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Vitamin D Deficiency. The place of calcifediol in the treatment of vitamin D deficiency - literature review.

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Abstract

Introduction:

Vitamin D plays a very important role in the human body. It affects bone health, immune system function, and is responsible for overall well-being. Vitamin D deficiency is a common worldwide. It contributes to the development of osteoporosis, cardiovascular diseases, and autoimmune disorders and many others. This article reviews the current state of knowledge about vitamin D deficiency, its causes, health consequences, diagnostic methods, and treatment options, with a particular focus on the effectiveness of calcifediol in treating this deficiency.

Aim of the Study:

The aim of this study was to summarize the current state of knowledge about vitamin D, vitamin D deficiency, its causes of health consequences, diagnostic methods, and treatment options, with a particular focus on the efficacy of calcifediol.

Materials and Methods:

The literature available in the PubMed database was reviewed using the following keywords: "vitamin D deficiency", "calcifediol treatment", "vitamin D metabolism", "epidemiology of vitamin D deficiency", "vitamin D diagnostic criteria", "calcifediol".

Conclusions: Vitamin D plays an important role in maintaining bone health, supporting the immune system and regulating various physiological processes. However, despite its importance, vitamin D deficiency is widespread, affecting populations around the world due to factors such as limited sun exposure, dietary habits and certain health conditions. Calcifediol has become particularly effective treatment of vitamin D deficiency due to its higher bioavailability and faster performance compared to other forms, such as cholecalciferol.

Keywords: vitamin D deficiency, epidemiology of vitamin D deficiency, calcifediol treatment.

Introduction

Vitamin D is a fat-soluble vitamin. It is essential for maintaining normal bone health, supporting immune system function, the nervous system, the cardiovascular system and regulating insulin levels in our bodies. [1] Despite its many important roles, vitamin D deficiency is a common worldwide. [2] Vitamin D deficiency can lead to a variety of health problems, including osteoporosis, rickets in children and an increased risk of chronic diseases such as cardiovascular disease, certain cancers, and autoimmune disorders. [3] There is evidence that normal vitamin D concentration also plays a role in depression, pain and cancer. [4] Vitamin D comes from three main sources: exposure to sunlight, dietary intake and supplementation. [5] Skin synthesis is still the main way of producing vitamin D. [6] Sunlight covers more than 90% of the body's daily vitamin D requirement. [7] When the skin is exposed to ultraviolet B (UVB) rays from the sun, skin keratinocytes synthesize vitamin D3 (cholecalciferol). [8] This form of vitamin D is then converted in the liver to 25-hydroxyvitamin D (calcifediol), which is the main circulating form and is used to determine vitamin D concentration. [9] Further hydroxylation in the kidneys converts calcifediol into the active form, 1,25-dihydroxyvitamin D (calcitriol), which is responsible for vitamin D action in the body. [10] In many parts of the world, factors such as limited exposure to sunlight, dietary habits and certain health conditions contribute to the high prevalence of vitamin D deficiency. [11] Populations at higher risk include people living in high latitudes, those with darker skin pigmentation, the elderly, obese people and those with malabsorption syndromes. [3] Using sunscreen, wearing clothing that covers most of the skin and spending a lot of time indoors can also reducr the skin's production of vitamin D. [3][12] In addition, certain medications, such as anticonvulsants and glucocorticoids, can interfere with vitamin D metabolism, contributing to deficiency. [13] Recent studies show that calcifediol, due to its higher bioavailability and faster action compared to other forms of vitamin D, is particularly effective in treating vitamin D deficiency. [7] This makes it a more preferred option for patients with severe deficiency or conditions that impair vitamin D metabolism. [14]

Synthesis and metabolism of vitamin D

Synthesis in the skin. The primary source of vitamin D for most people is its synthesis in the skin, induced by exposure to ultraviolet B (UVB) radiation from sunlight. When UVB photons penetrate the skin, they convert 7-dehydrocholesterol, a complex present in the skin, into previtamin D3. [1] Previtamin D3 then undergoes a transformation, turning into vitamin D3

(cholecalciferol). [15] This process occurs in the skin keratinocytes, where 7-dehydrocholesterol absorbs UVB radiation (290–315 nm), causing the production of previtamin D3, which is thermodynamically unstable and rapidly isomerizes to vitamin D3. [3] Vitamin D3 is then transported from the skin into the bloodstream, where it binds to vitamin D-binding protein (DBP) or GC-globulin for transport to the liver. [16]

Dietary sources. Vitamin D can also be obtained through dietary sources. Vitamin D3 (cholecalciferol) is found in foods of animal origin, such as fatty fish (e.g., salmon, mackerel, and sardines), cod liver oil, and egg yolks. [6] Vitamin D2 (ergocalciferol), on the other hand, is found in plant sources, mainly in mushrooms exposed to UV light (ee.g., oysters, shiitake mushrooms) and is formed by irradiating yeast. [17] Both forms are used to enrich foods such as milk, margarine, yogurts, breakfast cereals, and cooking oils. [7]

Absorption and transport. After ingestion of food-derived vitamin D, it is absorbed in the small intestine, where it is incorporated into chylomicrons and transported through the lymphatic system into the bloodstream. [3] From there, it is carried to the liver, where it hydroxylated.

Hepatic conversion. In the liver, vitamin D (both D2 and D3) is hydroxylated by the enzyme 25-hydroxylase to form 25-hydroxyvitamin D [25(OH)D], also known as calcifediol. [9] It is the primary circulating form of vitamin D and the most useful indicator of vitamin D concentration in the body. [3]

Renal conversion. The next step in vitamin D metabolism occurs in the kidneys, where 25(OH)D is further hydroxylated by the enzyme 1α-hydroxylase, forming 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol. [10] Calcitriol is the biologically active form of vitamin D, responsible for regulating calcium and phosphate homeostasis in the body. [3]

Regulation and function. The entire transformation process is stimulated by parathyroid hormone (PTH). 1,25(OH)2D acts through the vitamin D receptor (VDR) on nucleated cells. Its most important biological role is to ensure calcium homeostasis in the body. During hypocalcemia, the level of ionized calcium in the plasma decreases, which is detected by calcium receptors in the parathyroid glands. PTH is secreted by the parathyroid glands, which stimulates 1- α -hydroxylation in the kidneys to produce more 1,25(OH)2D. [6] Conversely, an

increase in serum calcium levels decreases PTH secretion and reduces the synthesis of 1,25(OH)2D. [7] Calcitriol acts on various target tissues, including the intestines, bones, and kidneys, to maintain calcium and phosphate balance. [18] It increases the absorption of calcium and phosphate in the intestines, promotes reabsorption of calcium in the kidneys, and facilitates the mobilization of calcium from bones. [3] Additionally, vitamin D receptors (VDR) have been discovered in various tissues, including the prostate, brain, breast, pancreas, colon, and immune cells. Vitamin D may also exert extra-skeletal effects. Calcitriol may play a role in immune system function and in regulating the proliferation and differentiation of cells in various cell lines (lymphocytes, endothelial cells, osteoblasts, and keratinocytes). [19]

Vitamin D Deficiency

Causes of vitamin D deficiency. Vitamin D deficiency is primarily caused by inadequate dietary intake of vitamin, limited sun exposure, and gastrointestinal problems that affect the absorption or metabolism of the vitamin. [20] High-risk populations include people who live in high latitudes with low sunlight exposure, those with darker skin pigmentation, the elderly, and patients with malabsorption syndromes. [2] Moreover, lifestyle factors such as the use of sun protection, wear of covering clothing, and spending a lot of time indoors may further increase the risk of deficiency. [21] Specific conditions such as obesity, liver and kidney disease can also impair the body's ability to metabolize and utilize vitamin D, causing lower serum levels. [14] Vitamin D can be found naturally in a some foods, such as fatty fish (e.g., salmon, mackerel, and sardines), fish liver oils, and egg yolks. [10] However, the amount of the vitamin provided from diet alone is often insufficient to meet daily needs, making supplementation and adequate sun exposure essentail to maintain optimal levels. [22] Some medications, such as anticonvulsants and glucocorticoids, can also interfere with vitamin D metabolism, contributing to deficiency. [13]

Health consequences of vitamin D deficiency. The health consequences of vitamin D deficiency are significant and quite common. One of the most well-known effects is its impact on bone health, leading to conditions such as rickets in children and osteomalacia or osteoporosis in adults. [1] In addition to bone health, vitamin D deficiency has been associated with an increased risk of cardiovascular disease, certain cancers, and autoimmune disorders. [23] Moreover, recent studies have suggested a potential role in mental health, with connections between low vitamin D levels and mood disorders such as depression. [12] Low vitamin D levels are also associated with an increased risk of respiratory infections, such as influenza and

COVID-19, and with worse results in patients with these infections. [24] The emerging evidence suggests that vitamin D plays a role in modulating the immune response and may help reduce the risk of chronic diseases such as multiple sclerosis, insulin-dependent diabetes mellitus, and rheumatoid arthritis. [3] Vitamin D receptors are present in almost all cells of the body, which indicates its wide range of biological functions. [8] Adequate levels of vitamin D are essential for the proper functioning of the immune system, and its deficiency can impair the body's ability to fight infections and inflammation. [18]

Epidemiology of Vitamin D Deficiency. Epidemiological researches indicate that vitamin D deficiency is a global health problem, affecting about 1 billion people around the word. [2] Prevalence varies widely by region, with particularly high rates in the Middle East, South Asia, and among ethnic minorities in Western countries. [1] Factors contributing to these differences include variations in sun exposure, dietary habits, skin pigmentation, and cultural practices. [5] For example, in regions with high air pollution or where people commonly wear clothing that covers most of their skin, rates of vitamin D deficiency are much higher. [25] In the United States, an estimated 42% of the population is vitamin D deficient, with higher rates seen in certain subgroups such as African-Americans, Hispanics, and the elderly. [26] In Europe, studies have shown that vitamin D deficiency is common in both northern and southern countries, with significant seasonal variations in serum 25(OH)D levels. [27] In Asian countries, despite plentiful sunlight, cultural practices such as avoiding sun exposure and wearing traditional clothing contribute to high rates of deficiency. [5]

Diagnosis of Vitamin D Deficiency

Methods for assessing vitamin D levels. The most commonly used method to assess vitamin D status is to measure serum 25-hydroxyvitamin D [25(OH)D] levels. [3] This metabolite reflects the total vitamin D stores in the body and is considered the best indicator of vitamin D status. [9] It is usually measured using techniques such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), and liquid chromatography-tandem mass spectrometry (LC-MS/MS**)**. [5] Regular monitoring of 25(OH)D levels is recommended for patients at high risk of deficiency, including those with chronic diseases, pregnant and lactating women, and elderly. [21] Population-based screening for vitamin D deficiency is not recommended for people who are not at risk. Measuring serum vitamin D levels can help guide supplementation and treatment strategies, ensuring that individuals achieve and maintain adequate vitamin D status. [3]

Diagnostic Criteria for Vitamin D Deficiency. Diagnostic criteria for vitamin D deficiency are different, but in general, serum 25(OH)D level below 20 ng/mL (50 nmol/L) is considered vitamin D deficiency, while levels between 21-29 ng/mL (52.5-72.5 nmol/L) indicate vitamin D insufficiency. [1] Optimal levels are usually defined as 30 ng/mL (75 nmol/L) or higher. [10] These thresholds are based on the association between 25(OH)D levels and various health outcomes, including bone health, muscle function, and the risk of chronic diseases. [12] There is debate among experts about the optimal levels of 25(OH)D needed to achieve the best health outcomes. [13] Some organizations recommend maintaining levels above 30 ng/mL to ensure sufficient vitamin D for bone and overall health, while others suggest that levels of 20-30 ng/mL may be adequate for most people. [21] Despite these differences, there is consensus that maintaining serum 25(OH)D levels above the threshold for deficiency is critical to preventing adverse health effects associated with low vitamin D status. [3]

The role of calcifediol in diagnosis. Calcifediol, also known as 25-hydroxyvitamin D3, plays a key role in the diagnostic process because it is the primary circulating form of vitamin D. [9] Measurement of serum calcifediol levels provides a direct indication of vitamin D status, which reflects both endogenous synthesis from sunlight exposure and dietary intake. [10] Moreover, calcifediol levels are not significantly influenced by recent dietary intake, making it a reliable marker for assessing long-term vitamin D status. [3] Calcifediol is often preferred in clinical practice because it provides a more accurate reflection of the vitamin D reserves in the body compared to measuring the active form, calcitriol. [14] This is because calcitriol levels can fluctuate due to variety of factors such as parathyroid hormone levels, calcium intake, and kidney function, making it a less reliable indicator of overall vitamin D status. [28] By assessing calcifediol levels, health care professionals can make more informed decisions about the need for supplementation and the appropriate dosing to correct deficiencies. [9]

Treatment of vitamin D deficiency with calcifediol

Characteristics of calcifediol. Calcifediol, also known as 25-hydroxyvitamin D3, is a prehormone produced in the liver by the hydroxylation of vitamin D3 (cholecalciferol). [7] It is the primary circulating form of vitamin D and is used as an indicator of vitamin D status in clinical settings. [3] Calcifediol is further hydroxylated in the kidneys to form the active hormone calcitriol (1,25-dihydroxyvitamin D3), which exerts various biological effects in the body. [10] Calcifediol has a higher bioavailability compared to cholecalciferol, meaning that it is more efficiently absorbed and utilized by the body. [29] This characteristic makes calcifediol

a preferred option for patients with diseases that impair the conversion of vitamin D3 to its active forms, such as liver disease or certain genetic disorders. [14] Additionally, calcifediol has a longer half-life than cholecalciferol, providing a more sustained increase in serum 25(OH)D levels. [3]

Mechanism of action of calcifediol. Calcifediol exerts its action mainly through conversion to calcitriol, the active form of vitamin D. [9] Calcitriol binds to the vitamin D receptor (VDR), a nuclear receptor that regulates the expression of genes involved in calcium and phosphate homeostasis, immune function, and cell proliferation. [8] By increasing the absorption of calcium and phosphate in the intestines, calcifediol helps maintain normal bone mineralization and overall skeletal health. [3] Calcitriol also plays a role in regulating the immune system by modulating the activity of immune cells such as T cells and macrophages. [18] This immunomodulatory effect may help reduce inflammation and lower the risk of autoimmune diseases. [3] Furthermore, calcitriol affects cell differentiation and apoptosis, which may affect cancer progression and metastasis. [8]

Efficacy of calcifediol in treating vitamin D deficiency. Clinical studies have shown that calcifediol is effective in rapidly increasing serum 25(OH)D levels in vitamin D deficiency. [30] Compared to cholecalciferol, calcifediol has higher bioavailability and results in a faster and more sustained increase in serum 25(OH)D levels. [29] This makes it a preferred option for patients with severe deficiency or conditions that impair vitamin D metabolism. [14] In a study by Bischoff-Ferrari et al. (2012), calcifediol supplementation improved muscle function and reduced the risk of falls in elderly patients, highlighting its benefits beyond bone health. [31]. Another study by Cavalier et al. (2018) found that calcifediol was more effective than cholecalciferol in achieving optimal 25(OH)D levels in patients with vitamin D deficiency. [28].

Dosage and administration of calcifediol. The dosage of calcifediol depends on the severity of the deficiency and the individual needs of the patient. [21] For adults with vitamin D deficiency, an initial loading dose is usually recommended, followed by a maintenance dose. [3] Calcifediol is available in oral formulations, that are generally well tolerated and convenient for long-term use. [14] Regular monitoring of serum 25(OH)D levels is important to ensure that the desired therapeutic range is achieved and maintained. [21] In cases of severe deficiency, high-dose calcifediol is administered initially, which is then followed by lower, regular doses. New formulations of calcifediol have been developed to allow for monthly dosing, which

enhances patient compliance and simplifies the treatment regimen. Studies have shown that monthly dosing of calcifediol can effectively maintain adequate vitamin D levels with fewer side effects compared to daily or weekly dosing. [21] This approach is particularly beneficial for patients with chronic conditions or those requiring long-term supplementation. [7]

Comparison of calcifediol with other forms of vitamin D. Compared to other forms of vitamin D, such as cholecalciferol and ergocalciferol, calcifediol has many advantages. [29] It has a more predictable pharmacokinetic profile and leads to a fastrer correction of vitamin D deficiency. [31] The intestinal absorption of calcifediol is almost 100%, and therefore higher than that of vitamin D alone. [32] Moreover, calcifediol does not require hepatic activation, making it a suitable option for patients with liver dysfunction. [14] Calcifediol is absorbed by intestinal cells and transported through the portal vein, and therefore immediately available to the circulation, while vitamin D is transported with chylomicrons through the lymphatic system. For this reason, in cases of fat malabsorption or after bariatric surgery, calcifediol is much better absorbed compared to vitamin D alone. [32] A meta-analysis by Tripkovic et al. (2012) showed that calcifediol was superior to both cholecalciferol and ergocalciferol in raising serum 25(OH)D levels. [29] Serum 25OHD increases linearly with increasing calcifediol dose, while serum 25OHD reaches a plateau when higher oral doses of vitamin D are used. [32] Additionally, the higher bioavailability of calcifediol allows for lower dosing and potentially fewer side effects, making it a safer and more effective option for long-term supplementation. [30] Calcifediol, on a body weight basis, is about 3 times more potent than vitamin D in people with mild vitamin D deficiency. The efficacy is up to 6-8 times that of vitamin D when baseline serum 25OHD concentrations are higher or when high doses are compared. In conclusion, calcifediol is an alternative option for correcting vitamin D deficiency and may even be the preferred strategy in cases of intestinal fat malabsorption, after bariatric surgery or for other conditions with suspected impaired hepatic 25-hydroxylase activity. [32]

Conclusions

This review highlights the important role of vitamin D in maintaining overall health and the serious consequences associated with vitamin D deficiency. [1] Calcifediol, due to its higher bioavailability and faster action compared to other forms of vitamin D, is particularly effective in treating vitamin D deficiency. [7] Clinical and observational studies have consistently show that calcifediol leads to rapid and sustained increases in serum 25(OH)D levels, making it a valuable option for patients with severe deficiency or conditions affecting vitamin D

metabolism. [31] Doctors should consider calcifediol as a preferred treatment option for patients with severe vitamin D deficiency or those with certain conditions that impair vitamin D metabolism. [3] Regular monitoring of serum 25(OH)D levels is recommended to ensure optimal dosing and to prevent potential toxicity. [21]

Author's contribution

Conceptualization, Julita Gmitrzuk; methodology, Julita Gmitrzuk and Martyna Opatowska; software, Tomasz Kucharski and Joanna Jakubiec; check, Katarzyna Wiśniewska and Marta Piotrowska; formal analysis, Julita Gmitrzuk and Zuzanna Malinka; investigation, Julita Gmitrzuk and Anna Jachymek; resources, Martyna Opatowska and Tomasz Kucharski; data curation, Joanna Jakubiec, Katarzyna Wiśniewska; writing – rough preparation, Julita Gmitrzuk; writing - review and editing, Julita Gmitrzuk and Marta Piotrowska; visualization, Julita Gmitrzuk, Zuzanna Malinka and Anna Jachymek; supervision, Joanna Jakubiec and Martyna Opatowska; project administration, Julita Gmitrzuk, Katarzyna Wiśniewska. All authors have read and agreed with the published version of the manuscript.

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