Impact of vitamin D on the immune system in kidney disease

Mohammad-Reza Ardalan[1], Houshang Sanadgol[2], Hamid Nasri[3], Azar Baradaran[4], Mohammad-Reza Tamadon[5], Mahmoud Rafieian-Kopaei[6*]

Abstract

When chronic kidney disease progresses, the capability to compensate for elevation in parathyroid hormone and fibroblast growth factor-23 and for decrease in 1,25(OH)2D3 become insufficient, which consequences in high serum phosphorus level, extra-skeletal calcification and abnormal bone disorders. Further to its effect on the regulation of parathyroid hormone, calcium and phosphate, vitamin D has various other non-calciotropic efficacies, comprising controlling cell proliferation/differentiation and having immunomodulatory properties. There are various immune disturbances that can be observed when function deteriorates. It is necessary to understand well both the classical and non-classical functions of vitamin D.

Keywords: Osteoporosis, Kidney, Vitamin D

Introduction

Chronic kidney disease (CKD) is an increasing dangerous situation which may not have any symptoms until considerable kidney damage. Chronic renal failure is described corresponding to the glomerular filtration rate and/or the presence of morphological injury to the kidneys or the presence of renal injury markers, such as proteinuria or hematuria, for three months (1-3).

Diabetes and hypertension are the most common causes of chronic kidney disease, however, there are several other causes such as:

a) Immune system involvement like hepatitis B and C, lupus and chronic viral illnesses such as HIV/AIDS, b) Inflammation in glomeruli within the kidneys, c) Pyelonephritis, d) Polycystic kidney disease, e) Congenital defects, often the result of malformation or urinary tract obstruction, f) Drugs and toxins, overuse of some drugs such as non-steroidal anti-inflammatory drugs (1-4).

Preventing aggravation of kidney function and its problems remains the principal conflict in the area of nephrology. Many complications are detected in these patients as the glomerular filtration rate worsens, consisting malnutrition, anemia, cardiovascular disease, fluid overload, protein energy-wasting, and mineral bone disorders (2-5).

As chronic renal failure extends, compensation for the raises in parathyroid hormone and fibroblast growth factor-23 and for decreased levels of 1,25(OH)2D3 becomes inefficient, ensuing in abnormal bone disorders, hyperphosphatemia and extra-skeletal calcification. In the treatment, activated vitamin D or its analogues are often used to treat individuals with secondary hyperparathyroidism and to prevent the kidney osteodystrophy (3-6). The classical actions of vitamin D are linked to skeletal health and mineral metabolism. Vitamin D controls parathyroid hormone, blood calcium and phosphate concentrations by actions affecting the parathyroid glands, intestines, bone and finally the kidneys. Moreover, non-classical functions for vitamin D, comprising anti-cell differentiation and anti-cell proliferative property with regard to several cell types, have become more and more crucial (1-7). The anti-cell differentiation impact has been associated with cancer epidemiology. More recently, serum vitamin D levels have been detected to be inversely correlated with

many malignancies, consisting breast cancer, pancreatic cancer, head and neck cancer, prostate cancer and colon cancer. Various studies had detected an inverse correlation between 25-hydroxyvitamin D levels and whole cancer incidence and mortality. Moreover, vitamin D has an immunomodulatory property, too (4-9). This immunomodulatory property is based on the broadly expressed vitamin D receptor that is present in the immune system. Traditionally most persons derive the majority of their vitamin D from the exposure to the sunshine. In this process, cholesterol in the skin, enzymatically converted to 7-dehydrocholesterol and subsequently converted to an unstable complex, previtamin D, by the action of ultraviolet. Various nutrients, like fatty fish and some types of mushrooms, also contain major forms of vitamin D, namely, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) (7-14). These substances are subsequently activated throughout a sequential two-step process that first comprises 25-hydroxylation in the liver to produce 25(OH)D and next 1-hydroxylation, which supposed to happen primarily in the kidney, to produce the active product 1,25(OH)2D3 or calcitriol. The key enzyme in this process is 1-hydroxylase, which is expressed principally in proximal tubular epithelial cells of the kidney (12-16). This enzyme is also expressed in various parts of the kidney and in extra-kidney tissues. An individual's It is generally accepted that, serum 25(OH)D level is a person's vitamin D condition (2-8,12-16). The major plasma carrier for vitamin D metabolites is vitamin D-binding protein. Vitamin D-binding protein, has the maximum affinity to 25(OH)D, and nearly all plasma 25(OH)D is bound to vitamin D-binding protein(VBP). The 25(OH)D-VBP complex is selected up by the proximal convoluted tubules by an endocytic receptor, megalin. The last step in the vitamin D metabolic pathway is its inactivation, a course catalyzed by 24-hydroxylase, which catabolizes the conversion of both 1,25(OH)2D3 and 25(OH)D into 1,24,25(OH)3D and finally into water-soluble calcitroic acid and the inactive plasma metabolite 24,25(OH)2D (3-9). In patients with chronic renal failure, serum 1,25(OH)2D3 levels decrease early in the course of renal dysfunction, even before any variations in serum phosphorus or calcium concentrations happen and preceding to any rise in serum parathormone levels. Increasing fibroblast growth factor-23 levels may play an even larger role in controlling 1-hydroxylase activity. Serum values of fibroblast growth factor-23 are regulated by circulating phosphorus levels and increase as chronic renal failure progresses, becoming noticeably elevated in patients with end-stage renal failure (1-5,12-19). In patients with chronic renal failure, calcitriol levels are inversely associated with levels of circulating fibroblast growth factor-23, proposing that the hormone may play a substantial role in mineral metabolism. In general, most patients of chronic renal failure have low levels of 25(OH) D. Consequently of the substrate-dependent process that forms 1,25(OH)2D3, a low 25(OH)D level contributes to vitamin D deficiency (6-10). Various other factors may contribute to vitamin D deficiency, consisting a low protein diet, a lack of sunlight exposure, reduced 1-hydroxylase activity resulting from a reduction in kidney mass and tubular dysfunction, decreased skin synthesis of 1,25(OH)2D3 in response to sunlight compared with an individual with normal kidney function and loss of 25(OH)D-VBP due to heavy proteinuria (8-16). Also diabetes and various chronic diseases. These data suggest that the mixed effect of a decrease in the ability of the kidney to produce 1,25(OH)2D3 and an increase in kidney metabolism of 1,25(OH)2D3 may be related to the high prevalence of vitamin D insufficiency among chronic renal failure patients (1-9).

Immune system in chronic renal failure patients
Immune dysregulation, compared to the general population, is a characteristic of chronic renal failure and end-stage kidney disease patients on the replacement therapy. These patients have a high vulnerability to infection and a poorer response to vaccination (7-12). Various factors affect the immunity of these patients, like chronic inflammation, malnutrition, uremic toxin, vitamin D-parathyroid hormone axis fluctuation. Many investigations have detected that the naive and acquired immune system are disturbed in these patients. According to their immunity dysregulation, hemodialysis patients have accelerated atherosclerosis, more vascular calcification, increased insulin resistance, a loss of appetite, increased muscle catabolism and kidney osteodystrophy. Importantly, they also have coexisting chronic immune activation presented as acute-phase

protein response, persisted hypercytokinemia and chronic immune suppression which present as a poor vaccination response and a high occurrence of infection and malignancy (10-19). Noticeably, monocytes of chronic renal failure patients are disturbed with respect to endocytosis and maturation. Chronic renal failure patients have a lower percentages of T and B lymphocytes, in the blood and peripheral T lymphocytes (4-12). Moreover, various studies have also found that there is an increased incidence of B cell apoptosis in chronic kidney failure. Importantly, end-stage kidney disease patients show increased apoptosis and abolished population of naïve and central memory T cells in association with impaired antigen-specific memory. The innate immune response, which comprises macrophages, natural killer cells and their monocyte precursors, play essential role in initial responses to pathogenic organisms or tissue injury. Their role is to consume pathogens and cell debris by phagocytosis and then remove the resulting waste material (8-16). The action of vitamin D on macrophages contains the capability to stimulate the differentiation of precursor monocytes into more mature phagocytic macrophages. Macrophages have 1-hydroxylase and need sufficient ambient quantities of 25(OH)D substrate to generate internal 1,25(OH)2D3 (5-14). In macrophages, vitamin D suppresses nuclear factor-B activity. Decreased macrophage function under circumstance of vitamin D inadequacy has been found in patients who are vitamin-D inadequate. Vitamin D could have a significant role in promoting tolerogenic dendritic cells by modifications in their morphology and function. Many investigations have focused on treatment with 1,25(OH)2D3 to modify immune function in chronic renal failure and end-stage kidney failure patients. 1,25(OH)2D3, when used in HD patients with secondary hyperparathyroidism, is able to enhance Th2 cell differentiation and decrease IL-6 expression. 1,25(OH)2D3, also can diminish inflammatory and oxidative stress in hemodialysis patients (15-22). In hemodialysis patients, a low plasma level of 25(OH)D is associated with a high panel of reactive T cell, which means that vitamin D insufficiency is associated with a poor post-transplant outcome. In the conditions of acute renal injury, vitamin D insufficiency appears to predispose patients towards an increased risk of sepsis, endothelial dysfunction and also prevents the healing of kidney ischemia-reperfusion injury. In hemodialysis patients, vitamin D is capable of reducing platelet activating factor/thrombin activity and metabolism and lower serum IL-6, IL-8 and IL-1 levels, while all of these factors are inflammatory markers (18-26).

Conclusion

The broad tissue distribution of 1-hydroxylase and vitamin D receptor has recognized a role for 1,25(OH)2D3

in the pathophysiology of various diseases and this has postulated a therapeutic role for the 1,25(OH)2D3. Increasing evidence point out that the usefulness of vitamin D expands beyond its classical role in maintenance of mineral homeostasis and, in this situation, the present use of active vitamin D contains the treatment of secondary hyperparathyroidism in chronic renal failure. Additionally, vitamin D inadequacy is common amongst chronic renal failure patients and indeed may contribute to deterioration in their renal function. Moreover to the supplementation of chronic renal failure patients with 1,25(OH)2D3, it is probable that, by reducing any 25(OH)D deficiency and treating secondary hyperparathyroidism, we may be able to adequately increase both the kidney and extra-renal pathways of 1,25(OH)2D3 synthesis. This will keep both the classical and non-classical functions of vitamin D and finally influence the clinical outcomes of this high-risk group of patients.

Authors' contributions

All authors wrote the paper equally

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflict of interests

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