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Vitamin D suppresses inflammatory responses in insulin resistance

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ABSTRACT

Vitamin D has been known as a vitamin for bone health and mineral homeostasis. However, since the discovery of vitamin D receptor (VDR) in various types of cell, that statement has changed. Immune cells are known to express VDR and enzyme 1α-hydroxylase that could convert vitamin D into its active form, 1.25 dihydroxyvitamin D. In immune cells, vitamin D works as an immunomodulator which affects various levels of immune response. The net effects of vitamin D are increasing mucosal immunity, but dampening the adaptive immune system. Vitamin D deficiency is commonly found in people with diabetes mellitus (DM) and obesity. It is also associated with increased insulin resistance and poor glucose control. This review will explain how vitamin D as immunomodulator dampens insulin resistance. In immune cells from subjects with insulin resistance, administration of vitamin D could reduce the expression of pro-inflammatory cytokines through the NF-κB and MAPK pathways, thus the levels of pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 are decreased. The same thing happens in preadipocytes and mature adipocytes cells. In these cells, vitamin D suppresses the expression of pro-inflammatory mediators such as IL-6 and MCP-1. Although in the *invitro* studies, the administration of vitamin D showed a promising effect in modulating the immune system, the clinical effect of vitamin D supplementation in reducing insulin resistance in individuals with type 2 DM (T2DM) and prediabetes is still inconclusive

ABSTRAK

Vitamin D dikenal sebagai vitamin untuk kesehatan tulang dan homeostasis mineral. Namun, sejak ditemukannya reseptor vitamin D (VDR) di berbagai jenis sel, pernyataan itu telah berubah. Sel kekebalan dikenal untuk mengekspresikan VDR dan enzim 1α-hidroksilase yang dapat mengubah vitamin D menjadi bentuk aktifnya, 1,25 dihydroxy vitamin D. Dalam sel kekebalan, vitamin D bekerja sebagai imunomodulator yang memengaruhi berbagai tingkat respons imun. Efek vitamin D itu sendiri adalah meningkatkan kekebalan mukosa, tetapi mengurangi system kekebalan adaptif. Kekurangan vitamin D umumnya ditemukan pada penderita diabetes melitus(DM) dan obesitas. Hal ini terkait dengan peningkatan resistensi insulin dan control glukosa yang buruk. Ulasan ini akan menjelaskan bagaimana vitamin D sebagai imuno modulator mengurangi resistensi insulin. Dalam sel imun dari subyek dengan resistensi insulin, pemberian vitamin D dapat mengurangi ekspresi sitokin proinflamasi melalui jalur NF-κB dan MAPK, sehingga tingkat sitokin proinflamasi seperti TNFα, IL-1β, dan IL-6 menurun. Hal yang sama terjadi dengan sel preadiposit dan adiposit matang. Dalam sel ini, vitamin D menekan ekspresi mediator proinflamasi seperti IL-6 dan MCP-1. Meskipun dalam penelitian *invitro,* pemberian vitamin D menunjukkan efek yang menjanjikan dalam memodulasi system kekebalan, efek klinis suplementasi vitamin D dalam mengurangi resistensi insulin padapasien DM tipe 2 dan pradiabetes masih belum dapat disimpulkan.

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INTRODUCTION

Since long ago, vitamin D has been known as a vitamin for bone health and mineral homeostasis. Vitamin D could enhance the absorption of calcium and phosphate in the intestine, stimulate the osteoclasts differentiation, enhance calcium reabsorption from bones and induce matrix mineralization.[1] However, in the last decades, the role of vitamin D affecting human health changed rapidly, especially after the discovery of vitamin D receptor (VDR) and enzyme 1α-hydroxylase (CYP27B1) in several cell types that not related to mineral and bone metabolisms such as intestine, pancreas, prostate and immune cells.[2] This indicates that vitamin D has a broader role than is currently known, including in the field of immunology.

In immunology, the active form of vitamin D, 1.25-dihydroxyvitamin D is able to influence the proliferation and differentiation of immune cells.[3] Moreover, vitamin D could modulate the innate and adaptive immune response. Some studies revealed that vitamin D deficiency was associated with autoimmune diseases, cardiovascular disorders, cancers, and infections.[1-3]

In metabolic disease, vitamin D deficiency is associated with metabolic disorders such as obesity, insulin resistance (IR), and type 2 diabetes mellitus (T2DM). Vanlint[4] revealed that obese people tend to have low vitamin D levels. In patients with T2DM and ingeneral population, low level of 25-hydroxyvitamin D is associated with higher fasting blood glucose level, higher HbA1c, increased HOMA-IR and increased risk of metabolic syndrome.[5-6] Survey conducted by NHANES III in 6228 people showed that the level of 25-hydroxyvitamin D more than 81 nmol/L was a protective factor against the development of T2DM.[7]

In this paper, the author would like to discuss the mechanism of vitamin D in the immune system. How vitamin D suppresses the secretion of proinflammatory mediators released by immune cells and adipose cells, and whether vitamin D supplementation can reduce insulin resistance in prediabetic and T2DM patients will be discussed.

DISCUSSION

Vitamin D

Source, metabolism, and regulation

There are two main forms of vitamin D, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Ergocalciferol is synthesized by plants in the presence of UV light, whereas cholecalciferol is endogenously produced by human body and it is also found in some dietary sources. The biological function of both forms of vitamin D is carried out by same active form, 1.25 dihydroxyvitamin D.[8] This paper would focus on vitamin D_3 since it is normally found in human body.

Vitamin D_3 could be obtained from 3 potential sources, which are nutrition, UVB-dependent endogenous production, and supplementation.[1] In human, vitamin D is synthesized in the skin after exposed to UVB, while nutrition contributes only small amounts of vitamin D.[1] There are very few natural food products which contain vitamin D_3, including fatty fish (salmon, sardines, mackerel, cod liver oil) and some types of fungi.[1] Some countries implement vitamin D fortification policy by adding vitamin D to various food products such as dairy products.[9] Thus, vitamin D intake is very dependent on nutritional intake and fortification policy in the country.[9] In addition, vitamin D levels are also associated with endogenous production of vitamin D which is influenced by genetic factors, locations, seasons, skin pigmentation, and lifestyle such as using sunscreen and wearing full-covered clothes.[9]

FIGURE 1 shows the metabolism

of vitamin D_3. First, in the skin, 7-dehydrocholesterol (provitamin D_3) is converted to previtamin D_3 when it is exposed to UVB with 290-312 nm wavelength and then it is immediately converted to vitamin D_3.[10] Cholecalciferol is biologically inactive and bound to vitamin D binding protein (DBP) or albumin.[10] Cholecalciferol which is bound to DBP enters the circulation and is carried to the liver. In the liver, enzyme CYP2R1 (cytochrome P450 vitamin D 25-hydroxylase) and CYP27A1 will hydrolyze cholecalciferol into 25-hydroxyvitamin D which represents the main metabolite of vitamin D and the most trusted parameter for determining vitamin D status in human.[10]

Almost all DBP-bound25 hydroxyvitamin D is filtered in the kidneys and reabsorbed by the proximal renal tubules. In the kidney, megalin, and cubitin, the member of the LDL receptor superfamily, endocytosis 25 hydroxyvitamin D. In this tubules, 25 hydroxyvitamin D is hydroxylated by enzyme 1α-hydroxylase (CYP27B1) to become its active form, 1.25 dihydroxyvitamin D.[10]

Converting 25 hydroxyvitamin D to an active metabolite, 1.25 dihydroxyvitamin D by the enzyme 1α-hydroxylase in kidneyis under the regulation of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23). PTH induces the transcription of 1α-hydroxylasegene and nuclear receptor 4A2 as a transcription factor of 1α-hydroxylase.[11] Low levels of calcium and phosphate will also increase the activity of 1α-hydroxylase.[11] In contrast, an increasedof 1.25 dihydroxyvitamin D level would suppress PTH production at the transcription level.[11] Increased 1.25 dihydroxyvitamin D leveland FGF-23 also inhibit enzyme 1α-hydroxylase and stimulateenzyme 24-hydroxylase (CYP24A1) which converts 1.25 dihydroxyvitamin D to an inactive and water-soluble form, thus it could be excreted.[10]
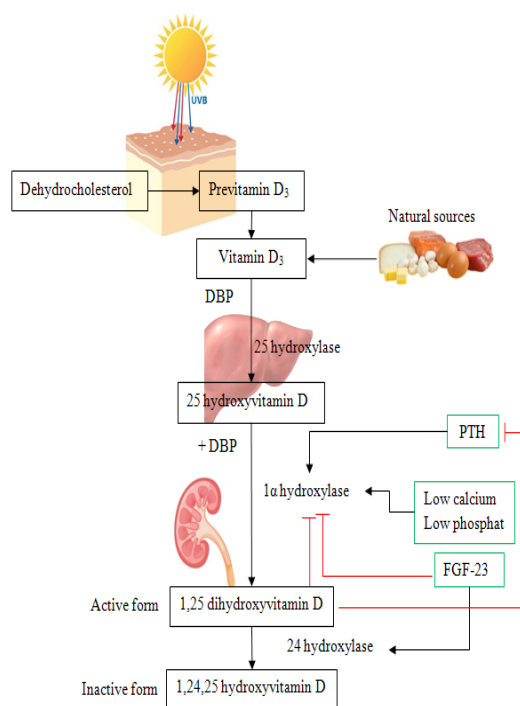

FIGURE 1. Synthesis, metabolism, and regulation of vitamin D. DBP: vitamin D binding protein; PTH: parathyroid hormone, FGF-23: fibroblast growth factor – 23

Various types of immune cells, such as monocytes, macrophages, dendritic cells, T and B cells also express theenzyme 1α-hydroxylase. Therefore, they could convert 25 hydroxyvitamin D to its active form, 1.25 dihydroxyvitamin D in the paracrine or autocrine environment.[12] Moreover, macrophages and dendritic cells, do not have negative feedback mechanism such as in the kidney, so these cells could produce 1.25 dihydroxyvitamin D in high concentration needed for immunomodulation.[12]

Vitamin D binding protein (DBP) and vitamin D receptor (VDR)

In order to reach the target cells, 25 hydroxyvitamin D is bound to the vitamin D binding protein (DBP). DBP is encoded by the GC gene which has a function as a specific transporter for vitamin D metabolites and plays an important role in endocytosis of vitamin D.[13] DBP is a glycoprotein that synthesized and secreted by the liver. DBP forms a vitamin D complex to maintain the availability of vitamin D in the target tissues.[14]

Vitamin D signaling occurs when 1.25 dihydroxyvitamin D binds to a vitamin D receptor (VDR) located either in the cytoplasm or in the nucleus.[15] VDR is a transcription activator or suppressor for several genes.[15] The VDR gene is located on chromosome 12q13.1. It consists of 14 exons and has a promoter region that could induce the transcription of specific genes in some tissues. VDR is expressed in more than 38 types of tissue and plays an important role in controlling vital genes such as bone metabolism and disruption of these receptor causes oxidative stress,

development of chronic diseases and inflammation.[15] After binding to its natural ligand, 1.25 dihydroxyvitamin D; VDR forms a heterodimer with retinoid X receptor (RXR), then it undergoes conformational changes and causes the complex to interact with genes that encode enzymes and proteins needed for remodeling and transcription activities.[15]

Role of vitamin D in suppressing inflammatory responses in insulin resistance

Mechanism of insulin resistance

Insulin resistance (IR) is a condition characterized by insulin-sensitive tissues, such as skeletal muscle, liver, and adipose tissues become less sensitive to insulin.[16] The pathogenesis of IR is often associated with low-grade inflammatory condition.[17] In patients with IR, there is an increase of proinflammatory cytokines such as TNFα, IL-1β, and IL-6 which are secreted by immune cells and adipose cells. These proinflammatory cytokines could phosphorylate the inhibitory kappa B kinase beta (IκKβ), a serine kinase I protein from the NF-κB pathway and Jun N terminal kinase I (JNK1) from the JNK/AP-1 pathway. Activated those pathways eventually could inactivate insulin receptor substrate 1 (IRS1) in the insulin signal transduction pathway (FIGURE 2).[18] Moreover, it is revealed that the proportion of Th1 and Th17 which secrete interferon γ (IFN γ) and interleukin 17 (IL-17) respectivelyincreased in IR.[19] Increased levels of IFNγ and IL-17 will activate more macrophages, thus it could worsen the low-grade inflammation condition.[19]
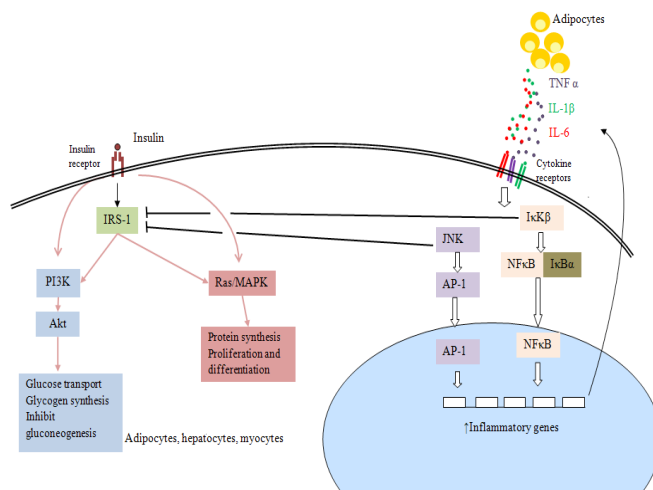
FIGURE 2. Mechanism of insulin resistance related to inflammatory cytokines in insulin sensitive tissues

Role of vitamin D in immune system

Vitamin D affects the immune system at various levels with the end effect isincreasing mucosal immunity, but suppressing the adaptive immune response.[13,20] At mucosal membranes, vitamin D enhance chemotaxis and phagocytosis activities of innate immune cells. Futhermore, a complex of 1.25 dihydroxy vitamin D, VDR, and RXR could directly stimulate the transcription of anti microbial peptides such as defensins-β2 (DEFB) and cathelicidin (HCAP) in macrophages.[12] Antimicrobial peptide would eliminate enveloped virus, bacteria, and fungi by disturbing the structure of their cell membranes.[12] Vitamin D could suppress adaptive immune system by altering the function of dendritic cells to be more tolerogenic that characterized by decreased expression of costimulatory molecules (CD80/86), MHC class II, and decreased IL-12 secretion, while IL-10 secretion increases.[11,12]

The previous study revealed that T and B lymphocytes express VDR and enzyme 1α-hydroxylase.[1] Expression of VDR in these cells is very low when cells are resting, but when activated, T and B lymphocytes significantly increase VDR expression, which causes vitamin D might influence cell differentiation and proliferation. Vitamin D exposure alsoinduces adaptive immune response to be more tolerogenic and affects various types of T lymphocytes. 1.25 dihydroxyvitamin D suppresses proliferation, differentiation effector T cells and modulates cytokines production from Th1 dan Th17 cells. On the other hands, vitamin D promotes proliferation and differentiation of Treg and Th2 cells.[13]

Vitamin D reduceslow-grade inflammation in insulin resistance

Low-grade inflammation is one of the causes of insulin resistance which increases the risk of T2DM. In LPS-stimulated macrophages, 1.25 dihydroxyvitamin D could increase IκB α, an NF-κB inhibitor, by increasing mRNA stability and decreasing phosphorylation of IκB α.[21] Increased level of IκB α would decrease nuclear translocation ofNF-κB.[21] In addition, other studies mentioned that 1.25 dihydroxyvitamin D interacted with IκKB, a protein kinase, soNF-κB activation is inhibited.[22] By inhibiting

phosphorylation IκKB, the activity of the IκK enzyme complex which phosphorylates IκBα decreases, thus this mechanism could inhibit degradation of IκB α.[22]

According to FIGURE 3, vitamin D could decrease the inflammatory response of innate cells such as TNF α, IL-6, IL-1, IL-8, COX-2, intercellular adhesion molecule (ICAM)1, and molecule B7-1 in macrophages.[10] Other studies revealed that 1.25 dihydroxyvitamin D and 25 hydroxyvitamin D could reduce the production of TNF α and IL-6 in LPS-induced macrophages through the MAPK pathway.[23] Moreover, 1.25 dihydroxyvitamin D also inhibits the release of IL-12, IL-2, IFN γ, and TNF α which play roles in pancreatic β cell dysfunction.

Vitamin D modulates T lymphocytes function by decreasing the development of Th1 and Th17 cells, but increasing the proliferation of Th2 and Treg cells. This modulating effect can protect target tissues such as pancreatic β cells, thereby reducing IR.[24] Moreover, treatment of vitamin D could reduce the number of Th1 cells in secondary lymphoid organs. In another study, treatment of vitamin D inhibited the transcription of IL17 gene by suppressing the nuclear factor for activates T cells (NFAT), inhibiting histone deacetylation, and blockingrunt-relates transcription factor 1 (Runx1).[25] Besides inhibiting effector T cells activation, vitamin D could induce apoptosis in those cells through FAS and TIM3 pathways.[25] Vitamin D induces the pro-apoptotic gene that encodes caspase 8-associated protein and inhibits cellular inhibitors of apoptosis protein 2 (cIAP-2).[25] Vitamin D also induces apoptosis by stimulating Treg cells to express galectin, a protein that induces effector T cell apoptosis through TIM3 receptor. In Treg cells and Tr1 cells, 1.25 dihydroxyvitamin D increases the transcription of Foxp3+ gene, CTLA-4 protein expression, and the production of IL-10.[25]
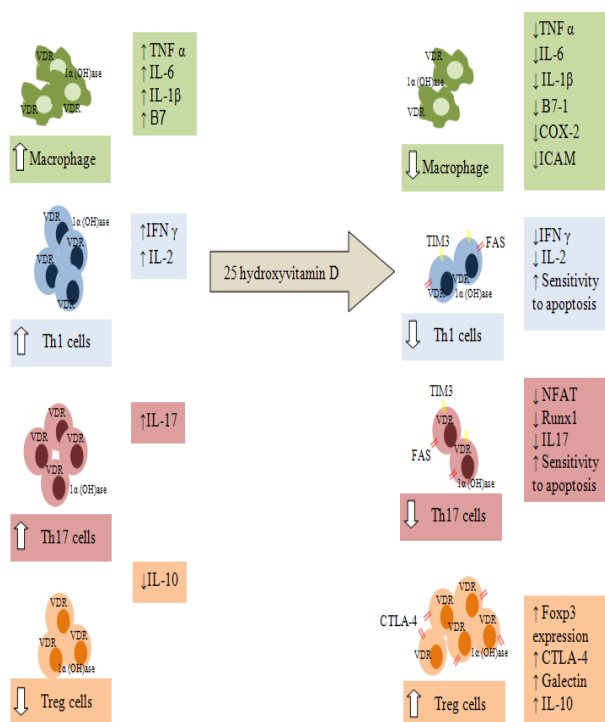

FIGURE 3. Vitamin D suppresses pro-inflammatory and enhances anti-inflammatory responses in T2DM

Role of vitamin D in adipose tissue

IR is closely related to obesity. In obesity, hypertrophy and hyperplasia of adipocytescause disruption of blood flow that makes tissue becomes hypoxic, inflammation, and infiltrated by macrophages.[26] This disturbance is characterized by an increased level of IL-6, IL-8, resistin, TNF α, and monocytes chemoattractant (MCP-1) and also changed in adiponectin secretion.[27] Previous study revealed that adipocytes expressed VDR and enzyme 1α-hydroxylase, therefore adipocytes could metabolize 25 hydroxyvitamin D into its active form, 1.25 dihydroxyvitamin D and utilize it.[27] In adipocytes, activation of NF-κB begins with the IκB α protein degradation that permits the NF-κB subunit migratesto the nucleus and inducesthe transcription of the proinflammatory genes.[26] The study conducted by Gao *et al.*[28] stated that 1.25 dihydroxyvitamin D could increaseIκB α protein in human pre-adipocytes and treatment with 1.25 dihydroxyvitaminvitamin D decreased IL-6 and MCP-1 secretion from human preadipocytes and decreased preadipocyte-induced macrophage activation. The latest study stated that 1.25 dihydroxyvitamin D could also inhibit the degradation of IκB α protein and decrease the expression of p65 NF-κB in human adult adipocytes.[29] In addition, Mutt *et al.*[30] revealed that 1.25 dihydroxyvitamin D could inhibit the translocation of p65 NF-κB to the adipocyte nucleus. Therefore, it could reduce the secretion of proinflammatory cytokines.

Research in obesity revealed that there was a relationship between obesity and vitamin D deficiency. Obese people tend to have a low vitamin D level.[4] Decreased vitamin D levels in obese people could be caused by low vitamin D intake, decreased vitamin D synthesis in the skin, decreased vitamin D absorption in the intestine, and changed vitamin D metabolism.[4]

Effects of vitamin D supplementation in insulin resistance

Although vitamin D deficiency is common in people with T2DM and obesity, the effects of vitamin D supplementation in reducing insulin resistance and improving glucose control in both T2DM and pre-diabetes are still controversial. In a systematic review study in patients with T2DM, it was found that vitamin D supplementation could reduce HbA1c and fasting blood glucose only in patients with T2DM who had vitamin D deficiency. However, vitamin D supplementation did not affect patients with T2DM with insufficient and sufficient vitamin D levels.[31] From a study conducted by He *et al.*[32] it was concluded that the effect of vitamin D supplementation varied depending on the initial serum vitamin D level and patient's body mass index. Furthermore, randomized clinical trial study from Iran revealed that 12 week-oral vitamin D did not affect insulin sensitivity in pre-diabetes patients.[33]

It has been described that vitamin D deficiency had a potential role in changes of glucose homeostasis and insulin secretion either *in vitro* or *in vivo* study. However, effect of vitamin D intervention in improving insulin sensitivity is still inconclusive. Many factors have been found influence the results, such as age, race, dietary habits, level of activity, and obesity. Obesity influenced the effect of vitamin D supplementation because vitamin D is a fat-soluble compound so it will be stored in adipose cells. Thus, it needs large-scale randomized trials with longer duration to analyze the advantageous effects of vitamin D.

CONCLUSION

In insulin resistance, vitamin D can suppress the expression of

proinflammatory cytokines through the NF-κBand MAPK pathways in the immune cells and adipocytes, hence the levels of proinflammatory cytokines such as TNFα, IL-1β, and IL-6 could bereduced. Vitamin D could inhibit the degradation of protein IκB α and inhibit phosphorylation of enzymes IκKβ, thus makes the translocation of protein p65 NF-κB to the nucleus decreases. Vitamin D also suppresses the activation and proliferation of effector T cells by inhibiting NFAT, Runx1, and histone deacetylation. In addition, vitamin D induces apoptosis in effector T cell through TIM3 and FAS pathways, and vitamin D could increase the transcription of the Foxp3 gene in regulatory T cells. Although in an *in vitro* study, administration of vitamin D showed the promising effect in modulating the immune system, the effect of vitamin D supplementation in reducing insulin resistance in individuals with T2DM and pre-diabetes is still inconclusive.

ACKNOWLEDGMENTS

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