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Review

Vitamin D and chronic kidney disease

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Abstract

Prevalence of hypovitaminosis D is increasing in the world especially among poor countries and it has many varieties of manifestation and disease including rickets in children and osteomalacia and osteoporosis in adult. It also can affect on functional of some organ like renal and cardiovascular system and even has effect on mortality rate of some of these patients. Inadequate vitamin D in food regimen is one of reasons of hypovitaminosis D. The production of active form of this vitamin mainly is located in kidney cells, therefore end-stage renal disease (ESRD) patients or patients who have chronic kidney disease (CKD), have high chance for low serum level of the active form of this vitamin. Secondary hyperparathyroidism and renal osteodystrophy which are important side effect of CKD, be happen because of deficiency and defect in absorption of this vitamin. According to rapid increase in the prevalence of hypovitaminosis D, the aim of this review article is to summarize some of investigation about hypovitaminosis D especially among patients who have CKD.

Keywords: Hypovitaminosis D, Secondary hyperparathyroidism, Renal osteodystrophy, Parathormone, Chronic kidney disease, End-stage renal disease, 25-hydroxycholecalciferol, Rickets, Osteomalacia

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Introduction

Nowadays, new studies evaluating epidemiologic and other statuses of vitamin D, addressed that prevalence of hypovitaminosis D is increasing especially in poor countries but in development countries this deficiency of vitamin D is not significant (1,2). Deficiency or insufficiency of vitamin D has many variety of manifestations and diseases. Because this important vitamin can change rate of absorption of some mineral metabolites like calcium and phosphor, low serum level of this vitamin decreases absorption of both calcium and phosphor and can cause rickets in children and osteomalacia and osteoporosis in adult. Except inadequate vitamin D in food regimen that is one of reasons of hypovitaminosis D, poor renal function or chronic kidney disease (CKD) in these persons, can trigger hypovitaminosis D. While, production of active form of this vitamin mainly is located in kidney cells, end-stage renal disease (ESRD) patients or patients who have CKD, have high chance for low serum level of this active form that has important role in absorption of calcium and phosphorus from gastrointestinal system and through renal function, according to its role. Such patients are at calcium deficiency risk and other related diseases.

Materials and Methods

For collecting data about this review article, we have used very relevant articles that discussed about different aspect of our subject from different databases like PubMed, Current Content, Embase. Selection of related articles from these sites was carried out by searching some keywords like hypovitaminosis D, secondary hyperparathyroidism, renal osteodystrophy, parathormone (PTH), chronic kidney disease, end-stage renal disease, 25-hydroxycholecalciferol, rickets, and osteomalacia. We included full text articles and abstracts in this review article that were written in English language.

Synthesis of vitamin D in body and its role

Vitamin D is one of the fat-soluble type of vitamins. This vitamin has five types that some types of this vitamin, are major form of this vitamin like vitamin D2 and vitamin D3 that respectively be called ergocalciferol and cholecalciferol. There are little food that contain this vitamin (3). The major way of production of this vitamin is by its production in skin under sun exposure. This type of vitamin D that synthesizes in skin, is its inactive type, but enzymes that are in liver and kidney can change it into active form. Both of vitamin D2 and vitamin D3, converted to 25-hydroxyergocalciferol and 25-hydroxycholecalciferol (calcidiol), respectively. Both of these types of vitamin D are measured to estimate status of vitamin D in body and its stores condition. Among various forms of this vitamin that circulate in human body, form of this vitamin (25(OH) D) that converted in liver has higher half-life time com-

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Implication for health policy/practice/research/medical education

Hypovitaminosis D has high prevalence among many countries. This vitamin can affect on functional of some organ like renal and cardiovascular system and even has effect on mortality rate of some patients like end-stage renal disease (ESRD) patients. While, deficiency of this vitamin, is very more common than its hypervitaminosis, more researches need to be carried out for determining exact needed supplement dosage for inhibition of vitamin D deficiency.

pared to other forms of vitamin D. In fact, 25(OH)D that produced by liver enzyme has about 14 to 21 days half-life time, but other form of this vitamin that converted by kidney enzyme (1,25(OH)2D) has shorter half-life time, about 4 to 5 hours in body. Kidney can convert calcidiol into calcitriol by its enzymes. Calcitriol that is produced in kidney is active form of vitamin D and has role as a hormone (4-6). This vitamin has very important role in some mineral homeostasis and metabolism like calcium. Not enough sun exposure and poor food regimen and dietary that contain low vitamin D, various malabsorptive disorders and impaired function of some enzymes in liver and kidney that convert vitamin D into active form, can result vitamin D deficiency. Vitamin D deficiency is becoming a global health issue because of its increasing prevalence of it in different communities especially in some groups of population like children and adult. Deficiency of this vitamin can cause different disease like rickets, osteomalacia (7-9).

Excess of vitamin D

On the other hand, excess of this vitamin is uncommon. Vitamin D toxicity can result hypercalcemia and its excess in human body causes its deposition in some organs like liver, kidney, heart and other soft tissues that are in body that can damage to these organs. Intake of more than 4000 IU/day can cause vitamin D toxicity. Some manifestations of vitamin D toxicity that hypercalcemia is one of them, is polyuria, polydipsia, weakness, confusion, weakness in muscle, anorexia, nausea, disturbance in nervous system, and pruritus. Some of these excess of calcium in serum in calcium can be manifested in renal (10-13). For example, proteinuria, existence of tubular casts, azotemia, metastatic calcification in renal, stone formation in renal and even renal failure in such patients can be seen (14).

Vitamin D and its relation with other diseases

Active form of this vitamin plays an important role in absorption of calcium in gastrointestinal system. In addition calcitriol affects to receptors in parathyroid gland and decreases release or production of PTH hormone (parathormone) by its binding to these receptors and then have important role for prevention of secondary hyperparathyroidism. According to this effect, in CKD patients, deficiency of calcitriol can predispose such patients to secondary hyperparathyroidism (15-18). According to this function, and role of this vitamin in absorption of calcium, deficiency of this vitamin, can cause some calcium deficiency related diseases like rickets in children that are in growing period of time. Except rickets, there are many other disorders that can manifest when this type of vitamin reach to deficiency level of its in body. Examples of diseases that are associated to vitamin D deficiency are; rheumatoid arthritis(19,20), some disorders in mood (21, 22), type 1 diabetes (23,24) and inflammatory bowel disease (IBD). Further researches showed that, there is associated risk in vitamin D deficiency and some cancers like breast, colon, and prostate in whom that have deficiency in vitamin D (25-28). These findings led to some recommendations for preventing of vitamin D deficiency.

Existence of guideline for prevention of hypovitaminosis D

Some new researches showed that intake of about 400 unit vitamin D daily in neo infants can prevent its vitamin deficiency and further problem and disorders that can happen through the vitamin deficiency. Intake of about 600 unit for young people between 1 to 18 years old is enough for preventing deficiency (7,29-31).

Vitamin D and its role on cardiovascular system

There are many researches that demonstrate, the link between level of calcium and 25OHD in blood circulation and blood pressure (32). Calcium supplementation and reaching of vitamin D serum level to higher than deficiency level can affect on diastolic blood pressure in hypertensive group (≥140/90 mm Hg) in two sexes, although this reduction in blood pressure was low. However, its effect on systolic blood pressure level was not as much as diastolic pressure (33-40). There is inverted relationship between serum level of calcitriol and calcification in cardiovascular system. It is interesting to note that, there is a form of vitamin D (alfacalcidol) which can prevent vascular calcification in such patients. In addition, relationship between level of some forms of vitamin D and vascular calcification can be very different among various races and descents. For example, high serum level of calcidiol can raise risk of aorta and carotid calcification plaque among African Americans, but this relationship has different results among other races (39-44). Besides effect of vitamin D on cardiovascular system, other researches on vitamin D showed that serum concentration of vitamin D and 25(OH)D can also have role in diabetes 1, 2 and obesity. Lower level of 25(OH)D can have linear correlation in developing diabetes in males. Relationship between this vitamin and type 1 diabetes can be because of its effect on other body system specially, on immune system (45-47). Except two types of diabetes, metabolic syndrome can be affected by the status of vitamin D in body (48,49). As discussed earlier, this vitamin has a role and effect nervous system and psychiatric status, because receptors of vitamin D and enzymes that converted this vitamin to active form of it, presented in the brain cells. According to the presence of these receptors and related enzymes, vitamin D has a role in neural function and its development. In

this regard, some researchers noted that, a lower than normal of vitamin D level in some nervous disorders like Alzheimer, in comparison to normal persons (50,51).

Deficiency in dihydroxyvitamin D3, can be happened in patients who have ESRD or chronic renal disease with poor renal function. This deficiency in vitamin D3 is due to decrease in kidney size and more production of fibroblast growth factor (FGF 23). This factor that is produced in osteocyte, is inhibitor of 1 alpha hydroxylase enzyme in kidney that can convert vitamin D3 into active form of it (52-55). In addition, some researches demonstrated that there is resistance to parathyroid hormone in such patients. Therefore, hypocalcemia that is one of the many manifestations of CKD and in long term of it, can cause other disorders like secondary hyperparathyroidism, osteodystrophy in renal in long time. These abnormalities in some mineral metabolisms like phosphorus, calcium and adjustment on their concentrations that happen in CKD, is due to defect in kidney dysfunction. For example, disorder in calcium metabolism may show itself in different ways in CKD patients. One of them, is defect in bone mineralization and its volume, calcification in vessels and other many calcium related abnormalities that can be seen in these patients (56-60).

Staging of renal failure and some of its manifestations

For determining stage of renal failure in CKD, there are some criteria. Glomerular filtration rate (GFR) is useful for staging of renal failure. Individuals that their GFR is lesser than 60 ml/minute/1.73m^2 in about 90 days, is considered as CKD whatever renal injury be present in kidney or not. In stage 1 of CKD, GFR is more than 90, in stage 2, between 89-69, in stage 3 is between 30-59, and between 29-15 in fourth stage, finally in fifth stage, GFR is below 15 ml/minute/1.73 m^2. In this stage, we called this situation ESRD. Renal replacement therapy is done in whom have stage 5, but this preparation for transplant, is better that be done in fourth stage of CKD patients. CKD can be identified by serum level of creatinine (breakdown metabolic that produced in kidney). However, it is important to note that in early stage CKD, serum level of creatinine is in normal range but this amount of creatinine , can rise after passing time and become higher in later stages. There are many signs and symptoms for CKD. Some of these signs and symptoms for CKD patients are; hyperphosphatemia, hypocalcemia, hyperkalemia, elevation in serum nitrogen and creatinine, metabolic acidosis, iron deficiency, decrease in erythropoietin level because renal dysfunction in such patients, fluid volume overload due to inability of kidney to excretion of fluid that cause edema or even pulmonary edema, and even some dysfunction in sexuality disorders. As CKD has many manifestations, there are different reasons for happening CKD. Diabetes mellitus, hypertension, glomerulonephritis are common causes of CKD, but among these reasons, diabetes mellitus has more prevalence. There are also other diseases like polycystic renal disease and vasculitis. But these types of disorders have lesser prevalence. When patients have CKD, risk of cardiovascular diseases such as heart disease, elevated level of lipids in blood, increase this elevation in cardiovascular disease in such patients has relationship with high mortality rate of CKD patients. Decreasing the progression rate of this disease, is main treatment of CKD. Some drugs like angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonist (ARBs) that decrease blood pressure, can slow progression rate of CKD. Moreover, these drugs that affect on CKD progression, have positive effect on decreasing hypertension that is very common in such patients. Therefore, these drugs, can also lower risk of cardiovascular disorders. In addition to these modalities, some researches, showed benefit in using of erythropoietin and calcitriol in people who are in high-level of renal dysfunction. For treatment of anemia in CKD patients, target hemoglobin level in blood is about 12g/dl. In addition, for treatment of other abnormalities that may cause by CKD, other drugs can be used, such as phosphate binders that is administered to control of hyperphosphatemia in these patients. Finally in fifth stage of CKD, renal replacement therapy is preferred (60-70).

Renal osteodystrophy

Advanced CKD is a life-threatening disease with significant complication including renal osteodystrophy (71-80).

When there is CKD, secondary hyperparathyroidism that occurred in such patients, this renal osteodystrophy is happened because of deficiency and defect in absorption of this vitamin. Some manifestations of this disease in CKD patients are; deformities in skeletal structure, and some joint abnormalities like slipped capital femoral epiphyses (81).

Growth of bone in CKD

As low serum dose of parathyroid hormone can cause decreased bone turn over, on the other hand excess secretion of this parathyroid hormone because of renal impairment in electrolytes balancing like sodium, potassium, calcium, and other minerals are in serum, epiphyseal and growth plat destruction and fracture in some parts of bone like metaphyseal can also be seen (82).

Hypovitaminosis D and cancer

Recent researches demonstrated that deficiency of vitamin D in some cancers can affect the outcome of these patients, but there is no enough data that can show vitamin D supplements can have sufficient effect on such cancerous patients with hypovitaminosis D. Moreover, according to the low level of this vitamin in cancerous patients, some other researches demonstrated that death risk in these patients decreased by administration of vitamin D supplements (83,84).

Obesity and vitamin D

Decreased serum level of vitamin D also is found in obese persons. This decreased serum level of vitamin D in blood is maybe due to decreased absorption of this vitamin in gastrointestinal system and also its lower pro-

duction in skin due to elevated fat cells under skin and in adipose tissue. In a research, carried out in Spain, more than 1200 persons evaluated in this analysis, and relationship between deficiency of this vitamin and obesity was shown (85).

Vitamin D deficiency in CKD

Recently it was detected that insufficiency of 25OHD is common whatever renal replacement therapy is done in such patients or not. Similarly, it was shown that, vitamin D supplementation may improve status of this vitamin in whom needed peritoneal dialysis (80-87). More recent findings demonstrated that supplementation can improve serum level of PTH and related electrolytes and its correction in in PD patients(80-86).

Mortality risk and vitamin D in CKD

Outcome of advanced CKD patients is catastrophic and is much worse than the general population (86-88). Pilz et al showed that, when serum level 25(OH)D is higher in CKD patients, survival of these patients is better, and this result in study demonstrated no difference between patients with dialysis or without it. Supplementation of one form of vitamin D that is vitamin D3 can improve and reduce mortality risk in older persons. However, in other studies supplementation of other forms of this vitamin for example vitamin D2, calcitriol has shown no effect on reduction in mortality risk (85-88).

Conclusion

Hypovitaminosis D has high prevalence among many countries. This vitamin can affect on functional of some organ like renal and cardiovascular system and even has effect on mortality rate of some patients like ESRD patients. While, deficiency of this vitamin, is very more common than its hypervitaminosis, more researches need to be carried out for determining exact needed supplement dosage for inhibition of vitamin D deficiency.

Authors' contribution

MAN, SS and ZBM, searched the articles and gathered the data, SAH, HK and FH, prepared the primary draft. FH prepared the final manuscript. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

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

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