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POLISH AND AMERICAN GUIDELINES FOR VITAMIN D DEFICIENCY PREVENTION AND TREATMENT FOR THE GENERAL POPULATION - A LITERATURE REVIEW

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ABSTRACT

Vitamin D plays a well-known role in calcium and phosphate homeostasis. Recent findings also indicate many extraskeletal effects. Studies have shown that a vitamin D deficiency has been associated with chronic conditions in musculoskeletal, cardiovascular, neurological and immune systems. There have been multiple national and international guidelines considering the problem of vitamin D supplementation and treatment. Recommendations for vitamin D prophylaxis and treatment show variability which may result in confusion in clinical practice. The aim of this review is to compare diagnostic thresholds of serum 25(OH)D levels and dosing strategies for prevention and treatment between selected vitamin D guidelines published in Poland, Central Europe and the United States of America. Future recommendations should integrate the results of observational studies and randomized control trials. This way they may benefit the clinicians and patients by simplifying treatment decisions and improving clinical outcomes.

KEYWORDS

Vitamin D, Guidelines, Recommendations, Supplementation, Treatment

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Introduction

Over the last decades, research on the role of vitamin D in every aspect of the human body has been growing in importance. Especially in the last few years after the SARS-CoV-2 pandemic, the interest in vitamin D has been spiking. [1] It has its benefits, as there are a number of effects attributed to vitamin D.

Vitamin D plays a crucial role in bone and mineral metabolism and, therefore, is essential for musculoskeletal health and calcium and phosphate homeostasis. Moreover, there is ongoing research over different effects vitamin D may have, as the vitamin D receptor (VDR) has been identified in almost all human cells. Many studies have already documented a beneficial effect vitamin D has for overall health, including cardiovascular diseases, diabetes, depression, cognition and multiple sclerosis. In addition, during the COVID-19 pandemic it was discovered vitamin D may also have an immune-modulating effect.

Extra-skeletal effects of vitamin D are still raising controversies as the studies are not unambiguous. However, there is a worldwide consensus that vitamin D deficiency may play a role in development of many metabolic and cognitive disorders and, therefore, its supplementation should be taken into consideration for every patient. The problem is a great heterogeneity of the recommendations for prevention of vitamin D deficiency. Over the last 15 years, guidelines recommendations for treatment of vitamin D deficiency have been showing great variability. [2]

However, the growing popularity of vitamin D in the general population also has its downsides.

Vitamin D supplements have increasingly been promoted on social media without appropriate regulation. The unsupervised intake of supplements creates a risk for serious vitamin D overdose, which may lead to hypercalcemia and other complications. In acute cases, patients may present acute kidney injury, cardiac arrhythmia and neuropsychiatric symptoms, while in chronic cases vitamin D toxicity may cause kidney stones, asterisk ulcers and chronic kidney disease or even nephrocalcinosis. Treatment may consist of pharmacological interventions or, in severe cases, hemodialysis. [3]

Although, it is worth taking into account that hypervitaminosis D is rare. Per usual, it is caused by over average doses of vitamin D due to misuse of over-the-counter supplements. Toxicity usually leads to an imbalance in the regulation of bone and mineral metabolism resulting in hypercalcemia and therefore presenting with its associated symptoms. [4]

There are numerous recommendations regarding vitamin D deficiency treatment and prevention. They vary significantly depending on the region of the world they were based in and on the kind of studies they included. It creates a challenge clinicians have to face daily when giving indications to the patients who require vitamin D supplementation or treatment. This study focuses on showing the evolution of guidelines for the general population over the years. The aim of this article is to provide an overview of selected guidelines for prevention and treatment of vitamin D deficiency from Poland, Central European countries and the United States.

Methodology

To comprehensively evaluate the guidelines for vitamin D deficiency prevention and treatment, this study employed a targeted narrative review of contemporary literature. A systematic search strategy was executed across three major electronic scientific databases: MEDLINE/PubMed, Scopus, and Web of Science. The retrieval process utilized a strategic combination of Medical Subject Headings (MeSH) and free-text keywords, specifically including "vitamin D guidelines," "vitamin D deficiency," "vitamin D recommendations," "vitamin D treatment," "vitamin D propylaxis."

Vitamin D Deficiency

Vitamin D presence in the human body depends on two factors: endogenous formation and exogenous intake.

The first factor which differs between societies is endogenous formation of vitamin D. [5] During the exposure to sunlight, a number of processes happen in the plasma membrane of keratinocytes and in the extracellular space of the human skin, which all combine into skin synthesis of vitamin D. It can create up to 80-90% of the body's vitamin D pool.

The second factor is dietary sources. The most important sources for vitamin D in food are fish and fish liver oil, eggs, meat, dairy products and fungi. However, the main source of vitamin D intake in the population varies significantly depending on the age and eating habits. In Japan it is mostly fish, in UK meat and in Czech Republic chicken eggs. For younger individuals, dairy products like butter and cheese will be considered most significant, especially taken into account that dairy products are also often fortified with vitamin D3, making it a great source for supplementation.

Insufficiency in one of the factors mentioned above can be a cause of vitamin D deficiency. The major reason is limited sun exposure leading to insufficient vitamin D endogenous synthesis in the human skin. There are many possible causes. First of all, insufficient sun exposure occurs naturally during colder months, so usually in the northern hemisphere it lasts from October to March and in the southern - from April to September, and it differs depending on the latitude of the region. It may also happen due to increased amount of skin pigment melanin, clothing covering the whole body because of cultural tradition and impaired mobility.

Insufficiency in dietary intake can be another reason. Since the majority of products rich in vitamin D is of animal origin, those who consume vegan or vegetarian diets are at risk of vitamin D deficiency. Other risk factors include diseases which impair vitamin D absorption, such as renal (chronic renal disease) and gastrointestinal disorders (food allergies, celiac disease, cholestasis, biliary obstructions and more) or genetic mutations of involved enzymes. [5] There are also situations when different mechanisms influence 25(OH)D plasma concentration, such as pregnancy, primary hyperthyroidism or interactions with certain drugs that alter the metabolism of vitamin D.

Since vitamin D receptors are present in almost all the cells of the human body, there can be many different symptoms of vitamin D deficiency. One of the vitamin D-dependent processes

is intestinal absorption of calcium and phosphate, thus vitamin D deficiency may present symptoms of hypocalcemia, hypophosphatemia and an increase in alkaline phosphatase. In children, it manifests as rickets, which results in soft bones and skeletal deformities, due to failure of bone tissue to become properly mineralized. In adults and adolescents, vitamin D deficiency is manifested as osteomalacia and osteoporosis, which are characterized by increased demineralization of bones during the remodelling process, resulting in weak bone structure. Therefore, vitamin D has two effects on the skeleton - it reduces bone mineral density and prevents bone mineralization.

Vitamin D deficiency may present also as muscle weakness and fatigue, increased susceptibility to infectious diseases and slower healing of epidermal wounds. It may also be one of the contributing factors to developing neurological disorders such as multiple sclerosis.

The question remains, how do we assess vitamin D deficiency? Globally, the prevalence of vitamin D deficiency has been estimated as 45% for the period 2000-2022. [6] Vitamin D deficiency impacts a great

number of populations all over the world - from 5% of the United States population to approximately 14% of the population of Europe. [7] Moreover, a significant proportion of the population in Middle Eastern and Gulf states, as well as up to 20% of individuals in Africa is affected by this deficiency. The numbers differ between different regions of the world because of the ways vitamin D enters our systems.

It shows just how important vitamin D supplementation is, considering the potential consequences of deficiency. Table 1 provides an overview of selected guidelines for prevention and treatment of vitamin D deficiency from Poland, Central European countries and the United States. [8,9,10,11,12,13,14]

Table 1. Selected guidelines for the **general population** for prevention and treatment of vitamin D deficiency in adults with a focus on Poland, Central European countries and the USA.

	Age	Oral Vitamin D for Prevention [daily doses in IU]	Oral Vitamin D for Treatment [daily doses in IU]	Diagnostics thresholds defining vitamin D sufficiency on the basis of serum 25(OH)D concentration [ng/mL]
Polish Recommendations 2009 [8]	>18 >75	800-1000 -	up to 7000 -	30-80
Endocrine Society 2011 USA [9]	>18 >70	600-2000 800-2000	6000 or 50,000/week	≥30
Central European Recommendations 2013 [10]	>18 >75	800-2000 -	7000–10,000 or 50,000/week	30-50
Polish Recommendation 2018 [11]	>18 >75	800-2000 2000-4000	6000	30-50
Poland 2023 Update [12]	>18 >75	1000-2000 2000-4000	4000	30-50
Endocrine Society 2024 [13]	>18 >70 >75	600 800 No supplementation beyond the recommended DRI*. Empiric supplementation recommended of approximately 900 IU /day.	Not defined; 2024 Guidelines do not provide guidelines for treatment.	Not defined;
National Institute of Medicine's Office of Dietary Supplements* [14]	>18 >70	600 800	Not defined;	≥20

*DRI - Dietary Reference Intake established by the National Institute of Medicine

Vitamin D Serum Levels

As shown in Table 1, scientific consensus over sufficient serum 25(OH)D level does not exist. While most of the guidelines suggest optimal serum 25(OH)D concentration to be over 30 ng/mL, the latest 2024 Endocrine Society Guidelines do not provide such information. At the same time, there are numerous observational studies showing correlation between higher serum 25(OH)D levels and better clinical outcomes in specific health problems. [15,16,17] This was not included in 2024 Endocrine Society Recommendations because they were based solely on randomized placebo-controlled trials. As explained by William B. Grant et al. [18], "RCTs do not supply much evidence for guiding recommendations due to their poor designs, enrolling participants with above-average 25(OH)D concentrations, providing the vitamin D treatment arm with low

vitamin D doses, and analyzing the results according to the intention to treat. Thus, observational studies provide the best evidence for recommendations.”

As shown in a review article [16] published in response to the new 2024 Endocrine Society Guidelines, better outcomes while maintaining >40 ng/mL were shown in autoimmune disorders, Cesarean section births, dental caries in infants and more. There are even situations, when higher serum 25(OH)D concentrations should be considered - such as >50ng/mL for pre-diabetes to T2DM and breast cancer incidence and >60 ng/mL for pre-eclampsia. All in all, achieving serum 25(OH)D levels above 40 n/mL can significantly reduce the risks associated with various diseases. [19] This being said, to benefit a greater number of people, it is recommended to maintain serum 25(OH)D concentrations between 40 and 70 ng/mL - this will overcome most of these disorders. [18,20]

As this article focuses on the general population, it will not include detailed information about when to examine serum 25(OH)D level. All of the guidelines mentioned in the article recommend against routine screening for a 25(OH)D level in the general population [7,8,9,10,11,12]. However, there are a number of patients at risk for deficiency which make them prone to vitamin D deficiency. 25(OH)D measurements should be considered in these high-risk groups, as they may particularly benefit from vitamin D supplementation. Given the fact that in certain conditions, as mentioned above, higher serum 25(OH)D levels are recommended, it is especially important to assess and, in case of deficiency, increase serum 25(OH)D concentration. These conditions include among others obesity, osteoporosis, chronic kidney disease, hepatic failure, malabsorption syndromes, hyperparathyroidism, chronic autoimmune diseases, pregnant and lactating women and more. [2,13]

Vitamin D Supplementation

Naturally, when there is no consensus over serum 25(OH)D level, there cannot be a consensus over the recommended vitamin D supplementation dose. Hence the differences in Table 1. between recommended oral doses for prevention of vitamin D deficiency. The recommended oral vitamin D doses as prophylaxis will always differ depending on the population they are created for. Serum 25(OH)D levels depend on many factors such as the season, latitude, sun exposure, body mass index (BMI), sex, age, skin pigmentation and dietary intake of vitamin D. [21] Considering that, certain populations will be at higher risk of vitamin D deficiency than the others. For this reason, there are suggested different solutions for specific populations, such as food fortification, which was successfully introduced in Finland. [18] Still, vitamin D supplementation remains the most efficient way to increase 25(OH)D concentrations.

To achieve around 30–40 ng/mL, vitamin D supplementation for many people with normal body weight must be at least 2000 IU/day (50 µg/day). [18] It is also suggested this dose can be taken weekly (15,000 IU) or monthly (60,000 IU) for better compliance. This is a recommended dose in most guidelines presented in recent years, as shown in Table 1. However, this is not the case for the recent Endocrine Society recommendations which suggest 600-800 IU/day as a sufficient vitamin D dose. There have already been published articles pointing out limitations of these guidelines. [16,18] The main concern is they are focused on randomized controlled trials (RCTs) and do not include prospective observational studies. RCTs are considered unsuitable for nutrients such as vitamin D, as there is no individual who is entirely vitamin D-depleted. Moreover, most RCTs taken into consideration have included participants with 25(OH)D levels at 30 ng/mL or above, hence they may not benefit from vitamin D supplementation, as 30 ng/mL is considered sufficient by most recommendations. In addition, most RCTs have been bone-centred and have failed to confirm vitamin D's vital role in extraskeletal diseases. Grant W.B. et al. also raise concern that TES recommendations do not sufficiently address environmental and lifestyle factors, such as latitude, diet, nutrition and sun exposure which may significantly influence 25(OH)D serum levels. As an example, they mention the Middle East, where because of cultural differences, such as wearing concealing clothing and consuming less meat-based products, risk of vitamin D deficiency is higher compared to Western developed countries. Since new guidelines do not recommend routine vitamin D testing in the general population and recommend relatively low doses of vitamin D supplementation, there is a concern it may lead to widespread under-diagnosis of vitamin D deficiency.

This heterogeneity in vitamin D recommendations needs further research so that clinicians have clear guidance while making treatment decisions for vitamin D-deficient patients.

Vitamin D Treatment

Vitamin D treatment should be based on 25(OH)D serum level, as a primary biochemical marker. It is recommended to use total 25(OH)D serum concentration based on measurements of both 25(OH)D₂ and 25(OH)D₃. Treatment recommendations vary between guidelines but also depend on the level of deficiency. It is worth mentioning that 2024 Endocrine Society Guidelines do not include treatment recommendations as they were focused on prevention of vitamin D deficiency. Other recommendations included in this article suggest different therapeutic doses based on 25(OH)D serum levels. One of the key differences is a threshold for deficiency, which some recommendations consider as low as 20 ng/ml, while most set it at 30 ng/ml, excluding specific chronic conditions mentioned earlier. A treatment duration should depend on the severity of the vitamin D deficiency, varying between 4 to 12 weeks. After approximately 6-12 weeks of treatment, 25(OH)D serum level is recommended to evaluate the effectiveness of the treatment. [2] When the concentration of 30-50 ng/ml is reached, it is recommended to consider consecutive maintenance dosing, individualized based on risk factors such as obesity, malabsorption, limited sun exposure or other conditions, as mentioned earlier.

Conclusions

Vitamin D deficiency is an important clinical problem which can be effectively prevented and treated in most cases when appropriately managed. However, there is still no consensus over the recommended doses for prophylaxis and treatment neither for the general population, nor for groups at risk of vitamin D deficiency. Guidelines for vitamin D prophylaxis and treatment show heterogeneity which may result in inconsistent care, under- or overtreatment and confusion in clinical practice. There is a great need for further research of the topic. Future guidelines should integrate the results of observational prospective cohort studies and randomized control trials. More consistent guidelines may benefit the clinicians and patients by simplifying treatment decisions and improving clinical outcomes.

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