydroxycholecalciferol.[10] The vitamin D response element in the gene-promoting receptor region indicates that vitamin D has a considerable corollary in regulating insulin action [Figure 1].[16] Several studies have reported that in vivo, a deficiency in vitamin D resulted in a fall in insulin levels. There was also noted impairment of secretion of insulin by

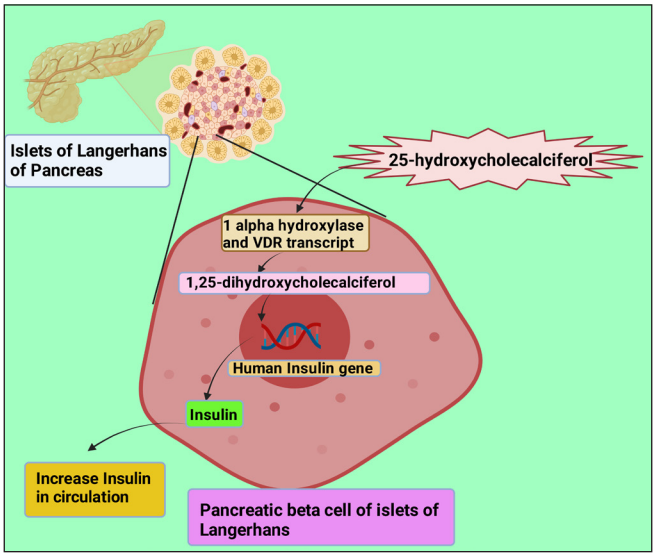

Figure 1: Illustrates the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (the active form of vitamin D) by 1-α-hydroxylase and Vitamin D receptor transcript in the pancreatic β-cells of Islets of Langerhans. This active form of Vitamin D promotes the human insulin gene and increases the formation of insulin. VDR: Vitamin D Receptor. This figure has been drawn with the premium version of BioRender (https://biorender.com/accessed on 01 November 2023) with license number EF261KOSYA. Image credit: Rahnuma Ahmad

***Corresponding author:** Dr. Mainul Haque, The Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia, Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia. runurono@gmail.com

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isolated islets.[17–19] Also, when vitamin supplements were introduced into mice with vitamin D deficiency, the insulin-secreting function of the islets was restored.[17,18,20–22] Such studies suggest that vitamin D directly affects the insulin-secreting function of pancreatic islets. A significant decrease in serum insulin levels and expression of Ins2 (gene providing instruction for insulin secretion) was observed in vitamin D receptor mutant mice.[10,21] Findings as such also indicate that the insulin expression-related gene involved in insulin expression and secreting is influenced by vitamin D and its receptor.

Clinical studies on T2DM, prediabetic, and non-diabetic subjects have noted the influence of vitamin D on β-cells of the islet of Langerhans in humans.[23–25] Despite evidence that connects vitamin D to the function of islets, it is not clear whether providing vitamin D treatment would improve insulin secretion based on several clinical trials.[26–28]

MECHANISMS AIDING IN THE REGULATION OF SYNTHESIS AND SECRETION OF INSULIN BY VITAMIN D

Several mechanisms help vitamin D in regulating the secretion and formation of insulin. One such mechanism is the binding of 1,25 dihydroxycholecalciferol with the vitamin D receptor, leading to gene expression for glucose transport, insulin secretion, and β cell growth.[16,29] There is also an influence of vitamin D on the concentration of Ca^{2+} within the cell, which may regulate the secretion of insulin indirectly. 1,25-dihydroxycholecalciferol causes β cell membrane depolarization, opening Ca^{2+} channels and increasing Ca^{2+} levels in the cell. Ca^{2+} promotes insulin vesicle mobilization and insulin release from β-cells by exocytosis.[30–33]

1,25-dihydroxycholecalciferol also causes activation of PKA and phosphorylation of Ca^{2+} channel-related protein and thus increases the activity of Ca^{2+}channels.[32] Voltage-gated Ca^{2+} channels are also regulated through activating receptors for vitamin D. The active form of the vitamin increases insulin secretion.[34] Ca^{2+} release from the endoplasmic reticulum is promoted by vitamin D through augmenting PLC production and activating inositol triphosphate.[33,34] Vitamin D also helps to maintain Ca^{2+} concentration by regulating the expression of calbindin (a protein that binds Ca^{2+}).[10,35,36]

ANTI-INFLAMMATORY AND STRESS FACTOR-REDUCING FUNCTION OF VITAMIN D

Vitamin D suppresses inflammation by directly suppressing the activation of the Nuclear Factor κB (NF-κB) transcription factor. Vitamin D also suppresses endoplasmic reticulum stress and Islet Amyloid polypeptide-mediated dysfunction of β-cells.[37] Vitamin D helps downregulate endoplasmic reticulum stress inducers from monocytes, islets, and liver like p-IREa, CHOP, and p-PERK.[38] This may be due to either direct repressing of gene expression for endoplasmic reticulum stress or effects secondary to the anti-inflammatory activity of vitamin D.[10]

Even though the protective effect of this vitamin on islets has been noted, supplementation with vitamin D has yet to clearly show improvement in glucose metabolism.[1,39–42] Such findings may be attributed to a fall in the receptor of vitamin D expression in islets in the case of subjects with diabetes.[43] A study performed in mice noted that vitamin D receptor overexpression in the islets was needed to improve the dysfunction of the islet's cells, indicating that vitamin D receptor activation above normal may be required to cause islets of Langerhans functional improvement.[43] Combining vitamin D and inhibitors of BRD9 can help simultaneous β-cells anti-inflammatory mechanisms activation and prevention of islet dysfunction, as has been observed in studies involving T2DM animal models.[37] Vitamin D also regulates non-endocrine cells and non-β endocrine cells of islets; for example, vitamin D receptors are expressed in macrophages of the islets, indicating that vitamin D influences the immune cells of the islet.[44]

SENSITIVITY OF INSULIN AND RESISTANCE AND VITAMIN D

In prediabetic and diabetic individuals, insulin's ability to promote glucose entry into cells is impaired, also known as insulin resistance (IR). Regulation of insulin sensitivity for cells by vitamin D has been observed.[39] It has been observed in several studies that the active form of vitamin D promotes the expression of insulin receptors, which leads to raised sensitivity to insulin.[16,45,46] An association between vitamin D-activated proliferator-activated receptor (PPAR) δ and increased insulin sensitivity has been found.[47,48] Studies recently have been performed to note the role of vitamin D in specific tissues concerning insulin sensitivity. Manna *et al*. found that GLUT-4 translocation in myotubes was promoted by 1,25-dihydroxycholecalciferol by activating Sirtuin 1 (SIRT1), Insulin receptor substrate-1 (IRS-1) phosphorylation and, therefore, enhancing uptake of glucose by skeletal muscle.[7] Zhou *et al*. suggested from their study that 1,25-dihydroxycholecalciferol reduced resistance to insulin myotube cells of skeletal muscle.[49] Also, translocation of GLUT-4 and rise in glucose uptake occurs when enhanced vitamin D activation promotes Ca^{2+} concentration in skeletal muscle [Figure 2].[50] Such studies indicate that vitamin D protects skeletal muscle against IR. In a study done with diabetic animal models, it was reported that a reduction in the expression of insulin receptor genes in the liver might be improved by using vitamin D.[51] However, another study did

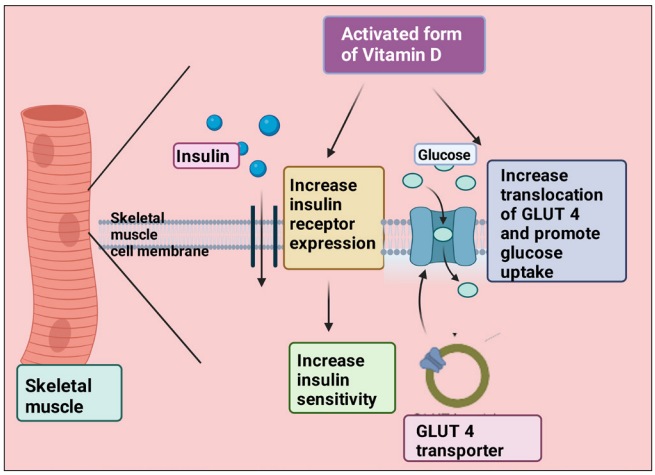

Figure 2: Demonstrate the promotion of insulin receptor expression and translocation of GLUT 4 transporter by an activated form of vitamin D and thus increase insulin sensitivity and glucose uptake. GLUT: Glucose Transporter. This figure has been drawn with the premium version of BioRender (https://biorender.com/accessed on 01 November 2023) with license number LA261KYXZE. Image credit: Rahnuma Ahmad

not find any effect of vitamin D on the transcription of the insulin receptor gene in mice's liver on a high-fat diet.[52]

A recent study on diet-induced obese experimental animals demonstrated the anti-inflammatory effect of vitamin D as they reported that activated vitamin D receptors acted on macrophages of the liver to lower inflammation in the liver, which in turn resulted in a decrease in IR.[53] Vitamin D causes downregulation of inflammatory cytokines like TNF-α, IL-1 β, and IL-6) and chemokines like CXCL10, CXCL11, and CCL5 from adipose cells and immune cells [54–57] and therefore decrease inflammation. A decrease in transcript and protein levels of TLR4 and TLR2 utilizing vitamin D receptors was suggested to be the possible mechanism for this downregulation of cytokines and chemokines by a study conducted on human monocytes.[58]

Vitamin D also suppresses MAPK signaling and NF-κB via vitamin D receptor to impart its anti-inflammatory activity.[59,60] Recruitment of monocytes is also inhibited by vitamin D and its receptor into adipocytes, and anti-inflammatory M2 macrophage is promoted in the adipose tissue.[61]

THE PLEIOTROPIC ROLE OF VITAMIN D AND VITAMIN D RECEPTOR IN RESISTANCE TO INSULIN

The pleiotropic role of vitamin D and its receptor in resistance to insulin may be through several mechanisms. There is induction of parathyroid hormone by vitamin D, which decreases resistance to insulin by raising the amount of GLUT-4 and GLUT-1 in muscle, liver, and adipose tissue deficient in vitamin D.[62,63] Renin-angiotensin-aldosterone system exhibits the ability to impair β cell activity. Vitamin D suppresses this system that, along with its β cell-impairing ability, also can cause hindrance of GLUT 4 recruitment.[64,65] The Ca^{2+}/CaMKKβ/AMPK pathway may be activated by high doses of vitamin D supplementation, which would reduce IR and endoplasmic reticulum stress.[66] Reactive oxygen species, an activating factor for IR formation, is prevented by vitamin D.[67]

The protective effect of 1,25-dihydroxycholecalciferol in resistance to insulin has been found in several studies. A study by Chiu *et al.* on individuals with normal glucose tolerance observed that subjects suffering from vitamin D deficiency had more risk of IR development.[68] Other research works noted that a low active form of vitamin D level in plasma was a factor for the risk of T2DM development.[69,70] Vitamin D supplementation has been shown to reduce IR and raise insulin secretion.[26,27,71] Another study on three T2DM subjects reported that supplementation with ergocalciferol improved IR.[10,72] However, a study performed on individuals with normal vitamin D found no improvement in glucose homeostasis on supplementation with vitamin D.[10,73] Such findings warrant further investigation on a broader scale to understand the effect of vitamin D on IR.

DEFICIENCY OF VITAMIN D AND TYPE 2 DIABETES MELLITUS

The association has been noted in previous studies between deficiency of vitamin D and dysfunction of islets, IR, and raised incidence of T2DM.[39] A cohort study conducted on 9841 subjects found a greater risk of T2DM in participants with low 25-hydroxycholecalciferol in plasma.[74] Several other studies have reported similar outcomes.[75–78] Song *et al.*, in a meta-analysis which included four thousand nine hundred and ninety-six T2DM cases, observed a link between a lower risk of diabetes and higher plasma vitamin D levels. A 10 nmol/L rise in 25-hydroxycholecalciferol in plasma was associated with a 4% decrease in the incidence of T2DM.[79] A study was performed in California in which islet secretion capacity and index of insulin sensitivity were measured, and they found a positive association between 25-hydroxycholecalciferol level in plasma and function of β-cells and sensitivity of insulin.[80] While some studies have found a link between vitamin D deficiency and T2DM, others have not observed any significant association between these parameters.[81–83]

A randomized, double-blinded, and placebo-controlled clinical trial found a significant increase in sensitivity to insulin on supplementing with vitamin D3 for six months compared to the placebo.[24] Other trials done with vitamin D-deficient overweight subjects[84] and individuals with

fasting blood glucose impairment[85] also noted similar findings. There was an improvement in fasting blood glucose and insulin levels after being supplemented with vitamin D[86] and HOMA-IR.[11,86] However, other trials with vitamin D supplementation did not reduce the risk of DM in subjects who were at high risk.[73,87] Thus, further research is required to understand whether vitamin D supplementation may prevent T2DM.

Genes involved in the insulin action and secretion pathway may be regulated directly. Vitamin D shows its anti-inflammatory effect by acting on the immune cells of tissue, decreasing systemic and local inflammation. This led to averting dysfunction of muscle, liver, and islets. In vitamin D deficient individuals, normalization of vitamin D has been found to lower the risk of T2DM. However, other clinical trials did not observe similar findings. Thus, the optimum level of vitamin D and whether supplementation with vitamin D has reversible and preventive effects for T2DM needs to be studied on a large scale.

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