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Vitamin D and Systemic Effects of Vitamin D Deficiency

D Vitamini ve D Vitamini Eksikliğinin Sistemik Etkileri

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Öz

Yağda eriyen bir prohormon olan D Vitamini, güneş ışınlarına maruz kaldıktan sonra deride üretilen bir secosteroiddir. Farklı metabolik yolaklarla kalsiyum ve fosfat metabolizmasında önemli rol oynayan kalsitriole çevrilir. D vitamini eksikliği, daha az güneş ışığına maruz kalma, D vitamini yetersiz alımı ve emilim sorunları gibi bazı faktörlerle ilgilidir. Son zamanlarda yapılan çalışmalar birçok insanda D vitamini eksikliğinin olduğunu göstermiştir. Literatürde D vitamini eksikliğinin kronik kas-iskelet ağrısı, Tip 1 ve Tip 2 Diabetes Mellitus (DM), obezite, multipl skleroz, romatoid artrit, kardiyovasküler hastalıklar, osteoporoz, mikroalbüminüri, kolon, prostat ve meme kanserini içeren böbrek yetmezliği gibi çeşitli hastalıklara ve fonksiyonel bozukluklara etkileri bildirilmiştir. D vitamini, hem doğrudan hem de dolaylı olarak organizma için hayati öneme sahip çok sayıda fonksiyon sağlayan çeşitli metabolik yollarda önemli bir rol oynayan temel yapısal unsurlardan biridir. Eksikliği halinde çok sayıda fonksiyonel bozukluk ve hastalığa neden olmasına rağmen, D vitamini replasman tedavisi ihmal edilmedikçe güvenli, ekonomik ve basittir. Bu derlemede D vitamininin metabolizmasını, fonksiyonlarını ve etkilerini, D vitamini eksikliğinde karşılaşılabilecek kronik hastalık risklerinin artmasını ve D vitamini replasman tedavisinin önemini göstermeyi amaçladık.

Anahtar Kelimeler: D vitamini, D vitamin eksikliği, kronik hastalık, kanser.

Abstract

Vitamin D is a liposoluble prohormon and a secosteroid which is produced in the skin after exposure to sun-shine. It is turned to calsitriol which has an important role in the calcium and phosphate metabolism by different metabolic pathways. Deficiency of vitamin D is related to some factors such as less sunlight exposure, inadequately intake of vitamin D and absorbtion problems. Studies recently done have shown vitamin D deficiency exists in many people. The effects of vitamin D deficiency on numerous diseases and functional disorders such as chronic musculoskeletal pain, Type 1 and Type 2 Diabetes Mellitus (DM), obesity, multiple sclerosis, rheumatoid arthritis, cardiovascular diseases, osteoporosis, microalbuminuria, renal failure involving colon, prostat and breast cancers either are reported in literature.Vitamin D is one of the main structural elements playing an essential role in several metabolic pathways both directly and indirectly providing numerous functions carring vital importance for organism. In spite of causing a lot of functional disorders and diseases, vitamin D replacement therapy in case of deficiency is safe, economic and simple unless neglected. In this review, we aimed to demonstrate the metabolism, functions and effects of vitamin D, increased risks of chronic diseases likely to be encountered in vitamin D deficiency and the importance of vitamin D replacement therapy.

Keywords: vitamin D, vitamin D deficiency, chronic disease, cancer.

INTRODUCTION

Vitamin D is a vital vitamin, which has antiproliferative, pro-differentiative, proapoptotic, and immunomodulatory functions. It is produced in the skin after exposure to sunshine. Recently, many diseases have been associated with vitamin D deficiency in the literature.

In this review, we aimed to demonstrate the metabolism, functions and effects of vitamin D, increased risks of chronic diseases that are likely to be seen in vitamin D deficiency and the importance of vitamin D replacement therapy.

Vitamin D sources

Vitamin D has two basic forms: Vitamin D2 (ergocalciferol), ergosterol exists in plants as an

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ultraviolet B-ray product. Vitamin D3 is sourced by dehydrocholesterol and occurs as a result of reaction of previtamin D3 with ultraviolet B-ray. Actually, the expression of vitamin D represents both vitamin D2 and vitamin D3 (1). Vitamin D can be synthesized endogenously, and it can also be received with in some food intake as well (2). Vitamin D3 can either be synthesized in the human epidermis, or taken from foods. After being activated following the solar ray exposure, 7- dehydrocholesterol constitutes previtamin D3 as the precursor (3). From this point, ultraviolet B-ray is the primary source of vitamin D for most of people (4). Diet- derived or endogenously synthesized vitamin D2 or vitamin D3 are stored in fat cells and released when necessary (5).

Vitamin D metabolism

Vitamin D binding protein (DBP) transports Vitamin D in the blood to the liver. 25-hydroxyvitamin D3 (25(OH)D3) is formed as a result of hydroxylation reaction in the liver by one or more cytochrome P450. DBP transport 25(OH)D3, which is the main circulating form of vitamin D to the kidney. As a result of the hydroxylation of 25(OH)D3 in the proximal renal tubule, 25(OH)D 1α hydroxylase is the hormonally active form of vitamin D. 1.25-dihydroxyvitamin D3 (1.25(OH)2D3) is responsible for most of the biological activities of vitamin D. According to feedback mechanism of vitamin D metabolism, low calcium and phosphate status cause increased activity of 1α(OH)ase. Stimulating the transcription of 1α(OH) ase, increased PTH triggers 1.25(OH)D3 synthesis in the kidney. Besides calcium, phosphate, PTH and 1.25(OH)2D3, fibroblast growth factor 23 and phosphaturic factor are also physiological promoters of vitamin D metabolism (2).

Vitamin D receptors

n addition, 25(OH)D can turn into 1.25(OH)2 D3 in both vascular and endothelial cells. There is vitamin D receptor in nuclear membrane of the cell, and 1.25(OH)2 D3 can control gene expression by binding to this. The liganded VDR and retinoid X receptor (RXR) combination affects transcription, binding to vitamin D response elements (VDREs) in target genes. 1.25(OH)2 D3 regulates 200 to 500 of the 20,488 genes in the human genome, directly or indirectly (7).

Basic functions of Vitamin D

The major function of 1.25(OH)2D is regulation of calcium metabolism. It increases absorbtion of calcium through duodenum and phosphorus through ileum (2). In case of vitamin D deficiency, only 10- 15 % of calcium and 60 % of phosphorus are able to be absorbed (8). These rates show increase to 30-40 % in calcium absorbtion and 80 % in phosphorus absorbtion with Vitamin D (5). 1.25(OH)2D decreases elimination of calcium through kidneys to provide the continuity of calcium level in plasma. At the same time, 1.25(OH)2D has an immunomodulator function providing occurance of cathelicidin which increases cytokine release from T lymphocytes and synthesis of Ig from B lymphocytes (2).

Vitamin D and Cardiovascular System

It has been claimed that there is a relationship between vitamin D and hypertension, cardiovascular diseases and coronary artery calcification (9). Higher latitudes cause enhanced risk of hypertension and cardiovascular disease (10,11). As a result of a study, exposure to ultraviolet B radiaton 3 times a week for three months increases vitamin D levels in patients with hypertension and at the end of research, the main blood pressure was evaluated as normal (12). Congestive heart failure and blood levels of inflammatory determiners, including CRP (C-reactive protein) and IL- 10 are also associated with vitamin D deficiency (10,12).

It is strongly proposed that renin-angiotensin system (RAS) is obviously associated with vitamin D level. Forman et al. investigated the association between renin-angiotensin system and 25(OH)D. Enhanced plasma renin activity and high angiotensin II levels were observed in the patients with vitamin D deficiency. Besides that, according to plasma flow measurement following angiotensin II infusion, the RAS activity was evaluated higher in patients with vitamin D deficiency. This study demonstrated that there is a relationship between low plasma 25(OH)D levels and elevated activity of the RAS.

Adequate vitamin D level prevents hypertension by providing down regulation of renin-angiotensin system. It has been stated that vitamin D prevents mortality due to heart attack and sudden cardiac arrest by repressing the cardiac contractility and ventricular hypertrophy (13).

Vitamin D and Diabetes Mellitus

It has been recently claimed that vitamin D has also essentially important effects on the regulation of glucose metabolism and thus it can cause Diabetes

Mellitus. There are some epidemiologic studies supporting the association between low vitamin D levels early in life and occurrence of type 1 DM. It has been revealed that vitamin D receptor gene polymorphisms are related with development of type 1 DM (14). Several contributing factors of type 2 DM such as failure in pancreatic βcell function, systemic inflammation and insulin sensitivity are known to be linked with Vitamin D deficiency. Based on the results of investigations, it has been clearly claimed that development of type1 DM can be prevented by supporting infants with vitamin D replacement (15). Numerous effects of vitamin D on some pathways and mechanisms such as insulin secretion, regulation of insulin activity and cytokine feedback mechanisms have been also proposed. According to statistical studies, there was also an adverse correlation between vitamin D replacement and the incidence of metabolic syndrome and type 2 DM (16).

Vitamin D and Infection

Vitamin D and its activated form 1.25-dihydroxyvitamin D have a complex role in immunological system. 1.25-dihydroxyvitamin D has a significantly important modulator effect on T lymphocytes. Patients with tuberculosis have lower levels of vitamin D compared to general population (17). Deficiency of vitamin D is also encountered frequently in patients with HIV(+). It was claimed that 1.25-dihydroxyvitamin D has effects on CD4(+) cells (17).

Osteomalacia and Osteoporosis

The increasing expression of calbindin 9K, a calcium-binding protein(CaBP) and epithelial calcium channel in small bowel following a 1.25(OH)2D reaction with the VDR-RXR combination, increases intestinal calcium absorption up. Interacting with its receptor in osteoblasts 1.25(OH)2D enhances the expression of the receptor activator of nuclear factor-κB ligand (RANKL). Binding of the receptor activator of nuclear factor-κB ligand (RANKL) with RANK, results in its receptor on preosteoclasts, and occurring mature osteoclasts to promote osteolysis for increasing calcium and phosphorus levels in the blood.

Vitamin D deficiency causes enhanced synthesis of parathyroid hormone (PTH). Causing high level bone turnover, this secondary hyperparathyroidism results in enhanced risk of fracture. In chronical background, osteomalacia is encountered obviously and patients with osteoporotic femoral neck fractures were investigated for this purpose. Histopathologically compatible images with osteomalacia were obtained in 13 to 33% of the patients at the end of the study.

In early ages, vitamin D deficiency causes rickets. Osteoporotic background of the elderly due to vitamin D deficiency can result in fractures, falls and muscular diseases. Fractures following minimal traumas can be encountered in individuals with osteomalacia. High level of alkaline phosphatase and PTH together with low blood calcium and phosphorus level should be directing in diagnostic algorithm of osteomalacia. 25-OH-vitamin D level in blood can be helpful for an early diagnosis. In order to become active, it must furthermore undergo two hydroxylations in the liver and kidneys. Misusage of suntan cream, less sunlight exposure and inadequate intake of vitamin D can all result in vitamin D deficiency.

The patients with nonspecific chronic pain, muscle pain, fall and weakness are diagnosed with chronic fatigue syndrome, fibromyalgia and even myositis. Malabanan et al. reported that vitamin D replacement decreases these complaints in 25 % of the patients in following two years (18).

Vitamin D and Cognition

According to the investigations, it is claimed that individuals with Alzheimer dementia have lower levels of vitamin D than the control group (19). Anatomical studies have shown that hippocampal formation holds vitamin D receptors. Based on antioxidant activity of vitamin D, it can be claimed that there is essentially important relationship between lack of vitamin D and cognitive disorders (19). Mini Mental Status Examination has been applied to the patients with Alzheimer disease and an association has been found between insufficient vitamin D level and examination scores of the patients (20).

Vitamin D and Chronic Diseases

It is known that children with rickets have quadruple risk of type 1 DM. 80 % decrease in the risk of type 1 DM was demonstrated in a Finland study which adminestered 2000 U vitamin D per day starting at 1 year old children until adult ages (18). It was claimed that there is a relationship between insufficient vitamin D level and cardiac insufficiency. There is an intense relationship between low vitamin D level and enhanced incidence of several psychotic diseases and depressive disorders. In recent years, some studies have found that vitamin D deficiency is

common among newborn patients with bronchiolitis and its severity can be related with vitamin D level. It was reported that women who had low vitamin D levels during pregnancy could cause wheezing disorders in their children following the birth (22). It was determined that respiratory tract infections are rarely encountered in babies born to pregnants with high levels of vitamin D; but there is no any difference in prevalance of asthma and wheezing (23). It was discovered that almost all immunological cells carry vitamin D receptor on them, and some genetic polymorphisms of the receptor were claimed to be related with enhanced prevalance of autoimmune disorders. It was reported that there is a relationship between vitamin D deficiency and several autoimmune disorders such as diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus.

Vitamin D and Cancer

Many studies in the literature support that vitamin D has an important role in cancer precaution. The preservative characteristic of vitamin D is probably linked with its control feature on cell proliferation and differentiaton (24). The Health Professionals Follow-Up research demonstrated that each increase in vitamin D level of 25mmol/L was related to the 17% decline of total cancer cases (25). On the other hand, The National Health and Nutrition Examination Survey (NHANES) program did not support the correlation between cancer survival and 25(OH) D level. In another research, vitamin D levels were investigated seperately related to the incidence of colorectal cancer, and vitamin D levels of 80 nmol/L conferred significantly obvious reduction in risk of colorectal cancer (26). The fact that individuals with adequate levels of vitamin D have also a lower incidence of colorectal malignancy was reported in 20 of 30 investigations. Besides that, rewarding effects of 25(OH)D on cancer rate and survival has been shown in nine of the thirteen studies related with breast cancer and thirteen of the twenty six studies about prostate, respectively (27). A randomized controlled trial study demonstrated that vitamin D and calcium replacement decreased cancer incidence in postmenopausal women following the first year of treatment (28).

Vitamin D deficiency

Most authors define vitamin D deficiency as a 25(OH)D level of less than 20 ng/ mL, though there is no consensus on optimal levels of 25(OH)D in serum (7). Severe deficiency It is defined as a serum 25(OH) D level is ≤10 ng/mL, deficiency as a level between 10-20 ng/mL, moderate deficiency or insufficiency of vitamin D between 20-29 ng/ mL, sufficient as a level ≥30 ng/ mL, optimal between 40-50 ng/mL, and toxic as a level >150 ng/ml (29). Skin pigmentation plays a significiantly important role in vitamin D insufficiency (30). High level of melanin in dark- skinned people blocks absorbtion of ultraviolet- B rays (31). As the vitamin D absorbtion is provided through ileal part of the bowel, most of gastrointestinal diseases, and malabsorbtion syndromes such as Crohn and Celiac are correlated with vitamin D deficiency. Due to storing vitamin D in fat tissues, obesity can also cause vitamin D deficiency (3). There are several risc factors of vitamin D deficiency such as advanced age, genetic determinants, cultural factors especially indoor clothing, protective suntan cream usage, physical inactivity, smoking, air pollution, renal and liver diseases, and drug usage affecting the metabolism of vitamin D like glucocorticoids and anticonvulsants (29).

Evaluation of serum 25(OH)D is supposed to be the best test for determination of vitamin D status. It can be appraised as follows (32):

- 21-29 ng/mL levels of vitamin D is defined as Vitamin D insufficiency.
- < 20 ng/mL levels of vitamin D is defined as Vitamin D deficiency.

CONCLUSION

In conclusion, vitamin D deficiency may be seen in all age groups. Adults, pregnants and even children are under risk in terms of vitamin D deficiency. Lack of vitamin D is related to some factors such as misusage of suntan creams, less sunlight exposure and inadequate intake of vitamin D. Control of vitamin D level through at yearly examinations will affect not only bone structure but also will be helpful in prevention of development of the diseases pointed above.

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