Review Article

Vitamin D and Kidney Diseases: A Narrative Review

Sahar Vahdat

Department of Nephrology, Khorshid Hospital, Isfahan Kidney Diseases Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Vitamin D (Vit. D) is among the most important elements of the human body that play pivotal roles in health and disease. It belongs to the fat-soluble secosteroid family, which is provided by either foods or direct exposure to sunlight that converts 7-hydroxycholesterol to the Vit. D precursor. An alternative step is bio-activation, which delivers an active form of Vit. D (Vit. D3), which participates in various noticeable functions including calcium regulation, bone remodeling, fertility, glucose control, and detoxification. The most recent literature is carefully reviewed (2049 articles) and the relative information was collected and discussed meticulously. Inclusion criteria were the articles that mentioned the relationship between Vit. D, adipokine, and kidney disease and exclusion criteria were nonrelevant articles. Vit. D plays several roles in the normal function of the kidney and metabolism. It has been revealed that Vit. D has a crucial impact on kidney disease and that its deficiency leads to kidney dysfunction and further renal disorder. Apart from the direct relationship of Vit. D with kidney disease, the association of adipocytes and adipokines with Vit. D and kidney function has also been studied. The noticeable role of Vit. D in kidney disease is investigated in various studies. It has been found that Vit. D has a pivotal role in kidney function and metabolism. Further study can reveal the better-detailed information about the exact relation of Vit. D and kidney disorders. The aim of the review was to provide a better insight into the exact role of Vit. D and adipokine in the kidney disease.

Keywords: *Adipokine, chronic kidney disease, vitamin D*

Vitamin D: Structure and Sources

Vitamin D (Vit. D) is a fat-soluble vitamin, which is present in two biological forms: Vit. D2 or ergocalciferol which is found in some fish and plants, and Vit. D3 or cholecalciferol which is present in the human body. Active Vit. D is synthesized in the skin by the effect of sunlight on the precursor of Vit. D. It is produced in the human body in two ways: ingesting or exposure to adequate direct sunlight. Vit. D has several crucial functions in the body from hormone properties to immune-modulating features.[1] It has a confirmed relationship with multiple disease states, and its deficiency is associated with overall morbidity in a variety of disorders such as cancer, autoimmune diseases, and cardiovascular diseases.[2]

Bio-activation and Function

At first, Vit. D is synthesized from 7-hydrocholestrol in the skin. Then, it is carried to the liver by its transporter (Vit. D-binding protein [DBP]). The initial hydroxylation is performed on the Vit. D precursor, which is transformed into 25-hydroxyvitamin D (25(OH)D), the inactive form of Vit. D, and at the end, it is transported to the kidney, where it undergoes the second hydroxylation, which produces 1,25(OH)D, an active form of Vit. D. The active circulating Vit. D then binds to the DBP in the plasma and impacts its various targets through the Vit. D receptor (VDR).[3]

The half-life of Vit. D in the body is 3 weeks, which should be supplemented either via nutrition or exposure to sunlight.[1] Vit. D exerts its effect by genomic reaction and protein synthesis via its specific receptor (VDR),[4] or non-genomic action through the cell membrane by another receptor, known as $1,25D_3$-membrane-associated, rapid response steroid-binding receptor (MARRS) (ERp57).[5]

In the bone, Vit. D regulates the genes responsible for bone remodeling, fertility, and glucose control. It seems that the optimal concentration of Vit. D facilitates

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Address for correspondence:
Dr. Sahar Vahdat, Department of Nephrology, Khorshid Hospital, Isfahan Kidney Diseases Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: s.vahdat11@yahoo.com

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the formation of bone, while higher levels of Vit. D lead to limited resorption and mineralization to sculpt bone. Vit. D has both catabolic and anabolic functions on the bone. The catabolic action of Vit. D is performed via attenuating osteoblastogenesis, which is opposed to parathyroid hormone (PTH). Vit. D has a beneficial effect on osteopontin as the activator of osteoblast, resulting in osteoblast survival, growth, and migration, which is the anabolic action on the bone.[3]

In the small intestine, Vit. D promotes the absorption of calcium through active (transcellulary in the duodenum) and passive (paracellulary across the length of the small intestine) mechanisms.[3]

In the colonocyte, as well as skin, VDR is expressed higher than other places such as the intestine, kidney, and bone. The main role of Vit. D in the colonocyte is detoxification by affecting the detoxification-related genes including CYPs, SULTs, and ABC transporters mRNAs.

Vit. D Action in the Kidneys

Vit. D2 and D3 are absorbed from diet in the intestine. Meanwhile, Vit. D3 can be produced by sunlight in the skin and both products are transferred to the liver where the initial hydroxylation occurs (23-hydroxylation). This major metabolite of Vit. D moves to external tissues and the kidneys for the final activation step, hydroxylation, and transforms into the active form of Vit. D (calcitriol),[6] which then conducts pivotal biological activities via its specific receptor (VDR).[7]

1,25D has a direct effect on phosphate reabsorption by VDR on the proximal tubule. The mentioned effect is achieved by the induction of the *klotho* gene and VDR element in renal tubules. In addition, 1,25D has a beneficial effect on the kidneys by a secreted form of klotho in cooperation with fibroblast-growth factors (FGFs).[8] 1,25D has also a noticeable effect on calcium absorption and metabolism.[9] 1,25D action in the kidneys impacts virtually every cell in the body by its receptor, VDR.[3]

On the other hand, Vit. D has a capital role in various diseases such as cardiovascular, brain, metabolism, cancer, and kidney diseases.[2]

Vit. D and Kidney Diseases

The level of Vit. D in various populations (e.g., 60% of older as well as younger people of North America)[10] is not desirable because of different reasons including inadequate outdoor activity, urbanization, air pollution, demographic shift, and lower production of Vit. D by the skin with the increase of age.[11] There are different reports regarding the status of Vit. D in various countries.[11-13] On the other hand, clinical studies have reported observations in patients with kidney disease. Levin *et al*. reported the abnormalities of mineral metabolism in early chronic kidney disease (CKD). In these patients, it has been observed that the level of the active form of Vit. D was higher than the glomerular filtration rate (GFR).[14] Moreover, the inverse relationship between Vit. D level and PTH, serum phosphate, FGF-23, and GFR was seen.[15] In a recent population-based study, an apparent association between PTH, Vit. D, and CKD was reported.[16] In CKD, the renal 1α-hydroxylase expression is inhibited to compensate for phosphate retention, which leads to an increased expression of 24-hydroxylase for the degradation of Vit. D. In dialysis patients, the level of Vit. D is lower than healthy people and the above adverse mechanism causes Vit. D deficiency in patients with kidney disease.[17] Kidney dysfunction, which is usually observed among patients with kidney disorders, participates in the production of Vit. D resulting in hypocalcemia and secondary hyperparathyroidism (HPT), which tend to cause secondary osteoporosis in the patients.[18] It has been observed that Vit. D deficiency in kidney disorders increases in severe disease stages.[19] Because Vit. D status has a reverse correlation with the progression of CKD, guidelines for diagnosis and treatment of CKD suggest that the level of Vit. D should be maintained at 30 ng/ml or higher.[20] Preventive insufficiency in Vit. D is common among more than 75% of CKD patients. However, impaired active form of Vit. D can sometimes be seen because of reduced renal enzyme 1α-hydroxylase.[21,22] In addition, Duranton *et al*. in their systemic review and meta-analysis reported that out of 13 eligible studies 10 concluded the inverse association between receiving Vit. D and the risk of death. In addition, they emphasized the beneficial effect of Vit. D in predialyzed and hemodialyzed patients. A 27% reduction of mortality rate was seen among CKD patients receiving suitable doses of Vit. D. The same beneficial effect of Vit. D was observed in early CKD while desirable effects were seen in severe HPT patients.[23] Kovesdy *et al*. reported the beneficial effect of Vit. D in predialysis CKD, including lower incidence of dialysis and reduced mortality rate among the Vit. D-user group compared to non-users of Vit. D.[24] Drechsler *et al*. found a significant association between Vit. D deficiency and adverse health outcomes in dialysis patients.[25] Teng *et al*. demonstrated that both mortality rate and cardiovascular-related mortality were significantly reduced during 2 years of using injectable Vit. D in comparison with the non-Vit. D group.[26] Filipov *et al*., in their investigation about the relationship between Vit. D status and immunosuppressive therapy in kidney transplant recipients reported that more than 80% of cases had Vit. D insufficiency.[27] Ngai *et al*. also found similar outcomes in more than 80% of CKD non-transplant patients.[28] Interestingly, Cankaya *et al*. found that Vit. D levels are higher in renal transplantation in comparison with peritoneal dialysis and hemodialysis patients.[29] However, it should be kept in mind that the beneficial effect of Vit. D does permit physicians to prescribe higher dosages for hemodialysis patients. It has been shown that a higher amount of 1 μg of active Vit.

D was not related to higher survival benefits, and conversely, could lead to adverse effects such as hypercalcemia.[30,31] In addition, the outcomes of insufficiency and deficiency of Vit. D in CKD and dialysis patients include secondary SHPT, high bone turnover markers, and low bone-mineral density, vascular classification, arterial stiffness, muscle weakness, insulin resistance, obesity, metabolic syndrome, left ventricular hypertrophy and atherosclerosis, higher mortality and progression of kidney disorders, and cognitive impairment.[18]

Vit. D, Adipose Tissue, and Adipokine

According to various molecular and clinical studies on the pathophysiology of kidney disease, it is a rational fact that adipose tissue has the most important role in the pathogenesis of kidney disorders. Hence, the effect of Vit. D in the adipogenesis and adipokines' activity will be discussed.

The association between Vit. D and obesity has been surveyed in observational human studies as well as *in vitro* and cell culture experiments. Vit. D has a direct effect on the adipogenesis process; however, the controversial reports have been received from human and murine investigations. On the other hand, clear results confirm the role of Vit. D in the different aspects of obesity measurement such as body weight and BMI.[32] Vit. D has a direct link with adipokine as one of the main elements having a capital impact on kidney function, and adipose tissue.[33]

An experimental animal study has shown that the enzyme that converts pre-Vit. D to active form is encoded in adipose tissue.[34] A study on humans also confirms this finding.[35] However, the exact role of Vit. D in human adipose tissue is still under investigation because only few studies have explored the expression of VDR in human adipose cell culture,[36,37] although it has been found in mouse adipocytes.[38,39] According to the reports about the evaluation of active Vit. D produced by human adipose tissue, the level of bio-activated Vit. D in mature adipocytes is considerably higher than in epithelial cells. Therefore, adipose tissue can provide biologically active Vit. D, which secretes in the blood circulation system and acts as an active hormone. Albeit, it should be kept in mind that the kidney is the main source of active Vit. D.[33]

Deficiency in Vit. D has been found to be the main cause of adiposity being one of the most significant public health concerns.[40] The results of 21 cohort studies from adult populations with more than 4200 subjects revealed that a higher incidence of BMI was in direct association with the lower levels of Vit. D.[41] Several studies have found that active Vit. D regulates inflammatory responses, which is the main cause of different metabolic disorders.[42-44] Vit. D inhibits adipogenesis and expands adipose tissue by suppressing numerous signaling pathways such as C/EBPα and PPARγ, which are required for adipogenesis.[45,46] It has been found that the mechanism of Vit. D on preadipocyte differentiation is due to its inhibitory function on the Wnt signaling pathway, which has a cofunction with β-catenin that leads to maturity of preadipocyte to adipocyte and further adipogenesis.[47] In reality, Vit. D performs this action by maintaining levels of Wnt and nuclear β-catenin, which leads to reduction of the peroxisome proliferator-activated receptors (PPARγ) transcription factor in these cells.[48] In bone marrow, Vit. D inhibits bone marrow stromal cell differentiation into mature adipocytes via suppression of Dikkopf-1 and secreted frizzled-related protein 2 through the Wnt signaling pathway.[49] On the other hand, it has been established that Vit. D has a positive effect on the differentiation of mesenchymal stem cells into adipocyte via promoting the levels of PPARγ, adipocyte adipocyte binding protein 2, and lipoprotein lipase (LPL).[50] A study on human tissue has revealed that Vit. D can trigger the expression of adipogenic markers such as FABP4 and LPL.[50] Further study about the role of Vit. D on mesenchymal stem cell proliferation showed that the presence of Vit. D causes the accumulation of lipids with enhanced adipocytes by adipogenic marker genes such as *FASN*, *PPARγ*, and *FABP4*.[51] Controversial functions of Vit. D on adipogenesis in different species and cell types clarify demand for further investigations about the exact role of Vit. D in adipose tissue in different species and different environments.

Excess accumulation of adipose cells leads to obesity, which is one of the main causes of metabolic diseases and kidney disorders.[52] Adipose tissue acts as an endocrine organ.[53] The secretory cells of adipose tissue such as adipocytes, foam cells, and precursor cells cause the release of adipokines such as adiponectin, leptin, and other factors, which take part in the regulation of appetite, energy expenditure, endothelial function, hemostasis, blood pressure, and inflammation.[54] Adipokines also regulate adipogenesis, migration of immune cells into adipose tissue, and modulate adipocyte metabolism and their function.[55]

Various studies have demonstrated that obese people are more likely to experience lower levels of Vit. D[40,56-59] due to increased sequestration via white adipose tissue, which could be a possible reason for the reduction of Vit. D bioavailability.[40,60] However, the thorough mechanism explaining the whole molecular pathway between Vit. D deficiency and adiposity is yet to be discovered. Recent investigations have presented the possibility of Vit. D in modulating adipogenesis (formation and function) by targeting adipose tissue directly.[34,35,38,45,61]

Regarding the fact that adipokines have a pivotal role in the health and diseases,[62] it seems that Vit. D can manage the adipogenesis well, directly or indirectly.

Conclusions

Vit. D has many benefits in bone, blood, homeostasis, and different organs such as the kidneys. As mentioned,

Vit. D has a capital role in the kidneys and related diseases. Many investigations have surveyed for the determination of the exact role of Vit. D in the kidney function and its relation with other organs such as adipocyte. Adipokines in cooperation with Vit. D can produce beneficial effects on health progression and disease prohibition. Considering the relationship between PTH and minerals (including phosphorus and calcium) and Vit. D and the role of Vit. D supplements in people with kidney failure and dialysis patients, Vit. D should be consumed sufficiently. Furthermore, these are some clear examples of the important roles of Vit. D in kidney function. The abovementioned close connection between Vit. D and adipokines guides us to become aware of the hidden possible functions of Vit. D in cooperation with adipose tissue; thus, physicians should consider many factors pertaining to patients with kidney diseases.

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Conflicts of interest

There are no conflicts of interest.

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