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DIFFERENT ASPECTS OF VITAMIN D

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Review
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Abstract

Vitamin D is a steroid hormone synthesized by sunlight and this takes place in the skin. It under goes various metabolic changes in different tissues in the body and turns into its active form. Although it shows its main effect on bone tissue due to calcium phosphorus metabolism, it has also been proven to have extra-bone effects. Starting from intrauterine life until the endof life; it is effective on growth-development, immune system, neuronal development. In this review prepared in the light of up-to-date information; it is aimed to emphasize the importance of vitamin D use especially from childhood by reviewing the effects of vitamin D on different systems.

Key Words: Vitamin D, Non-Skeletal Effects, Deficiency

Özet

D vitamini güneş ışığı ile sentez edilen steroid yapıda bir hormondur. Vücutta farklı dokularda çeşitli metabolik değişikliklere uğrayarak aktif formuna dönüşür. Temel etkisini kalsiyum fosfor metabolizması dolayısı ile kemik doku üzerinde göstermekle beraber kemik dışı etkileri olduğu da kanıtlanmıştır. İntrauterin yaşamdan başlayarak hayatın sonuna kadar; büyüme gelişme, immün sistem, nöronal gelişim üzerine etkilidir. Güncel bilgiler ışığında hazırlanan bu derlemede; D vitamininin farklı sistemler üzerindeki etkilerinin gözden geçirilerek özellikle çocukluk çağından itibaren D vitamin kullanımının önemini vurgulamak amaçlanmıştır.

Anahtar Kelimeler: D vitamini, İskelet Dışı Etkiler, Eksiklik

1. Introduction

Vitamin D is essentially a steroid hormone involved in calcium and phosphorus homeostasis and bone turnover. Vitamin D began to be recognized after the 1950s, proving its importance in the treatment of rickets. In the last decade, the prevalence of vitamin D deficiency in industrialized countries has paved the way for an increase in vitamin D studies with the documentation of its effects on non-skeletal tissues.

1.1. Vitamin D Metabolism

Approximately 90% of vitamin D is synthesized in the human skin by ultraviolet B at the appropriate wavelength (290-310 nm). Non-enzymatic photolysis of 7-dehydrocholesterol leadsto the formation of previtamin D and then provitamin D. Vitamin D synthesis in the human skin occurs in a short time, depending on the needs of the body. Long-term exposure to sunlight produces inactive forms of lumisterol and tachysterol to prevent toxicity (Hochberg, 2003). Of orally ingested animal (cholecalciferol) or plant (ergocalciferol) vitamin D, 60-90% is absorbed from the intestinal surface and enters the bloodstream (Lo et al., 1985). After vitamin D enters the blood circulation system, because of its longer half-life (21 days), it is converted from the active form to 25-hydroxyvitamin D (25OHD) in the liver by the enzyme 25-hydroxylase, and often used to determine serum vitamin D levels. The kidney converts 25OHD to 1,25-hydroxyvitamin D [1,25 (OH)2D], which is the active form of vitamin D, with the help of the enzyme 1-alpha-hydroxylase.

All vitamin D in the body, albeit in different forms, is bound to the vitamin D binding protein and transmitted to the relevant places. Vitamin D exerts its effect by binding to the receptor on the cell surface (non-genomic) or in the cell nucleus (genomic). Active vitamin D's the most important task is to balance calcium-phosphorus levels with PTH. The increase in the effect of 1-alpha-hydroxylase, an enzyme, occurs with the effect of PTH. Increasing the absorption of calcium from the kidney tubules and gastrointestinal tract is one of the effects of vitamin D. When calcium intake is insufficient, it attempts to keep serum calcium levels in balance by increasing the release of calcium from bone tissue. Long-term low calcium intake leads to rickets. Although it can be stored in fatty tissue, previous studies have shown that a wider distribution of vitamin D causes low serum vitamin D levels in obese individuals (Holick, 2007). Many factors affect serum vitamin D levels. Factors affecting vitamin D synthesis include

geographic location, air pollution, type of clothing, use of sunscreen (factor 15 or greater), skin melanin content and skin temperature, and malabsorption (Holick, 2011; MacLaughlin et al., 1982; Tsiaras & Weinstock, 2011).

Due to the activity of the 1-alpha-hydroxylase enzyme, active production of vitamin D from 25 OHD also occurs in tissues other than the kidney. This activity is observed in the skin, prostate, colon, placenta, brain, breast, monocytes, and macrophages. It is stated that active vitamin D synthesized in these tissues acts paracrine and intacrine and does not contribute to serum levels (Bouillon et al., 2008; Weisman, 2010). In contrast, however, hypercalcemia has been reported to occur to varying degrees (2-63%) in diseases with granuloma formation such as tuberculosis and sarcoidosis (Sharma, 2000).

It has been noted in previous studies that vitamin D deficiency is also involved in the development of diseases affecting other systems, apart from rickets and osteomalacia, which are widely known effects (Holick, 2004). Vitamin D deficiency is one of the public health problems that have not yet been eliminated in our country (Celep & Durmaz, 2021). It is reported that the incidence of rickets caused by vitamin D deficiency varies between 1.6% and 19% in Turkey (Hatun et al., 2003). It was found that the vitamin D content in the milk of mothers who received vitamin D (400 units) at the prophylaxis level was 20-78 IU/L, leading to the conclusion that this level could not protect infants from vitamin D deficiency. Especially in winter, the necessary vitamin D intake for nursing mothers is recommended at 2000 IU/day (Canadian Pediatric Association, 2007). For all these reasons, since 2005, the Ministry of Health has been providing 400 units of vitamin D daily free of charge to all infants (Hatun et al., 2003). Thanks to this measure, the incidence of rickets has decreased especially in the eastern region (Ozkan et al., 2009). The upper limit of vitamin D intake that does not lead to intoxication in children receiving vitamin D supplementation was determined for different age groups. Tolerable vitamin D levels have been reported as 1000 IU/day for children 0-1 years of age, 2500 IU/day for children 1-3 years of age, 3000 IU/day for children 3-8 years of age, and 4000 IU/day for adults > 8 years of age (Özkan & Döneray, 2011).

There is currently no consensus on what serum levels should be for vitamin D deficiency and insufficiency. The British Paediatric and Adolescent Bone Group reported that a 25OHD level of less than 10 ng/ml impairs bone mineralization, and defined levels between 10-20 ng/ml as insufficiency (Saggese et al., 2015). The American Society of Pediatric Endocrinology defines a 25OHD level between 15-20 ng/ml as insufficiency and > 150 ng/ml as intoxication

(Munns et al., 2016). In determining these levels, the main concern is to establish the baseline serum vitamin D level that does not increase PTH secretion and does not cause bone loss

1.2. Extraskeletal Effects of Vitamin D

Numerous experiments in animals and the human body have shown that vitamin D is also effective on tissues other than the skeleton. This was first noticed when serum vitamin D levels were high in patients followed for sarcoidosis.

The vitamin D's effects arise in the womb. Therefore, it is important for women to take vitamin D supplements during pregnancy. It has been observed that maternal vitamin D levels affect fetal growth, newborn calcium balance, skeletal and immune system development and respiratory system development (Gürz et al., 2015).

The initial reaction against microorganisms in the human body is triggered by the stimulation of Toll-Like receptors, which are found in neutrophils, monocytes, macrophages and epithelial tissue and are elements of innate immunity. Vitamin D ramp up the production of antimicrobial peptides (defensin, cathelicidin) released as a result of stimulation of innate immunity, thus contributing to the activating the immune system response that begins at birth (Behzat, 2013). Following the demonstration of this relationship, the idea that low vitamin D levels predispose to upper respiratory tract infections, otitis media and flu has come to the fore, and many studies have confirmed this finding. (Muhe et al., 1997; Wayse et al., 2004).

The adaptive immune system is activated by antigen presentation to CD4 cells by macrophages and dendritic cells. T and B lymphocytes generate a specific response against the presented antigen by producing cytokines and immunoglobulins. At this stage, it has been proven that vitamin D suppresses the production of immunoglobulin, the proliferation of T cells, and therefore the release of inflammatory cytokines. (Szodoray et al., 2008). Recent research has emphasized the effect of vitamin D on the development of multiple sclerosis, rheumatoid arthritis, type 1-2 diabetes, and inflammatory bowel disease, which are known to involve the triggering of proinflammatory mechanisms. The increase in the incidence of the above autoimmune diseases has been associated with lower levels of vitamin D in people living above sea level. (Munger et al., 2006; Teegarden & Donkin, 2009).

Vitamin D receptors are found not only in the aforementioned but also in myocytes, endothelial cells of the cardiovascular system, and vascular smooth muscle cells. It is predicted that vitamin D inhibits apoptosis in these cells, suppresses the release of proinflammatory

cytokines associated with atheromatous plaque instability, and has protective effects on cardiovascular health. It is known that the renin-angiotensin system is activated in the development of hypertension. It has been shown that the cells secreting renin from the kidneys are not insensitive to vitamin D and that the release of renin is negatively affected by the enrichment in serum vitamin D level. This is probably a protective factor against hypertension (Artaza et al., 2009; Lind et al., 1989). A large-scale study onadolescents found that vitamin D deficiency causes a risk, and this risk is the risk of developing hypertension and metabolic syndrome. (Artaza et al., 2009). Cases of pediatric dilated cardiomyopathy resulting from vitamin D deficiency have also been reported in the literature at a substantial rate. (Çakır et al., 2021; Olgun et al., 2003). In summary, although vitamin D has a protective effect on the cardiovascular system, hypercalcemia carries the risk of vascular and soft tissue calcification.

It has been reported that proximal muscle weakness and muscle pain may develop in vitamin D deficiency before rickets develops, and hypotonia may occur in children, but the mechanism isnot fully understood (Behzat, 2013).

The vitamin D's effect on the neuronal system is mostly based on studies in animals. Proteins whose production is impaired in neuronal tissue may be associated with schizophrenia, depression, and multiple sclerosis. There are studies propose that low maternal vitamin D levels increase the incidence of schizophrenia in children. It has also been shown to be associated with Alzheimer's disease in adulthood and autism in childhood (McGrath et al., 2003; Oudshoorn et al., 2008; Özlü et al., 2020).

The hypothesis put forward to represent the antineoplastic effect of vitamin D is the inhibition of proliferation and the induction of apoptosis and differentiation. It is believed to suppress angiogenesis and invasion, which are necessary to spread tumor tissue. Vitamin D has been proven to induce apoptosis in breast, prostate, and colon tumors, but the mechanisms are not clear yet (Behzat, 2013; Muñoz & Grant, 2022).

The skin is an organ where vitamin D is both synthesized and its effects can be observed Vitamin D has a differentiation-promoting and proliferation-inhibiting effect on keratinocytes Taking advantage of this effect, it was used in the treatment of patients with psoriasis and it was observed that it heals the lesions (Holick, 2010).

2. Conclusion

Insufficient intake of vitamin D; It paves the way for many health problems in all age groups starting from the intrauterine period, especially rickets, respiratory tract infections, autoimmune diseases such as Type 1 diabetes, cardiovascular diseases and mental diseases. Vitamin D requirement varies with age. Age and gender are important for ideal level of vitamin D. In our country, maternal vitamin D use is important for both infant and maternal health. According to the vitamin D usage program initiated by the Ministry of Health; Vitamin D support is started for expectant mother from the 12th week and continued for 6 months after delivery. It is aimed for babies to take 400 IU of vitamin D per day from the first week of life, regardless of their diet, until at least one year old. As a result of the studies, it is recommended to keep the serum level of 25 OHD above 20 ng/ml to prevent rickets and regulate bone turnover, and above 30 ng/ml to prevent diseases such as autoimmune diseases, cardiovascular diseases and cancer (Stechschulte, Kirsner, &Federman, 2009). To reach this level, an average of 800-1000 IU/day of vitamin D should be taken every day. In addition to all these, there is a need for new studies toinvestigate the cause and effect relationship between vitamin D and chronic diseases.

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Conflicts of interest

None

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