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Impact of vitamin D deficiency on health with regard to kidney disease; an updated mini-review

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ABSTRACT

Vitamin D or cholecalciferol, as a steroidal hormone, regulates the calcium homeostasis, and bone formation with reabsorption through kidneys, parathyroid glands and bowel. There are at least 800 human genes connected with vitamin D. Previous research has confirmed the relationship between vitamin D and colorectal cancers, infections, heart diseases, multiple sclerosis (MS), bone disorders, inflammatory and autoimmune diseases, inflammatory bowel diseases, diabetes mellitus type-I and II and also progression of kidney disease. However, the relationship of vitamin D deficiency and developing of breast cancer, rheumatoid arthritis and osteoporosis is unknown. In fact, the effect of vitamin D deficiency on pathogenesis of different diseases is controversial. To cope with vitamin D deficiency, there are different recommendations such as daily intake of vitamin D supplements and more exposure to sunlight.

Mini-Review

Implication for health policy/practice/research/medical education:
Vitamin D deficiency was only limited to rickets in children and bone related disorders in adults in the past. However, nowadays it has also been associated with the pathogenesis and/or progression of many other diseases such as hypertension, multiple sclerosis (MS), diabetes, cancer, and renal disease. Despite this close relationship of vitamin D deficiency with human diseases, vitamin D insufficiency is not widely recognized as a problem by people, especially patients and physicians as well as health policy makers. It is recommended to conduct further studies on this association to clarify the exact effect of vitamin D deficiency as well as supplement therapy with vitamin D on human diseases.

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Introduction

Vitamin D (cholecalciferol), is a hormone with steroidal structure, regulates the calcium homeostasis, and bone formation with reabsorption through kidneys, parathyroid glands and bowel (1). There are many studies regarding the reported association between vitamin D and various diseases and their treatment as well as health maintenance mentioning the high prevalence of vitamin D deficiency, most of them because of diet as well as other potential reasons such as low exposure to sunlight (2). In addition, there are at least 800 human genes connected with vitamin D (3). In fact, vitamin D

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has many substantial roles in many vital processes such as cellular growth and differentiation, metabolism of calcium, bones, cardiovascular and immunity functions (4). For example, it has been confirmed that vitamin D can prevent rickets and osteomalacia and may have an influence on immune modulatory, anticancer and innate immune through vitamin D receptor (5). Moreover, vitamin D is vital for function of muscles through affecting on muscle metabolism (6). The main potential risk factors for vitamin D deficiency may include age more than 65 (7), obesity (8), kidney disease (9), liver disease (10) and environmental factors such as frailty, decrease outdoor physical activity and institutionalization (11). However, the effect of vitamin D deficiency on pathogenesis of various illness is controversial (12).

In the 1980s, Barker et al reported that low-birth weight in early life could lead to coronary heart diseases later in life (13). In fact, vitamin D can play a substantial role in the development of fetal organs such as brain, lungs and bone which has been supported by experimental studies; it is recommended that until conducting more studies in this regard, using the vitamin D supplement by pregnant women could be very helpful (14). In addition, previous research has confirmed the relationship between vitamin D and colorectal cancers, infections, heart diseases, multiple sclerosis, bone disorders, inflammatory and autoimmune diseases, inflammatory bowel diseases, diabetes mellitus type-I and II; however, the association of vitamin D deficiency and developing of breast cancer, rheumatoid arthritis and osteoporosis is unknown (15).

Materials and Methods

The databases of PubMed/Medline, EBSCO, EMBASE, Web of Science, directory of open access journals (DOAJ), Scopus, and Google Scholar were searched with keywords of vitamin D deficiency, kidney diseases, cancer, cardiovascular diseases, sunlight, chronic kidney disease, end-stage renal disease, hemodialysis, hypertension, all-cause mortality, diabetes mellitus, cholecalciferol, left ventricular hypertrophy, proteinuria, insulin resistance, inflammation, albuminuria and Sunlight.

Vitamin D deficiency in general

The relationship between vitamin D deficiency and different diseases have been reported in many studies, both observational and randomized trials (16). It has also reported that lower vitamin D consumption during pregnancy or early childhood could increase the risk of wheezing and asthma in later childhood and the offspring, respectively (17). The linkage between vitamin D and many health conditions have been investigated such as cardiovascular diseases (18), cancer (19), metabolic disorders and diabetes (20), early age at menarche (21), multiple sclerosis (MS) (22) and mortality (23). However, despite these relationships, the clear role of vitamin D is not known yet (16). Vitamin D could also play an important role in periodontal disease by maintaining oral health via its potential effects on metabolism of minerals and bones as well as innate immunity (5). If these relationships are causal, it would highlight the importance of vitamin D deficiency for public health, especially among residents of high latitudes or people who prefer lifestyles of indoor-oriented (24).

Vitamin D deficiency and kidney

The kidney is the main organ involving in the production of bioactive forms of vitamin D (25). Vitamin D could also play an important role in the survival of chronic kidney disease (CKD) and end-stage renal disease patients regardless of dialysis situation (26). CKD with or without hemodialysis could be considered as an independent risk factor for cardiovascular, progression of hypertension and all-cause mortality (27). In addition, it has been reported that vitamin D deficiency is prevalent in CKD patients. It may have a substantial role in mortality and morbidity related to CKD (28). Additionally, CKD can be considered as a risk factor for the development of vitamin D deficiency (25). There are also various non-skeletal actions of vitamin D such as immune modulation, anti-inflammatory actions and endothelial protection. Likewise, vitamin D deficiency may associate with many conditions like left ventricular hypertrophy, proteinuria, atherogenicity, insulin resistance, decreased thrombolysis, susceptibility to infections, perpetuation of inflammation and immune imbalances (28). Generally, the decline of albuminuria would be the main target in renoprotective-based therapy with extra help of vitamin D supplementation (29).

Vitamin D deficiency and lung diseases

For lung diseases, vitamin D deficiency could lead to chronic airway disease as well as systemic inflammation, increasing the risk of infections and reducing bacterial clearance simultaneously (30). Hushmand et al reported that higher vitamin D concertation has been correlated with better lung function through better measured forced expiratory volume in one second (FEV1) measurement (31). There is also an association between epidemic influenza and vitamin D deficiency (32). In addition, there was a dose-response relationship between serum vitamin D and forced expiratory volume (FEV1) without any statistically significant association (33). Moreover, vitamin D deficiency has been correlated with increasing risk of respiratory infection from influenza A and mycobacterium tuberculosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), interstitial lung disease, asthma and respiratory infections (34). Since COPD patients may have a high prevalence of vitamin D deficiency (ranging from 30% to more than 75%) (35), many studies have been conducted to assess this association; for example, in a study in Turkey, it has been reported that COPD patients with vitamin D deficiency had poor balance, less muscle strength and severe physical

functioning as well as severe disturbed lung and peripheral muscle functions (36). On the contrary, in another study, there was no significant relationship and monthly consumption of vitamin D supplement was detected. They found no benefits of administration of vitamin D therapy in COPD patients (37). Moreover, inactivity, absence of sun exposure, lower food intake, reduced capacity of skin for synthesis of vitamin D and glucocorticoids resulting in increased catabolism could contribute vitamin D deficiency to COPD patients (38). In another study, it was reported that exercise capacity and lung function did not improve using vitamin D supplementation in COPD patients (39). It should be noted that many questions regarding the impact of vitamin D deficiency on pulmonary function or structure, especially chronic pulmonary disease still exist. Therefore, further studies should be conducted about the direct/indirect effects of vitamin D on mechanisms of lung function and lung injury as well as clarifying potential benefits of vitamin D supplementation to preclude or handle of chronic lung disease (40).

Various studies have also shown that the incidence of vitamin D deficiency would be high in ear, nose and throat diseases (ENT) and also otolaryngological diseases. Thus promising results for the administration of vitamin D supplementation in patients with pharyngitis, upper respiratory tract infections with asthma, post-operation of chronic suppurative otitis media, mastoidectomy and cholesteatoma spread was existed (41).

Cardiovascular diseases and vitamin D deficiency

Cardiovascular diseases (CVDs) are the first cause of death worldwide (42). Their substantial risk factors are smoking, older age, diabetes, obesity, hypertension, dyslipidemia, physical inactivity, metabolic syndrome, a family history and personal history (43). However, there are still some patients who their disease cannot be explained by above mentioned risk factors (44). The potential mechanism of effect of vitamin D on maintenance of normal cardiovascular activity could be through the capability of this hormone (vitamin D) to control of blood pressure, reduce the risk of thrombosis, support cardiovascular contractility and prevent cardiac and blood vessels calcification (12). In addition, there are pieces of evidence regarding the association between cardiovascular diseases and vitamin D deficiency (45). However, despite evidence regarding the cardioprotection role of vitamin D, there is still no causal effect between vitamin D deficiency and chronic cardiovascular diseases (46). Low levels of vitamin D can also be correlated with higher coronary artery calcification scores, inflammation, impaired endothelial function and increased vascular stiffness (47). Moreover, it has been confirmed that patients having cerebrovascular disease, associated musculoskeletal diseases, stroke and arterial hypertension could be considered as a high-risk group for vitamin D deficiency. Thus, evaluation of vitamin D level in these patients is a suitable suggestion (48). Besides the association of vitamin D deficiency with kidney dysfunction and inflammation as well as arterial hypertension, there are also supporting documents that show low levels of vitamin D could also be related with other classic cardiovascular risk factors such as obesity, physical inactivity and type I and II diabetes (49).

Chronic liver diseases and vitamin D deficiency

Vitamin D could also influence the progress of chronic liver disease (50). It has reported that vitamin D deficiency could associate with the severity of chronic liver disease while supplementation of vitamin D can be helpful in the treatment of liver disease (51). Accordingly, patients with vitamin D deficiency are more prone to chronic liver disease, because of the severity of impaired synthesis of some proteins as well as severe liver damage (52). Moreover, hepatitis C virus (HCV) may play an important role in not only inhibition of synthesis of 25 (OH)D through fat metabolism but also prevention of producing of pre-vitamin D (53). On the other hand, vitamin D deficiency may be related to the severity of chronic liver disease and fibrosis in chronic hepatitis C (CHC) (54). Furthermore, vitamin D can be acted as an independent prognostic factor in chronic liver diseases. These findings indicated that vitamin D levels may decrease with the progression of liver cirrhosis (51).

Vitamin D deficiency and autoimmune diseases

Autoimmune diseases may occur through disturbance of body's immune system (12). The effect of immune regulatory activity of vitamin D on both adaptive or innate immune systems has been confirmed (55). Moreover, research has confirmed that vitamin D could act as a neurosteroid (56) and is required for the normal development of the brain and its function (56). In addition, the active form of vitamin D may have immunomodulatory effects on immune system cells especially T lymphocytes and cytokines (57). The prevalent autoimmune diseases may include MS, rheumatoid arthritis, type 1 diabetes mellitus and Crohn's disease (58), amyotrophic lateral sclerosis, Parkinson's and Alzheimer's diseases as well as neurocognitive disease (59), and patients who are at risk fractures (such as hips, shoulders, and spine) (60) and inflammatory bowel diseases (IBD) are prone to vitamin D deficiency (61). Graves' disease (GD) is another autoimmune disease with hyperthyroidism secondary to circulating autoantibodies causing by multiple factors such as genetic and environmental factors which vitamin D deficiency may have a role in extension of disease (62). Likewise, the deficiency of vitamin D may have an impact on the onset and progression of Graves' disease while intake of vitamin D supplement may improve the disease (62). It has been reported that vitamin D supplementation not only could prevent developing of autoimmune diseases but could also apply for their treatment (55). For

neurological diseases, it has been suggested that optimal levels of vitamin D in the bloodstream are also needed to preserve the neurological development as well as to protect the brain (59).

It has also reported that sufficient vitamin D could be a necessary factor to prevent osteoporosis and might diminish the hazard of conditions unrelated to mineral metabolism and bone diseases. Additionally supplementation of calcium could not be considered as the main treatment of osteoporosis and more research is necessary to identify the minimum required daily dose of vitamin D supplementation (63).

Treatment of vitamin D deficiency

To cope with vitamin D deficiency, there are different recommendations. The daily intake of vitamin D is one of the most important methods, but it seems that higher amounts would be required to have better preventive or treatment effects (2). Another method would be the exposure to sunlight (64). It has been reported that sunlight could have a positive effect on mortality originated from cancers of colon, prostate and breast (65). However, sunlight exposure may lead to various risks such as skin ageing, inflammation and even cancer (66). Sunlight exposure plays an important role to improve vitamin D status other than oral supplementation with the advantage of prevention from vitamin D intoxication as well as disadvantage of erythema based on wavelength and duration of exposure (2). Intake of vitamin D supplements is another recommendation. In a randomized controlled trial, a three-mouth consumption of low-fat yogurt with supplementing of vitamin D-fortified had a positive effect on quality of life indices in diabetic postmenopausal women (67). It has been reported that cholecalciferol (vitamin D3) is mainly stronger than vitamin D2 (ergocalciferol) as well as the fact that the safe higher intake level for vitamin D3 would be 10 000 IU/d (68). However, there is an uncertainty about the preventive effect of vitamin D on diseases. It is recommended that high-risk people are better to have sunlight exposure and diet as well as low dose vitamin D supplements (400-800 IU/d) as an individual basis. However, current evidence could not support the consumption of vitamin D supplementation to preclude diseases (69).

Conclusion

In conclusion, vitamin D deficiency was only limited to rickets in the children and bone related disorders in adults in the past. However, nowadays it has also been associated with the pathogenesis and/or progression of many other diseases such as hypertension, MS, diabetes, cancer, and kidney disease. Despite this close relationship of vitamin D deficiency with various diseases, vitamin D insufficiency is not widely recognized as a problem by people, especially patients and physicians as well as health policy makers. It is recommended to conduct further studies on this association to clarify the exact effect of vitamin D deficiency as well as supplement therapy with vitamin D on human diseases.

Author's contribution

ND, SB, MD, MRK, ZK and AHD searched the literature and gathered the data. MA prepared the primary draft. MB completed the paper. MA finalized the 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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