New perspective actions of Vitamin D

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Abstract

The classical view of Vitamin D is responsible for regulation of hemostasis of bone, calcium, and phosphorus intestinal absorption. In addition to the classical function of Vitamin D, VitD plays non-skeletal biological actions like bone metabolism, cell proliferation and immune cells activation because VitD receptors spread in different types of tissues including intestine, prostate, skeletal muscle, heart muscle, breast, colon, pancreas, brain and immune cells. Type 2 diabetes mellitus is spread around the world which caused by inadequate insulin secretion following long time insulin resistance. There several proposed causes that connect insulin resistance with overweight or obesity, genetic background and genes polymorphism. Similar studies have studied the possible association of insulin resistance with immune regulation and inflammatory cells. The purpose of this review to handle the new information regarding the possible association of VitD deficiency with insulin resistance and deactivating inflammatory cells like macrophages and monocytes.

1. Introduction:

Forms and synthesis of Vitamin D

Vitamin D is responsible for the absorption of calcium and phosphate in the body. VitD found naturally in the food such as fish, mushrooms, avocado, eggs and milk, or it can

be manufactured in vertebrates and human skin. Ultraviolet sun light exposure triggers 7-dehydrochelestrol, which presents in large amount in the dermal layer, to transfer into provitamin D (vitamin D3) to turn into cholecalciferol by thermal isomerization (1-5). The second step of VitD manufacturing happens in the liver to add hydroxyl group on cholecalciferol to turn into 25-dehydroxyvitamin D2 (calciferol) by the action of 25-hydroxylase enzyme. VitD transports then to different tissues in particular the tissues that rich with 1α hydroxylase enzyme (CYP27B1) to add another hydroxyl group to get the final active ingredient which called 1,25 dehydroxyvitamine D3 (cholecalciferol) (6-12).

Calciferol is defined the synthetic structure and the most common type of VitD. Calciferol can be synthesized by irradiating yeast, fungus and plants. Due to the short half-life of VitD3, serum calciferol levels are used to determine the body status of VitD. VitD3 in the other hand is 78% more potent than calciferol to maintain body needs of vitamin D in the blood (13-15).

However, VitD2 and VitD3 are both considered prohormone which need to convert into biologic active metabolic molecule to give their actions (16,17). The first step of activate VitD3 is conversion into calciferol in the liver that converted into the active form (calcitriol, 1,25 dihydroxycholecalciferol) which happens primarily in the kidney and controlled by parathyroid hormone, calcium/phosphate concentration in the blood and the concentration of calcitriol in the blood. Calcitriol circulates in the blood like hormone looking for the target tissue (18-21). When calcitriol reaches the cell, it binds to its receptor called calcitriol/VitD receptor, which works as transcription factor and deck another complex receptor called retinoid X receptor (RXR)(21,22). Finally, calcitriol/VitD/RXR complex binds to vitamin A to form a big complex structure called nuclear VitD receptor nVDR that binds to DNA to exert the genomic affects which amplitude in different types of cells including monocytes, macrophage, T-cells and activated lymphocytes (23-26).

The defined keys VitD biological activity that mediated by nVDR are regulation of intestinal calcium/phosphate absorption, regulates the expression of many genes that involve in differentiation, proliferation and activation of many cells in particular immune

and inflammatory cells. These findings provide the key evidence of consider VitD deficiency a serious problem which may develop to different diseases like cancer, autoimmune disease, depression, cardiovascular disease and infection (27,28).

Calcitriol gives non-genomic actions through binding to the membrane receptor called VitD membrane receptor mVDR that is recruit caveolin-1 at the cell surface and perinuclear area. VitD/mVDR/caveolin-1 complex activates other cytoplasmic transcription receptors like PI3K, MAPK and PKC, which, in turn, activate another transcription factors like SP1, SP3 and RXR (27-30).

Mutations of nVDR develop pathological case called hereditary VitD resistance rickets a rare autosomal recessive disorder due to unresponsiveness to VitD. The patients with rickets syndrome represent hypocalcemia, hyperthyroidism and early onset of rickets, which can be reverse by intravenous calcium injection (31).

In addition, recent studies have described polymorphism in more than 70 VDR associated genes like BsmI, ApaI, TaqI and FokI, which are associated with a number of pathological conditions such as autoimmune diseases and inflammatory response (32-34).

2. Physiology of VitD

Vitamin D has two main forms VitD2 or name ergocalciferol (plant origin) and VitD3 or name cholecalciferol (animal origin). The physiological impact of VitD3 exerts via the active metabolic molecules called 1,25 dihydroxyvitamin D3(calcitriol), which in turn acts as nuclear hormone, that has high affinity to interact with nVDR. VDR forms the majority of tissues as well as several types of cells in particular immune and inflammatory cells like monocytes, lymphocytes, macrophages and T-cells (15-17,19,22,35).

The important physiological functions of VitD3 are to keep the bone healthy and strong, keep healthy and functioning muscles and potent immune cells. When we ingest calcium, calcium reaches the small intestine to the intra cellular through binding to calcium transporter. Calcium transporter binds to protein molecule called calbindin D28K that pumps the calcium molecules to the blood stream by ATP-dependent Ca

pump. VDR plays important role in this scenario; when nVDR binds to its receptor on the DNA, it activates transcription, translation and expression of calcium transporters and calbindin D28Kin the epithelial cells of small intestine that increase the chances of increasing calcium absorbance and increase calcium pump to the blood stream (36-38).

Calcitriol regulates intestinal phosphate absorption as well. In the absence of calcitriol, about 60% of phosphate is absorbed. Calcitriol increases mRNA expression in osteoclasts that result in phosphate excretion in the kidney (39-41) .

Furthermore, 1,25(OH)2D agonist parathyroid hormone to release more calcium from different tissues like bone, kidneys, intestine and muscles to the blood stream. level of 25OHD below 30 ng/ml characterizes as insufficient amount of VitD, which consequently activate PTH hormone to release more calcium and phosphate from bones resulting into bone fracture, hypophosphatemia and bone loss (40,41).

3. Risks of vitamin D deficiency

Unlike the other types of vitamins, VitD works like hormones and almost every cell in our body has VitD receptor. According to American nutrition, 25-OH-VitD blood levels below 20ng/ml classified as VitD deficiency, 30-80 ng/ml classified as VitD optimal level and above 90 ng/ml classified as possible toxic level. Overall rate of VitD deficiency in USA adults is 46.1%. Statistician and researchers have estimated around 1 billion adults in worldwide have diagnosed with VitD deficiency or ViD insufficiently (42,43). This is probably because of limited sunshine exposure and skin pigmentation, which makes ultraviolet light less efficacious. The prevalence of VitD deficiency is higher in adults who always use sun protection, or they limit their outdoor activities. In addition, VitD deficiency is common in Arabic gulf area because people in such places always cover their bodies with clothes that protect their skin from direct sun light exposure (44,45).

The most common symptoms of VitD deficiency are loss energy, fatigue, severe headache, and loss bone and sever bone pain, getting infection so frequently, feeling cold and depression (24,25,46).

The consequence of VitD deficiency may lead to the several diseases that associated with mode, memory, bone, muscle and cardiovascular system (24,25,46-48).

a. Possible mechanism by which VitD may influence type 2 diabetes:

Clinical cohort studies have found a strong positive association between improvement VitD level and pancreatic insulin release. One clinical study has concluded that the prevalence of hypovitaminosis D in diabetic people ($P<0.001$, 24%) is significantly higher than control people (16%) (49-51).

Elevated blood glucose triggers pancreatic β cells to increase insulin secretion. Insulin hormone regulates glucose hemostasis by stimulating GLU-1 and GLU-2 on the cell membrane to receive glucose molecules. Researchers have found that interacting VDRs with their DNA domain activate insulin transcription factor in human β-cells. Using animal models the studies confirmed that β-cells loss their insulin secretion function in the absence of VDRs, which may restore by adding Vit D supplements. Furthermore, VitD deficiency associated with gene polymorphisms of DBP, VDRs, or vitamin D 1alpha-hydroxylase (CYP1alpha) genes, which may lead to insulin resistance or impaired insulin release, and disturbed VitD transport, metabolism and action (23,29,30,52,53).

b. Possible association of sufficient Vit D and immune enhancement:

Although it is widely known that VitD associated with rickets and osteoporosis, VitD has become a pluripotent regulator for several biological functions beyond and above its classical effects on bone and calcium hemostasis. There is general agreement that VitD associated with tuberculosis, multiple sclerosis, inflammatory bowel disease, allergy, asthma and cancer (54-57).

Rook and colleague have done an interesting study that concluded treating human monocytes and macrophages with cholecalciferol metabolites remarkably improve their ability to control proliferation of M. tuberculosis (58).

Clinical study on 192 British people have TB has concluded that Taking single oral dose 2.5mg of VitD significantly enhanced immune cells to restrict M. tuberculosis (59,60). Consequent studies have investigated the antimicrobial effects of VitD. In the first studies, screening human genome using in silico technique suggested that VDRs interacts with vitamin D binding protein (VDBP) that target cathelicidin promotor, one of a class of antimicrobial peptides named defensins. Subsequently, several studies have confirmed the ability of 1,25(OH)2D to activate cathelicidin mRNA expression in myeloid cell lines, bronchial epithelial cells and keratinocytes (60-62).

To clarify the mechanism by which 1,25(OH)2D enhances innate immune response, Liu and colleagues arrayed macrophages DNA that treated with mycobacterial 19 kDa lipoprotein, a TLR2-interacting PAMP. The DNA array showed increased expression of both CP27B and VDR, and demonstrated autocrine induction of cathelicidin and bacterial killing in response to 25OHD. Hence, 1,25(OH)2D mediated modulation of cathelicidin expression in monocytes exposed to M. tuberculosis (63,64).

In recent years, there are growing researches trying to mark the keys of understanding the mechanism of vitamin D interacting with innate immunity. The mechanism that unmasks TLR2 mediated induction of CP27B expression needs to be clearly elucidated. Similarly induction of $1,25(OH)_2D$ has been reported in immune cells in particular monocytes and macrophages that exposed to TLR4 ligand, but whither getting the same effect by using another types of TLR members need to be determined (65-67).

Perhaps, the most acceptable answer to conclude from these studies of innate immunity concern the biological advantage of using VitD- mediated pathway to promote bacterial killing. One possible explanation is $1,25(OH)_2D$ synthesis in macrophages and monocytes to support host innate immunity by activating expression of cathelicidin that are inhibited by pathogens like Shigella (65,67).

Shigella infects macrophages and epithelial cells lead to inhibit cathelicidin and human β-defensin 1 as part of an apparent mechanism for evading antibacterial innate immunity. Under these circumstances, enhanced localized synthesis of $1,25(OH)_2D$ might act to 'rescue' cathelicidin expression and thereby maintain antibacterial surveillance (66,68).

In addition, VitD enhances immunity by feedback control mechanism that limits antibacterial activity, which lead to prevent potential inflammatory damage that arises from over toleration of immune responses. Interestingly, recent researchers have found that $1,25(OH)_2D$ supplement can induce inflammatory hyporesponsive by inhibit expression of TLR2 and TLR4 on monocytes (69-71). However, more translational researches need to be done to confirm the truly robust correlation of deficiency the active form of vitamin D and pathological conditions.

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