Vitamin D deficiency in chronic renal failure patients; current knowledge and new trends

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Abstract
Chronic kidney disease (CKD), or chronic renal failure at final stages requires hemodialysis treatment. One of complication of these patients on hemodialysis and even CKD is the deficiency of vitamin D. Inadequate exposure to sun rays and poor dietary containing vitamin D can lead to its deficiency. Vitamin D deficiency in these patients may lead to osteomalacia in adult and rickets in children. Appropriate levels of 25(OH)D and parathyroid hormone, can decrease complication of extra-renal disease and mortality in both hemodialysis and chronic kidney disease patients.

Keywords: Vitamin D, Chronic kidney disease, Hemodialysis, Osteomalacia, Vitamin D deficiency

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Introduction
There are two primary forms of vitamin D including dermal and dietary (cholecalciferol), that principally have non-functional activity. For activation of this vitamin and playing its important roles on the human body, these two primary forms need to be activated by specific hydroxylase enzymes that are located in the liver and kidney. Vitamin D transfers by the bloodstream to the liver and by hydroxylase enzyme, it converts to 25(OH)D (calcidiol). This form of vitamin D (cholecalciferol), that is also a prohormone, has not affinity as much as an activated form of vitamin D for binding to vitamin D receptors. Then, calcidiol is converted to calcitriol by 1 alpha-hydroxylase enzyme in the kidney. Studies showed that not only kidney can convert calcidiol to the active form of vitamin D (calcitriol), but other cells can convert cholecalciferol to calcidiol. Except for 1-a hydroxylase in liver, other cells in colon, parathyroid glands and even activated macrophage have also this enzyme (2,5-7).

Materials and Methods
For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; vitamin D, chronic kidney disease, hemodialysis, osteomalacia, chronic renal failure, vitamin D deficiency, 25(OH)D, 1-a hydroxylase, calcitriol, vitamin D receptor, parathyroid glands, parathormone, PTH, calcidiol, kidney and cholecalciferol.

Causes of vitamin D deficiency
Chronic kidney disease (CKD) at final stages requires hemodialysis treatment. One of complication of these patients on hemodialysis and even CKD is the deficiency of vitamin D. Inadequate exposure to sun rays and poor dietary containing vitamin D can lead to its deficiency. Vitamin D deficiency in these patients may lead to osteomalacia in adult and rickets in children. While we can categorize vitamin D deficiency in normal population into different subgroups like race, geographic latitude,
the rate of sun exposure, the rate of skin pigmentation and intake of dietary vitamin D, however in CKD patients requiring hemodialysis, these causes have a wider range (8,9). For example, decreased physical and outdoor activity (10,11) and lower rate of cholecalciferol skin synthesis (12) may be responsible. In addition, deficiency of vitamin D 25-hydroxylase enzyme which is located in kidney, is another important factor for this deficiency. Furthermore, deficiency of activated form of vitamin D or deficiency of calcidiol is also detectable in CKD patients. For determining normal serum levels of 25(OH)D for both general population and CKD patients, there is no established reference. It should be noted that serum levels of calcidiol lower than 50 and 25 nmol/L should be regarded as insufficiency and deficiency of this hormone respectively. However, some other studies suggested serum levels of 25(OH)D of 30 ng/mL as optimal values. This recommended level for 25(OH)D is accompanied by maximal suppression rate for parathyroid hormone hypersecretion and other aspects like decreased rate of fracture and even health situation of dialysis patients (12-18). Recent investigations for insufficiency and deficiency of 25(OH)D in patients with stage 5 CKD demonstrated that low 25(OH)D is prevalent in CKD. Additionally, other conditions like gender, high BMI level and decreased rate of sun exposure can worsen serum levels of 25(OH)D too (19).

Many researches showed deficiency of both 25(OH)D and 1,25(OH)2D in hemodialysis patients. This deficiency in both forms of vitamin D is an independent factor for mortality in such patients beside other factors like residual renal function that is known as a predictor factor mortality in hemodialysis patients (20,21).

Vitamin D deficiency and other hormones

Studies demonstrated a reverse relationship between serum level of PTH with circulating 25(OH)D seasonal serum level variation (22). In addition, an association between serum level of 25(OH)D and sun exposure is also confirmed, however the variation in serum level of 25(OH)D, did not cause a significant effect on calcium absorption, fraction and urinary calcium excretion in healthy men (23). However, seasonal variation of 25(OH)D has relationship and mineral density of skeletal system (24). Although serum level of 25(OH)D in hemodialysis patients is usually low, studies demonstrated that by correction of food regimen for hemodialysis patients, the decreased serum level of 25(OH)D will improve. For example, giving cholecalciferol in hemodialysis patients can improve their decreased serum level of calcidiol (25). In a prospective study, an inverse correlation between 25(OH)D level and future insulin resistance and hyperglycemia status was detected (26). Evaluation of another aspect of 25(OH)D on endocrine system showed a significant inverse relationship between risk of diabetic type 2 and serum level of 25(OH)D (27).

Vitamin D deficiency and cancer

Nowadays, pathological findings of cancer causes revealed some hidden actions of 25(OH)D on prevention of cancers. In a study in the United Kingdom, a relationship between increased rate of breast cancer and lower serum level of 25(OH)D was detected (28). In addition, the rate of both breast cancer incidence and its metastases were decreased with higher 25(OH)D serum level compared to group with lower serum level (29). Evaluation of cholecalciferol on esophageal squamous cell carcinomas revealed that increased concentration of 25(OH)D has a linear relationship with risk of esophageal squamous cell carcinomas. However, the increased risk of esophageal squamous cell carcinomas was observed in men but not in women population. This study could not find any correlation between the serum level of this vitamin with risk of gastric adenocarcinoma (30). It is possible that the deficiency of 25(OH)D has various effects on different population. As an example, the effect of 25(OH)D on ovarian cancer was different among women. Overweight women with decreased pre-diagnostic serum level of 25(OH)D have higher risk of ovarian cancer, but this study on thinner women did not show any association (31). Individuals with higher serum level of 25(OH)D than 33 ng/mL have about 50% decrease in the incidence of colorectal cancers (32,33).

Vitamin D deficiency and autoimmune disease

Except for cancers, autoimmune disease can also have a relationship with concentration of 25(OH)D. In a cohort study that divided individuals into three groups according to their 25(OH)D serum levels, in first group serum level was normal (more than 30 ng/mL) and second was in insufficient range lesser than 30 ng/mL and third group was in deficiency range (less than 15 ng/mL). In such study, comorbid autoimmune illness had a direct relationship with very low 25-hydroxyvitamin D. In the insufficient group, Fitzpatrick phototypes increased (34). The musculoskeletal system can also be under influence of vitamin D. A recent study carried out in the UK showed that the deficiency of vitamin D may be a common finding in patients who have psoriasis (35). Another study evaluating vitiligo and its associated comorbidity showed that more than half of patients have insufficiency of 25-OH vitamin D. These finding demonstrated the impact of vitamin D on autoimmune diseases (36).

Complication of 25(OH)D deficiency

There are numerous studies that evaluated serum level of 25(OH)D among many different diseases. Besides its significant effect of this vitamin on skeletal system,
it has been detected that low concentration of 25(OH)D is associated with worse prognosis of patients who have heart failure (37). There is also an increase in the incidence of cardiovascular disease and vitamin D deficiency (38-40). One of these reasons that deficiency of 25(OH)D has a significant effect on the cardiovascular system is due to detection of vitamin D receptors in many structures of this system like endothelial and cardiac myocytes (41). Regarding concentration of 25(OH)D and its association with systolic and diastolic blood pressure, there are no definitive studies. Some studies demonstrated its significant effect on blood pressure; however, other studies did not detect this result (42,43). Deficiency of this vitamin has also effect on psychological and mood disorders. Some studies evaluating serum level of 25(OH)D in such patients, showed that 25(OH)D has lesser concentration in patients having depression disorders. Interestingly, the severity of depression was directly related to low levels of 25(OH)D in such patients (44,45). Effect of this vitamin on muscular activity is also noted. In a study carried out on patients with lower serum level of 25(OH)D, the relationship of 25(OH)D level with inferior physical activity, low gait speed and balancing was demonstrated. Furthermore serum level of 25(OH)D less than 20 ng/mL can increase the risk of bone fracture in such patients (46). Decreased 25(OH)D has a negative impact on risk of surgery and complications of intestinal bowel disease (IBD). Importantly, the correction serum level of 25(OH)D decreased these complications. Correction of serum level of 25(OH)D had an ameliorative impact on inflammatory bowel disease (47). As deficiency of cholecalciferol has a relationship with prognosis and complication of several diseases, it is associated with early mortality among hemodialysis patients too (48). On the other hand, in a cohort study, parathyroid hormone (PTH) had a role in controlling of calcium, independent of vitamin D status. PTH acts on kidney and bone mass, which is associated with a higher mortality rate in aging population and hemodialysis patients too (49).

Conclusion
These studies showed that fine follow-up of some important elements like serum level of 25(OH)D and PTH can decrease complication of extra-renal disease and mortality in both hemodialysis and CKD patients.

Authors’ contribution
MAN and AN contributed equally to wrote the manuscript.

Conflicts of interest
The authors declare no conflict of interest.

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

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