Preprints.org

Review

Not peer-reviewed version

Daily and Weekly “High Doses” of Cholecalciferol for the Prevention and Treatment of Vitamin D Deficiency for Obese or Multi-morbidity and Multi-treatment Patients Requiring Multi-drugs – A Narrative Review

Pawel Pludowski *, Ewa Marcinowska-Suchowierska, Galym Togizbayev, Zhanna Belaya, William B. Grant, Stefan Pilz, Michael F. Holick

Posted Date: 19 July 2024

doi: 10.20944/preprints202407.1527.v1

Keywords: vitamin D in high dose; 7,000 IU per day; 30,000 IU per week; 50,000 IU per week; effectiveness; safety; intermittent doses

Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

Daily and Weekly "High Doses" of Cholecalciferol for the Prevention and Treatment of Vitamin D Deficiency for Obese or Multi-Morbidity and Multi-Treatment Patients Requiring Multi-Drugs—A Narrative Review

Pawel Pludowski [1,*], Ewa Marcinowska-Suchowierska [2], Galymzhan Togizbayev [3], Zhanna Belaya [4], William B. Grant [5], Stefan Pilz [6] and Michael F. Holick [7]

[1] Department of Clinical Biochemistry, The Children's Memorial Health Institute, 04-730, Warsaw, Poland; pludowski@yahoo.com
[2] Department of Internal Medicine and Geriatric Cardiology, and the Department of Geriatrics and Gerontology, School of Public Health, The Center of Postgraduate Medical Education, 02-673 Warsaw, Poland
[3] Kazakh National Medical University, 050000 Almaty, Kazakhstan
[4] The National Medical Research Center for Endocrinology, 117036 Moscow, Russia; jannabelaya@gmail.com
[5] Sunlight, Nutrition and Health Research Center, San Francisco, CA 94109, USA
[6] Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, 8036 Graz, Austria
[7] Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University School of Medicine, Boston, MA 02118, USA
* Correspondence: p.pludowski@ipczd.pl

Abstract: Daily vitamin D supplementation using higher than normal dosing (up to the upper limit value) and intermittent (once or twice per week) dosing were studied in patients with increased risk of vitamin D deficiency. Using a PubMed database, a thorough search for published randomized controlled trials and other studies was conducted and results were analyzed. This review provides an overview of the use of 7,000 IU daily, and 30,000 IU per week or twice weekly, or 50,000 IU weekly of vitamin D for obtaining and maintaining 25(OH)D concentrations to at least 30 ng/mL in patients at high risk of vitamin D deficiency. The abovementioned dosing should be considered in adults with obesity, with liver disease or malabsorption syndromes, or multi-diseased patients, mainly seniors requiring multi-drug treatment, including drugs affecting vitamin D metabolism. The simple schedule for 7,000 IU/day and 30,000 IU/week or twice weekly, or 50,000 IU/week for use by patients with an increased risk of vitamin D deficiency were provided for consideration. Without monitoring of 25(OH)D, the daily dose of 7,000 IU or intermittent 30,000 IU/week should be considered for a prolonged time as prophylactics or maintenance doses, mainly in obese patients, patients with liver disease, with malabsorption syndromes and in seniors with polypharmacy. For the treatment of possible vitamin D deficiency without assessment of 25(OH)D in these groups, the intermittent doses of 30,000 IU twice weekly or 50,000 IU per week should be considered for a 6–8-week period only. The higher daily doses or the intermittent doses suggested above are effective, safe, and responsive based on patient's preferences.

Keywords: vitamin D in high dose; 7,000 IU per day; 30,000 IU per week; 50,000 IU per week; effectiveness; safety; intermittent doses

© 2024 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

1. Introduction

Vitamin D is a mediator in the regulation of skeletal, calcium and phosphate metabolism and has already been shown to play an important role in musculoskeletal health as well as in the prevention of nutritional rickets, osteomalacia and osteoporosis. The expression of vitamin D receptors (VDRs) in human cells suggests an even more general, extraskeletal impact of vitamin D on human health [1]. Vitamin D may be important for various organs and tissues due to the presence of VDR in almost every tissue and cell. Consequently, vitamin D deficiency might have detrimental effects on these organs. In line with this, a decrease in the concentration of 25-hydroxyvitamin D (25(OH)D - the main marker of vitamin D supply) – has been associated with many chronic diseases. It has been shown that low concentrations of 25(OH)D (Table 1) are associated with the risk of developing cancer, malabsorption syndromes, osteoporosis and other diseases and complications characterized by bone metabolism disorders, autoimmune diseases, allergies, endocrine diseases, or obesity and its complications [1,2].

Table 1. Target threshold values for 25(OH)D concentrations.

25(OH)D concentration	Vitamin D status
<20.0 ng/mL (<50 nmol/L)	Deficiency - requiring treatment
20.0–29.9 ng/mL (50–75 nmol/L)	Suboptimal status - requiring prevention
30.0–50.0 ng/mL (75–125 nmol/L)	Optimal status - requiring prevention*
40.0–60.0 ng/mL (100–150 nmol/L)	Preferred range - requiring prevention**
60.0–100.0 ng/mL (150–250 nmol/L)	Increased status, an area of potential benefits and risks
>100 ng/mL (>250 nmol/L)	Potential risk of toxicity symptoms from vitamin D overdose*
>150 ng/mL (>375 nmol/L)	Serious risk of toxicity (with hypercalcuria, hypercalcemia, reduced PTH)**

* According to Polish Guidelines [1]; ** According to the older Endocrine Society Guidelines (USA) [2].

The high incidence of vitamin D deficiency in the world requires actions to improve this situation. General screening for vitamin D deficiency is not recommended; however, 25(OH)D testing is suggested in certain risk groups susceptible to vitamin D deficiency to determine the optimal vitamin D dosage regimen and ensure sufficient vitamin D intake [1]. Assessment of the 25(OH)D value is suggested in obese people and in patients chronically treated with drugs affecting vitamin D metabolism (e.g., anticonvulsants, glucocorticosteroids, antiretrovirus medications, etc.), malabsorption syndromes (e.g., cystic fibrosis, inflammatory bowel diseases, bariatric surgery, radiation enteritis), liver failure, chronic kidney disease, osteomalacia, chronic musculoskeletal pain, hyperparathyroidism, autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis), in older people (> 65 years), especially in those who have had a history of falls or non-traumatic fractures (osteoporosis), in patients with granulomatous diseases (e.g., sarcoidosis, tuberculosis), in patients with a 24-hydroxylase deficiency, in people with chronic infections, and in people with dark skin pigmentation [1]. In many of these cases higher doses of vitamin D are required to achieve the target 25(OH)D value. Recently, the Endocrine Society published new guidelines available for clinicians suggesting against routine vitamin D empiric supplementation for prevention of disease (except in pregnancy and pre-diabetes) and screening of 25(OH)D in adults aged 18-74 years [3]. The “empiric vitamin D”, according to “technical remarks”, “include daily intake of fortified foods, vitamin formulations that contain vitamin D, and/or daily intake of vitamin D supplement (pill or drops)” [3]. Both seniors 75 years of age and older as well as children and adolescents appeared to not be subject to these suggestions related to prevention of disease due to hypovitaminosis D. Previous Polish guidelines published in 2023 and Central and Eastern European statements, recommend considering 25(OH)D measurements in patients at risk, and in cases where this is not possible, dosing recommendations for the general population that should be followed, considering the possible co-occurrence of obesity [1,4].

It should be emphasized that synthesis of vitamin D in the skin (limited by use of sun protection creams, by age, religion, seasons of year, etc.) or ingestion from the intestine, adipose tissue storage,

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

and release of fat soluble vitamin D, liver status and its disorders or diseases, kidney status and its disorders or diseases, medications influencing the anabolic or katabolic arm of the vitamin D endocrine pathway, multi-morbidity that needs multi-treatment with multi-drugs, etc., are known to affect the vitamin D dosing scheme and a proper choice of dosage. These factors always should be considered during a medical visit of a patient looking for help, despite the rules of the evidenced-based medicine. Another quote from the recently published Endocrine Society guidelines [3] is: "Based on the panel's best estimates of treatment effects in adults aged 50 years and older, the panel judged that any desirable effects of intermittent, high-dose vitamin D (compared to lower-dose, daily vitamin D) are likely trivial, while the anticipated undesirable effects are likely to be small".

Due to the prevalence of vitamin D deficiency around the world and the positive effects of greater vitamin D supplementation in high risk groups, the aim of this study was to evaluate the available data on daily 7,000 IU or 30,000 IU/week or twice weekly or 50,000 IU/week as the intermittent dose of vitamin D in high risk groups.

This narrative review, "likely trivial" with obvious limitations, was aimed to evaluate the maintenance/prophylactic dosing of vitamin D in higher daily doses – for specific patient's condition (obesity, malabsorption, etc.), or therapeutic dosing in the intermittent weekly doses – due to patient's preferences, effectiveness, adherence, and safety.

2. Methods

A narrative review of the literature focused on high vitamin D dosing for groups at risk of vitamin D deficiency was performed using the electronic database PubMed.gov. The aim of the analysis is to provide practical suggestions, not a strict recommendations, based on search results as well as our medical experience, for vitamin D dosing in obese patients as well as those with multi-disease and on multi-drug therapy with or without 25(OH)D monitoring, as a groups in high risk of vitamin D deficiency. Therefore, a review was performed on vitamin D deficiency in obese patients, patients with liver disease or malabsorption syndromes, and in seniors with polypharmacy due to investigate the current prevention and treatment trends in these groups, if those possible suggestions or even guidelines were available. Then, the final target was to review the studies of 7,000 IU per day for prevention and 30,000 IU per week or twice weekly and 50,000 IU per week used for treatment of vitamin D deficiency in the above groups of patients. In the final stage of search of PubMed database a words such as: "cholecalciferol 7,000 IU daily", "cholecalciferol 30,000 IU", "cholecalciferol 50,000 IU", together with additional words such as "daily", "weekly", have been used in the research of adult population at high risk groups of vitamin D deficiency, mentioned below, respectively. Randomized controlled trials, clinical trials and then meta-analyzes, and all studies focused on these doses were selected for analyzes.

3. Results

3.1. Groups at Significantly Increased Risk of Vitamin D Deficiency

3.1.1. Obesity—Prevention and Treatment of Vitamin D Deficiency

According to the World Health Organization, the problem of excessive body weight affects over 2 billion people and contributes to approximately 2.8 million deaths annually [5,6]. For example, in Poland, overweight (i.e., body mass index (BMI) in the range of 25.0 - 29.9 kg/m^2) can be diagnosed in 60% of adult Poles, and in people with very high cardiovascular risk can be diagnosed in 85% [5,6]. Obesity (BMI ≥ 30.0 kg/m^2) is currently diagnosed in over 20% of adult Poles, and the National Health Fund estimates that in 2028 the percentage of adults suffering from obesity in Poland will be 30% [7]. This means that each Family Doctor in Poland, among the 2,500 patients in his or her practice, takes care of 1,500 overweight people, including 500 obese patients, and this number will increase 1.5-fold by 2028 [7].

Obesity, leading to over 200 complications affecting virtually all organs and systems in the human body, is a significant cause of disability and increased mortality, making it an significant

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

social and economic problem [8]. Complications related to obesity also include vitamin D deficiency, which requires treatment. Epidemiological studies indicate that the probability of satisfactory vitamin D supplementation is inversely proportional to the BMI value and, conversely, the higher the BMI value, the greater the probability of vitamin D deficiency [9]. Based on meta-analyses, it was estimated that obesity increases the risk of vitamin deficiency by approximately 1.5 times [10]. The potential causes of the increased risk of vitamin D deficiency among patients with overweight or obesity include (a) limited cutaneous cholecalciferol synthesis associated with lower exposure to sunlight (lower physical activity and social exclusion); (b) abnormal eating habits; (c) accumulation/sequestration in adipose tissue ("fat trap"); and (d) disruption of hepatic hydroxylation of cholecalciferol at position 25 [11].

Vitamin D deficiency in obese patients is a factor that increases the likelihood of metabolic complications of this disease [12]. On the contrary, prospective studies have estimated that adequate vitamin D supply protects overweight patients from developing type 2 diabetes (odds ratio 0.6) [13]. Pathophysiological mechanisms linking vitamin D deficiency with an increased risk of carbohydrate metabolism disorders include the regulatory influence of the active metabolite of cholecalciferol - calcitriol ($1,25(OH)_2D$) on the expression of pro-inflammatory genes (which leads to the silencing of metabolic inflammation causing insulin resistance) and genes controlling insulin secretion [14]. However, vitamin D supplementation at a dose of 25,000 IU/week improved insulin sensitivity by 50% in obese patients [15]. Meta-analyses have also shown a beneficial effect of vitamin D supplementation (up to 60,000 IU/week) on fasting glucose levels and the percentage of glycated hemoglobin in patients with prediabetes [16]. For the record, 60,000 IU/week is a higher dose than 7 days X 7,000 IU/day (49,000 IU/week).

Regular vitamin D supplementation is an essential element of comprehensive care for obese patients. The guidelines suggest that to achieve and maintain 25(OH)D concentration >30–50 ng/mL [1], the supplemented dose should be adjusted to the BMI value, and, importantly, the daily dose of cholecalciferol should be on average 2-3 times higher than the dose used in people with normal body weight, up to 10,000 IU/day without additional control [1,17]. It should be emphasized, however, that even when using high doses of vitamin D, it is generally difficult for overweight and obese patients to equate serum 25(OH)D concentration to the recommended values [1,18]. Until recently, this problem was associated primarily with the sequestration of vitamin D in excessive adipose tissue; currently, impaired hydroxylation of cholecalciferol at position 25, associated with fatty liver disease, is increasingly being documented [19].

When determining individual dosage, factors such as age, body weight, dietary intake of vitamin D, comorbidities and medications taken should be considered [1]. An important aspect when determining the dose should be obesity. Recommendations regarding supplementation in people diagnosed with obesity indicate the need to double or triple the daily dose of vitamin D compared to the dosage in people without the above weight problems [1]. Therefore, obese people over 75 years of age, usually suffering from several morbidities and often treated with many drugs, including those affecting the metabolism of vitamin D, should regularly take 7,000-10,000 IU/day (up to 250 μg/day). In the case of persistent vitamin D deficiency, doses should be increased accordingly and adjusted to the degree of deficiency, if assayed, using therapeutic dosing, i.e., 30,000 IU twice weekly or 50,000 IU weekly.

3.1.2. Digestive Tract Diseases—Prevention and Treatment of Vitamin D Deficiency

Digestive system diseases are some of the strongest risk factors for vitamin D deficiency. Chronic liver diseases and malabsorption disorders of various etiologies should be mentioned. The most common causes of vitamin D deficiency related to digestive tract diseases are presented in Table 2.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

Table 2. The most digestive tract diseases leading to vitamin D deficiency - indications for the use of high dosing of vitamin D.

Liver failure during:	**Malabsorption syndromes during:**
Primary cholangitis (formerly: primary cirrhosis biliary)	Celiac disease
Primary sclerosing cholangitis	Crohn's disease
Alcoholic hepatitis	Cystic fibrosis
Autoimmune hepatitis and overlap syndromes	Pancreatic exocrine insufficiency
Infections with hepatotropic viruses	Bariatric procedures
	Whipple's disease
	Short bowel syndrome

Under physiological conditions, 25(OH)D is mainly produced in the liver because of hydroxylation of cholecalciferol at position 25; therefore, the synthesis of this metabolite is impaired in patients with chronic liver diseases. Vitamin D deficiency is found in over 90% of patients with liver failure, both in the case of damage to the liver during cholestatic diseases, including primary sclerosing cholangitis, as well as in liver cirrhosis of post-inflammatory or alcohol-related etiology [19–23]. The major cause of vitamin D deficiency in liver disease is, however, malabsorption due to lack of bile and other secretions that help the absorption of vitamin D into the lymphatic system [2]. In recent years, the number of patients with severe liver damage due to metabolic associated fatty liver disease (MAFLD) has been increasing rapidly, which also leads to reduced 25-hydroxylase activity and impaired 25(OH)D synthesis. Therefore, patients with liver dysfunction can benefit by increasing the vitamin D intake 2-3-fold (i.e., 7,000 - 10,000 IU/day) and this strategy is an effective and safe solution [1].

The absorption of fat-soluble cholecalciferol in the intestine is estimated at approximately 70% in HEALTHY people; however, in people with intestinal absorption disorders, e.g., after bariatric surgery, or in patients with celiac disease, short bowel syndrome, pancreatic insufficiency, or biliary cirrhosis, the efficiency of cholecalciferol absorption is limited, deteriorates significantly, and may drop below 50% to several percent, depending on the disease [24]. Therefore, in patients with digestive system diseases, doses starting from 7,000 IU/day, and 10,000 IU/day as part of a PREVENTION strategy and higher doses, for example 30,000 IU twice weekly or 50,000 IU per week, as part of the TREATMENT of vitamin D deficiency should be considered [1]. However, patients exposed to TREATMENT dosing should be monitored for their vitamin D status at least once every 2-3 months, until a stable dose has been established and then less frequently, usually once or twice a year.

3.1.3. Prevention and Treatment of Vitamin D Deficiency in Elderly People—The Problem of Multi-Morbidity and Multi-Drug Use

Taking into account that as a result of the physiological aging process, there are changes in the pharmacokinetics of vitamin D (i.e., decreased absorption from the gastrointestinal tract, distribution in the body - increased amount in adipose tissue) as well as the fact that at least in Poland, multi-morbidity affects almost 70% of the youngest seniors and 90% of the oldest seniors, which results in an increased rate of multi-drug users (> 10 drugs), it is understandable that the senior population

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

requires different procedures in PREVENTION and TREATMENT of vitamin D deficiency (compared with younger people).

In the (sub)population of HEALTHY seniors, the most common cause of vitamin D deficiency is insufficient supply in the diet and reduced effectiveness of skin synthesis, associated with the development of atrophic skin lesions and a gradual decrease in the concentration of the vitamin D precursor 7-dehydrocholecalciferol [25]. As a result of these changes, the efficiency of skin synthesis is 4 times lower in people over 70 than in young people with the same exposure to the sun. Additionally, an increase in the amount of adipose tissue, including overweight and obesity, and a decrease in lean body mass with age increases vitamin D deficiency [26].

Vitamin D deficiency occurs more often and is much more severe in older people with multi-morbidities and multi-drug use (geriatric patients). This is due to the overlapping states of impaired bioavailability and/or pharmacokinetics of vitamin D, which are the consequences of individual diseases and treatment of the physiological changes associated with aging. Reduced absorption of exogenous vitamin D from the gastrointestinal tract occurs in patients with malabsorption syndromes (e.g., with inflammatory bowel diseases, celiac disease, after bariatric surgery). Chronic liver diseases, including fatty liver disease, lead to impaired vitamin D absorption, hepatic 25-hydroxylation and reduced 25(OH)D production, whereas chronic kidney disease impairs 1-α hydroxylation and calcitriol synthesis. The highest prevalence of vitamin D deficiency is observed in elderly patients with fragility fractures. It is usually associated with bone mineralization defects. This group of patients also requires a higher dose of vitamin D.

Multidrug use and unfavorable drug interactions occur frequently enough in older people to remember them and take them into account when PREVENTING vitamin D deficiency. The drugs used have an unfavorable effect on the pharmacokinetics of vitamin D, leading to its systemic deficiency, and can be divided into drugs that reduce absorption of vitamin D from the gastrointestinal tract and drugs affecting its metabolism [27]. The first category includes lipase inhibitors, which are widely used in the treatment of obesity, much more often in younger people than in seniors. They increase the excretion of fats in the feces from 5% to 30%, including fat-soluble vitamin D, leading to systemic vitamin D deficiency. The second category includes drugs that affect the metabolism of vitamin D, including anticonvulsants, glucocorticosteroids, HIV medications and statins. Anticonvulsants (antiepileptic drugs), such as carbamazepine, phenobarbital or phenytoin, but also gabapentin (used not only in the treatment of epilepsy, but also in the treatment of chronic pain, including neuropathic pain), lamotrigine (used in psychiatry as a mood stabilizer), or valproic acid used in bipolar disorder, increase the activity of 24-hydroxylase - a key enzyme for vitamin D catabolism. As a result, this leads to increased elimination of all vitamin D metabolites and symptomatic osteomalacic achiness in the muscles and bones. Chronic glucocorticosteroids, regardless of the route of administration, promote the development of hypovitaminosis D and steroid-induced osteoporosis. Glucocorticoids have been documented to increase 24-hydroxylase expression and 24-hydroxylase mRNA expression. Studies also indicate direct inhibition of liver 25-hydroxylase by these drugs - glucocorticosteroids. Moreover, glucocorticosteroids directly block the vitamin D receptor. Statins widely used in the treatment of lipid disorders (e.g., atorvastatin, lovastatin, and simvastatin) are metabolized in the liver with the participation of the CYP3A4 enzyme, which is part of cytochrome P450. CYP3A4 also participates in vitamin D metabolism and promotes vitamin D metabolism disorders, including increased elimination.

It should also be noted that vitamin D deficiency may also reduce the effectiveness of some medications. Thus, in patients with osteoporosis treated with bisphosphonates, denosumab, and in the presence of vitamin D deficiency, the increase in bone mass is much lower than in people undergoing treatment who are vitamin D sufficient [28]. Thus, it is widely recommended to first treat vitamin D deficiency and only then start with osteoporosis drugs when 25(OH)D concentrations are sufficient.

It should be noted that in the geriatric population, often with multi-morbidities and multi-drug use, to reach and then maintain appropriate vitamin D status requires the use of doses starting from 7,000 IU/day.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

However, a dose of 30,000 IU twice per week or 50,000 IU weekly as a treatment scheme for 6-8 weeks should be considered for those suffering from multi-morbidity and multi-drug use.

Regarding safety issues, vitamin D toxicity was most often observed in people who took very high doses without a prescription and medical control of 50,000–100,000 IU per day of vitamin D for several months to several years, depending on age and body weight and other factors described above [29].

3.2. Cholecalciferol Supplementation at a Dose of 7,000 IU Daily

In a double-blind study, 52 people aged 18 to 50 years with obesity (BMI > 30 kg/m^2) and 25(OH)D concentration < 20 ng/mL were randomly assigned to 26 weeks of treatment with 7,000 IU of vitamin D administered daily or placebo [30]. Body composition and fat distribution [e.g., subcutaneous fat (SAT) and visceral fat (VAT)], insulin resistance (HOMA-IR), blood pressure, plasma lipids, and circulating inflammatory markers were assessed. Half-year (26 weeks) supplementation with 7,000 IU/day resulted in an increase in the average 25(OH)D concentration from 13.2 ng/mL (33 nmol/L) to 44 ng/mL (110 nmol/L; $p < 0.0001$) and in a reduction in parathyroid hormone (PTH) concentration from 5.3 to 4.5 pmol/L ($p < 0.01$) in the intervention group using 7,000 IU/day of cholecalciferol. Supplementation did not cause changes in the examined adipose tissue parameters (SAT, VAT) compared with placebo. Supplementation with 7,000 IU/day also had no significant effect on insulin resistance, blood pressure, plasma lipids, or any of several inflammatory markers tested, including high-sensitivity C-reactive protein (hsCRP). In their conclusions, the researchers stated that increasing 25(OH)D concentration because of the supply of vitamin D at a dose of 7,000 IU/day for 26 weeks had no effect on obesity complications in adults with low initial 25(OH)D concentration, apart from correcting vitamin D deficiency [30]. Interestingly, after analyzing body composition, including data determined by Dual X-ray Absorptiometry and bone turnover markers, a significant increase in bone mineral density (BMD, g/cm^2) in the forearm was revealed by as much as 1.6 ± 0.7% ($p = 0.03$), which is not usually reported after 26 weeks on the study, and a positive effect of this dose of cholecalciferol (7,000 IU/day) on bone turnover in people with obesity compared with placebo was observed [31].

Vitamin D deficiency is common in HIV-infected patients and is associated with an increased risk of disease severity and morbidity. HIV-infected people were invited to participate in a study determining the safety and effectiveness of using 7,000 IU of vitamin D daily for 12 months to achieve and maintain increased serum 25(OH)D concentrations and improve immune status [32]. This was a double-blind study in women with perinatal HIV infection (PHIV) and behaviorally acquired HIV infection (BHIV) (5.0–24.9 years). Safety, serum 25(OH)D concentration and immune status were assessed at baseline, 3, 6, and 12 months. After 3, 6, and 12 months of the study, 25(OH)D concentration was higher in the case of supplementation with 7,000 IU/day compared with the baseline value and higher than in the placebo group ($p < 0.05$). At baseline, and then at 3, 6, and 12 months, a placebo group had a 25(OH)D concentration of 17.0 ± 9.2 ng/mL, 17.7 ± 9.0 ng/mL, 18.4 ± 10.4 ng/mL, and 16.9 ± 9.3 ng/mL, respectively. The treatment group using 7,000 IU/day had a marked increase in 25(OH)D. At baseline, 3, 6, 12 months, the respective 25(OH)D concentration values were 18.2 ± 8.4 ng/mL, 32.5 ± 13.6 ng/mL, 29.2 ± 14.4 ng/mL, and 28.4 ± 19.8 ng/mL. In the group supplemented with a dose of 7,000 IU/day, the percentage of naive T helper cells (Naive Th%) in the treatment group was higher ($p < 0.01$), as was the percentage of T helper cells (CD4%), which increased with supplementation in subjects taking highly active antiretroviral therapy (HAART) – a factor strongly affecting the vitamin D metabolism pathway. Additionally, viral RNA titer was reduced ($p \leq 0.05$). The change in 25(OH)D concentration recorded during the study was a predictor of changes in viral RNA titer after 3 and 12 months and CD4% after 3 months ($p < 0.05$). Daily administration of 7,000 IU of vitamin D for 12 months was safe in HIV-infected people and effectively increased 25(OH)D concentration [32]. Supplementation improved some clinically important markers of HIV resistance in patients taking HAART [32]. Moreover, a review of several studies on the potential protective role of vitamin D supplementation at a dose up to 14,000 IU per day in HIV-1 infection showed that the most effective dose in restoring adequate 25(OH)D concentration was

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

7,000 IU per day [33]. Optimal 25(OH)D concentrations (> 30 ng/mL) after supplementation with 7,000 IU daily were found in 80% of patients, with higher concentrations observed after 12 months of treatment [33].

The effects of vitamin D supplementation on the cardiovascular system by the assessment of arterial stiffness and autonomic nervous system activity was performed as RCT in overweight or obese people in Brazil [34]. Patients aged 40 – 70 years with BMI 25.0 – 39.9 kg/m^2 and 25(OH)D concentrations < 30 ng/mL were exposed to 7,000 IU/daily for 8 weeks. The vitamin D group and control group at baseline had 25(OH)D concentration values of 22.8 ± 4.9 ng/mL and 21.7 ± 4.5 ng/mL (p = 0.590), respectively. After 8 weeks of treatment, the group taking 7,000 IU daily, but not controls, had a significant increase in 25(OH)D values (p < 0.001), showing the concentrations close to 35.6 ng/mL. This coincided with a significant reduction in systolic blood pressure (SBP) from a baseline value of 123 ± 15 mmHg up to 119 ± 14 mmHg (p = 0.019) and alkaline phosphatase (213 ± 55 mg/dL to 202 ± 55 mg/dL, p = 0.012). The vitamin D treated group showed lack of augmentation pressure (AP) and augmentation index (Alx) after 8 weeks; AP: 8 mmHg at baseline and 8 mmHg after 8 weeks, and AIx: 26 vs. 25% at follow up, respectively (p > 0.05). The controls, conversely, showed an increase in augmentation pressure (AP: 9 vs 12 mmHg, p = 0.028) and augmentation index (AIx: 26 vs. 35%, p = 0.020) [34]. Furthermore, the vitamin D-treated group showed after 8 weeks a significant increase in the parasympathetic nervous system index (PNSi) (-0.64 ± 0.94 at baseline and -0.16 ± 1.10 at follow up, p = 0.028) and the mean intervals between each heartbeat (R-R) from 866 ± 138 ms at baseline to 924 ± 161 ms after the study, p = 0.026). This RCT revealed that daily treatment of 7,000 IU was safe and effective both for restoring of proper vitamin D status in overweight or obese patients and to improving blood pressure and autonomic balance [34].

3.3. The Use of Intermittent Dose of 30,000 IU Once or Twice per Week and 50,000 IU Weekly

In a randomized, placebo-controlled trial, 30,000 IU per week was given for 24 weeks to prevent worsening of aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) in women starting letrozole therapy for breast cancer [35]. Pain, 25(OH)D concentration, quality of life, fatigue, disability, and hand grip strength were assessed at baseline, 12, and 24 weeks. Median age of the 160 subjects (80/arm) was 61. Median 25(OH)D concentration value in the placebo group was 25 ng/mL at baseline, 32 ng/mL at 12 weeks, and 31 ng/mL at 24 weeks. In vitamin D-treated women 25(OH)D, as expected, appeared markedly higher, with respective medians of 22 ng/mL at baseline, 53 ng/mL at 12 weeks, and 57 ng/mL at the end of the study (24 weeks) [35]. No serious adverse events were noted in treated groups. At week 24, the higher percentage (51%) of women from a placebo group tended to have worse AIMSS events. In the vitamin D treated group, the prevalence of AIMMS events was lower (37%); however, the difference between placebo and vitamin D-treated groups was not significant (p = 0.069). When the brief pain inventory (BPI) was assessed and compared between these groups, the difference became significant. In the vitamin D-treated group, 39% revealed pain vs. 56% in placebo (p = 0.024). The authors concluded that discontinuation of letrozole, disability from joint pain, or worsening of joint pain using a categorical pain intensity scale (CPIS), all assessed as AIMMS events, did not change significantly after 24 weeks but post-hoc analysis using a different tool - brief pain inventory (BPI) - suggested potential benefit of 30,000 IU weekly at reducing AIMSS [35]. The dose of 30,000 IU per week of oral cholecalciferol appeared as safe and effective in achieving proper vitamin D status [35].

In another RCT study aimed at evaluating the safety and efficacy of obtaining proper vitamin D status, two protocols of cholecalciferol dosing to 69 patients with 25(OH)D < 20 ng/mL were studied [36]. The first protocol introduced the dose of 30,000 IU weekly for 10 weeks with the mean 25(OH)D baseline concentration of 14.1 ng/mL ±4.0. In the second protocol, where the baseline 25(OH)D value was 14.9 ng/mL, 30,000 IU given twice weekly for 5 weeks was investigated. After 10 weeks of 30,000 IU weekly 79% of patients had a 25(OH)D of 30 ng/mL. The second protocol appeared to be more effective. All subjects (100%) in the group exposed to 30,000 IU of vitamin D twice per week had a 25(OH)D concentration of at least 30 ng/mL. The mean increase in 25(OH)D concentration value was significantly higher in the group exposed to 30,000 IU twice weekly for 5 weeks. In that group, the

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

25(OH)D concentration increased by 46.6 ± 1.9 ng/mL. In the group receiving 30,000 IU only once per week but for 10 weeks, the increase in 25(OHD concentration was lower; 38.6 ± 1.8 ng/mL ($p = 0.003$). Both protocols appeared to be safe and effective; however, a larger increase in 25(OH)D concentrations was noted for 30,000 IU given twice weekly for 5 weeks. Therefore, this dose was recommended by authors as proper for quickly obtaining 25(OH)D to the proper concentrations [36]. Of note this study was performed in patients with normal or slightly increased body weight (BMI = 26 ± 5 kg/m^2). The effectiveness of using these doses for restoring proper vitamin D status in obese patients so far had not been studied.

Obesity affects a significant proportion of the global population and has been associated with vitamin D deficiency. Low serum 25(OH)D concentration appeared very common in obese people. Body weight related problems were shown to increase the risk of several life-threatening diseases due to co-existing low-grade inflammation. Adequate 25(OH)D concentration of 30-50 ng/mL [1], showing good vitamin D supply, appeared as an immunoregulatory factor with markedly decreased adipogenic effects. In the double-blind placebo-controlled randomized clinical trial, 44 obese subjects with vitamin D deficiency, i.e., 25(OH)D < 20 ng/mL were assigned for 12 weeks into the vitamin D or placebo groups [37]. The vitamin D group was treated with 50,000 IU weekly and the placebo group with edible paraffin weekly. Additionally, both groups were exposed to a weight reduction diet. The study aimed to evaluate the dose of 50,000 IU of vitamin D given once per week as intervention to decrease fat mass and low-grade inflammation in vitamin D deficient obese patients. %Fat mass, body weight, parathyroid hormone (PTH), calcium, 25(OH)D concentrations and toll like receptor 4 (TLR-4), interleukin-1β (IL-1β) and monocyte chemoattractant protein 1 (MCP-1) were assayed at the start as well as after the intervention. After 3 months of 50,000 IU taken weekly, circulating concentration of PTH ($p < 0.001$), significantly decreased TLR-4 ($p < 0.05$), IL-1β ($p < 0.05$) and MCP-1 ($p < 0.05$) compared with the baseline values in the vitamin D group. These observations were accompanied by a marked increase in 25(OH)D concentrations ($p < 0.001$), as expected after 3 months of intervention (50,000 IU/week). At the baseline 25(OH)D in treatment group was 11.5 ± 5.5 ng/mL and after 3 months surprisingly reached only 26.1 ± 7.2 ng/mL. In placebo group a baseline value was 10.0 ± 5.1 ng/mL and after 12 weeks did not change (11.2 ± 5.8 ng/mL; p = NS). In both placebo and vitamin D groups, a significant decrease in % fat mass, body weight, and BMI were also noted ($p < 0.05$); however, in the vitamin D-treated group, a more marked decrease in body weight (7.0 kg vs. 4.8 kg; $p < 0.05$), % fat mass (4.6% vs. 3.3%), and serum MCP-1 levels (77.0 pg/mL vs. 19.1 pg/mL) was observed compared with placebo. The observed decreases in body weight, % fat mass, and MCP-1 together with increased 25(OH)D concentrations in the vitamin D group suggested the potential role of cholecalciferol in treating synergistically low-grade inflammation, obesity and vitamin D deficiency using 50,000 IU per week [37].

A similar study was performed in Jordan. As in other countries, the prevalence of vitamin D deficiency and obesity have increased recently, leading to well-known health problems. The study evaluated the possible impact of cholecalciferol and/or calcium on body weight reduction and metabolic profile markers in 45 obese Jordanian females with vitamin D deficiency [38]. The study comprised 4 groups. The first group was treated with vitamin D at a dose of 50,000 IU weekly for 12 weeks. In this group the baseline 25(OH)D was 11.1 ± 0.5 ng/mL. The next group was treated with calcium (1200 mg daily) together with vitamin D (50,000 IU/week), with baseline values of 12.0 ± 1.2 ng/mL. The third group was exposed to calcium (1200 mg daily). In this group, the baseline value was 12.7 ± 0.8 ng/mL. The fourth one was a control group, with a baseline 25(OH)D concentration of 11.9 ± 0.8 ng/mL [38]. Additionally, all groups were exposed to a weight reduction diet. After a 3 month study, Subih and colleagues noted a significant reduction in metabolic profile markers ($p \leq 0.05$), including triglycerides (0.53 ± 0.21 mmol/L), cholesterol (0.56 ± 0.20 mmol/L), PTH (27.6 ± 8.9 pg/mL) as well as body weight (10.5 kg), body fat percentage (2.4 ± 1.7%), BMI (4.6 ± 2.0 kg/m^2) and waist circumference (11.4 ± 8.9 cm), compared with the group treated only with daily calcium or controls. Furthermore, after 3 months, the increase in 25(OH)D concentration appeared significant in all treated groups, showing the final values of 41.3 ± 2.3 ng/mL in vitamin D only treated group ($p < 0.001$), 45.6 ± 3.1 ng/mL in group treated with calcium and vitamin D ($p < 0.001$), 17.5 ± 0.8 ng/mL in

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

calcium only treated group ($p < 0.001$), and in the placebo group the increase was not significant (1.8 ± 1.1 ng/mL; p = NS) and the final 25(OH)D concentration was 13.7 ± 1.1 ng/mL. The intervention with 50,000 IU per week together with calcium appeared to increase body weight reduction and improve biomarkers of metabolism as well as providing an interesting schedule, with no adverse effects, for the treatment of vitamin D deficiency in obese women from Jordan [38].

In a single-blinded randomized clinical trial, 100 Iranian patients before a bariatric surgery to reduce severe obesity were treated for 7 weeks using weekly doses of 50,000 IU of vitamin D. All patients were vitamin D deficient or insufficient; 25(OH)D < 30 ng/mL [39]. In the group treated with 50,000 IU per week for 7 weeks, 25(OH)D concentration values increased markedly from 15.2 ng/mL to 32.9 ng/mL ($p < 0.01$). In the group treated with a single loading dose of 300,000 IU, the increase was lower, from 25(OH)D concentration values of 13.2 ng/mL to 24.7 ng/mL at the end of study. Authors concluded that proposed treatment with 50,000 IU of vitamin D weekly for 7 weeks before bariatric surgery in patients with severe obesity should be considered and appeared as safe [39]. Other methods used in this study were not recommended by authors. No adverse effects were reported [39].

Table 3 provides summing up of studies showing data on the effectiveness of use of 7,000 IU daily, 30,000 IU weekly, 30,000 twice per week and 50,000 IU weekly on obtaining proper concentration of 25(OH)D. Although the population, duration of supplementation of vitamin D, the age, BMI (if available) or outcomes differed between studies, all showed positive increase in 25(OH)D concentration values. Furthermore, all studies have not reported adverse events related to use of vitamin D dosing.

Table 3. Effectiveness of studies using 7,000 IU per day, 30,000 IU per week, 30,000 IU twice weekly and 50,000 IU per week in adults for obtaining proper vitamin D status.

Study	Population	Age, yrs	BMI, kg/m²	Dose and duration	Baseline 25(OH)D; ng/mL	Follow up 25(OH)D; ng/mL	Outcomes	Adverse effects
Wamberg et al. [30,31]	Obesity vs. placebo	18-50	>30	7,000 IU/d for 26 weeks	13.2	44.0	PTH decreased, BMD increased, SAT, VAT, hsCRP, blood pressure, plasma lipids – ns	Not reported
Stallings et al. [32]	HIV infected vs. placebo	5-25	No data	7,000 IU/d for 12 months	18.2	At 3 month: 32.5; at 6 months: 29.2; at 12 months: 28.4	Naive Th% increased, CD4% increased, viral RNA reduced,	Not reported
Faria et al. [34]	Overweight and obesity vs. control	40-72	25.0-39.9	7,000 IU/d for 8 weeks	22.8	At 8 weeks: 35.6	SBP decreased, ALP decreased, PNSi increased, R-R increased	Not reported
Khan et al. [35]	Breast cancer vs. placebo	Mean age 61	No data	30,000 IU weekly for 24 weeks	22.0	At 12 weeks: 53.0; at 24 weeks: 57.0	AIMMS trended lowered, BPI lowered	Not reported

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

Takacs et al [36]	Clinical study, no placebo	No data	26	30,000 IU weekly for 10 weeks; 30,000 IU twice weekly for 5 weeks;	14.1 14.9	At 10 weeks: 52.7; At 5 weeks: 61.5;	Restore of proper vitamin D status; Restore of proper vitamin D status;	Not reported Not reported
Lotfi-Dizaji et al.	Obesity vs. placebo	18-59	35.1	50,000 IU weekly for 12 weeks	11.5	At 12 weeks: 26.1	BMI decreased, % FM decreased, PTH decreased, MCP-1 decreased, IL-1ß decreased, TLR-4 decreased	Not reported
Subih et al. [38]	Obesity	18-48	37.5	50,000 IU weekly for 12 weeks	11.1	41.3	Restore of proper vitamin D status;	Not reported
Sayadi Shahraki et al. [39]	Obesity before bariatric surgery	36	43.4	50,000 IU weekly for 7 weeks	15.2	32.9	Restore of proper vitamin D status;	Not reported

Abbreviations: PTH – parathyroid hormone; BMD – bone mineral density (g/cm^2); SAT – subcutaneous adipose tissue; VAT – visceral adipose tissue; hsCRP – C-reactive protein; SBP – systolic blood pressure; ALP – alkaline phosphatase; PNSi – parasympathetic nervous system index; R-R – mean intervals between each heartbeat; AIMMS – aromatase inhibitor-associated musculoskeletal symptoms ; BPI – brief pain inventory; %FM – percent of fat mass; MCP-1 – monocyte chemoattractant protein 1; IL-1ß – interleukin 1ß; TLR-4 – toll like receptor 4.

Even in children with obesity living in the United States, the dose of 50,000 IU of cholecalciferol appeared to be safe and effective in correcting vitamin D status [40]. In the study of children aged 12.3 years with obesity (BMI of 31.6 kg/m^2), a single dose of 50,000 IU and then 6,000 IU or 10,000 IU per day were given for 16 weeks. Specifically, in the first group, a 50,000 IU single dose was followed by 6,000 IU/day for 16 weeks. After the 16 weeks 67% of children achieved 25(OH)D concentration values ≥ 40 ng/mL, with the mean increase in 25(OH)D of 23.2 ± 14.2 ng/mL. In the second group, 50,000 IU single dose plus 10,000 IU given daily have both achieved 25(OH)D concentration values ≥ 40 ng/mL in 73% of studied children. The mean increase of 25(OH)D was in that group of 31.3 ± 20.1 ng/mL. Interestingly, in the group of children with obesity who were exposed to 6,000 IU daily for 16 weeks, only 50% achieved 25(OH)D values of ≥ 40 ng/mL, with a mean increase of 27.8 ± 18.9 ng/mL. Finally, a single dose of 50,000 IU and then 8,000 IU/day were tested. In this group, up to 78.6% of children reached the concentration of 25(OH)D of ≥ 40 ng/mL, with a mean increase of 40.1 ± 22.9 ng/mL. No serious adverse effects related to vitamin D dosing were reported [40], and this study concluded that a 50,000 IU single dose plus 8,000 IU per day of vitamin D is safe and effective in increasing 25(OH)D concentration in children and adolescents with overweight or obesity values ≥ 40 ng/mL. It appeared that children and adolescents with obesity can safely increase their 25(OH)D concentration values to the 40–60 ng/mL range [2], which seems necessary for an anti-inflammatory effect on the proposed 16-week dosing regimen [40].

Finally, in a randomized controlled trial of zoledronic acid in reducing clinical fractures and mortality after hip fracture patients, including those with unknown 25(OH)D concentrations,

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

received a loading dose of vitamin D (50,000 to 125,000 IU given orally or intramuscularly) 14 days before the first infusion of zoledronic acid 5mg [41]. The treatment was effective and safe, including fracture risk reduction and possible restoration of proper vitamin D status. Thus, the patients after fragility fracture may benefit from a single treatment dose even when the 25(OH)D value is not available.

4. Discussion

Vitamin D deficiencies are common in both the general population and risk groups, such as patients with musculoskeletal diseases, systemic connective tissue diseases, glucocorticosteroid users, endocrine and metabolic diseases, malabsorption syndromes, overweight and obesity, chronic kidney disease, cancer, reduced immunity, and even diseases of the central nervous system. Several peer-reviewed studies have demonstrated the benefits of vitamin D supplementation for various risk groups, often given at markedly higher doses compared with recommendations for the general population. Overall, ensuring adequate vitamin D intake is crucial to maintaining optimal health across a wide range of conditions [42–44].

Although vitamin D supplementation may be beneficial, it is important to exercise caution due to the potential risks associated with higher doses. Over–supplementation may lead to rare side effects like hypercalcemia and hypercalciuria. Concomitant use of vitamin D and calcium supplements may also increase the risk of kidney stones, without proper hydration of organism. The recommended upper limit of daily intake of cholecalciferol for the prevention of vitamin D deficiency, at least in Poland, was set at 4,000 IU per day for adults of normal body weight and 10,000 IU per day for obese people [1,4].

Treatment of vitamin D deficiency in otherwise healthy patients (general population) with vitamin D up to 7,000 IU per day should be enough to maintain the 25(OH)D concentration in the range of 40 to 70 ng/mL throughout the year. In vitamin D deficient patients suffering from serious diseases the dosage regimen should be more stringent compared to healthy and considered as an adjunct treatment, but should never replace standard treatment.

Even though several of the mentioned risk groups (Tables 2 and 4) suffer from hypovitaminosis D, currently no guidelines are available for clinicians regarding vitamin D dosing, except in overweight and obese people. The guidelines recommend considering 25(OH)D measurements in patients at risk, and in cases where this is not possible, dosing recommendations for the general population should be followed, of course considering the possible co-occurrence of obesity [1]. Due to the frequent occurrence of vitamin D deficiencies and some possible effects of greater vitamin D supplementation in risk groups, the aim of this study was to document the validity of using a dose of 7,000 IU per day or 30,000 IU and 50,000 IU as the intermittent weekly dose in the mentioned risk groups, which should be considered absolutely safe. Both 7,000 IU/day or 30,000 IU/week or twice weekly or 50,000 IU/week were proposed by us to be considered by medical doctors for the risk groups listed in Tables 2 and 4, even without a 25(OH)D test.

Table 4. Groups of very high risk of vitamin D deficiency in adults - indications for the use of high doses of 7,000 IU of vitamin D per day or intermittent doses of 30,000 IU weekly or twice weekly and 50,000 IU per week.

Risk groups	**Diseases, comorbid conditions, lifestyle**
Multi-diseases and multi-drugs	All/selected diseases or conditions listed below, with treatments
Obesity disease	Obesity, overweight (and dyslipidemia)
Absorption disorders	Exocrine pancreatic insufficiency (old age, pancreatitis, type 2 diabetes, etc.), inflammatory

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

	bowel disease (Crohn's disease, ulcerative colitis), cystic fibrosis, celiac disease, bariatric surgery
Liver and bile duct diseases	Liver failure, liver cirrhosis, cholestasis, fatty liver disease
Endocrine and metabolic diseases/disorders	Type 1 and 2 diabetes, metabolic syndrome, hypoparathyroidism and hyperparathyroidism, hypertension, polycystic ovary syndrome
Eating habits and age	Veganism and other types of vegetarianism, low-fat diet, senior age with multi-morbidities and polypharmacy
Diseases of the musculoskeletal system	Rickets, osteoporosis, osteopenia, bone pain, myalgia, myopathy, muscular dystrophy, recurrent low-energy bone fractures, repeated falls, deformities

In clinical practice, healthcare professionals often consider prescribing vitamin D even without result of 25(OH)D test. In everyday life, the patient has the right to medicine with an appropriately high dose of vitamin D. Therefore, a simplification was proposed by us due to the benefits of using different doses of vitamin D for the high risk groups mentioned in Tables 2 and 3 and the higher dosing for consideration, starting from 7000 IU/day up to the 50 000 IU/week (equivalent of 7000 IU/day given for 7 days, approximately), especially for obese patients or for multi-morbidity and multi-treatment patients or any combination of these medical conditions. High-dose vitamin D formulation in matrix form (50,000 IU/week), due to the fast achievement of expected therapeutic effect, good tolerability, safety of the drug and the convenience of intermittent administration to achieve greater patient compliance with the treatment, should be considered in that risk groups by medical doctors.

This study has some limitations. Firstly, the search of clinical studies or RCTs for the use of 7,000 IU daily or 30,000 IU weekly or twice a week or 50,000 IU per week performed in high risk groups of vitamin D deficiency, including obese patients or patients with liver disease or malabsorption syndrome or patients with multi-morbidity and multi-treatment requiring polypharmacy, revealed very often a limited number of studies or even a lack of searching results. For example, when we tried to investigate the effectiveness of use 7,000 IU per day in obese patients only one study was available in PubMed, so the comparison between different studies using 7,000 IU/day or different doses provided in one study of obese patients was not possible. On the same, at least Polish guidelines [1] and Central and Eastern European statements [4] provided suggestion for obese patients of using doses 2 – 3 times higher (up to 10,000 IU per day, equal to UL value) compared to those proposed for general population (with normal weight), what was previously evidenced by Ekwaru and colleagues ten years ago [45].

Further, there was a limited number (7,000 vs 30,000 IU) or even lack of studies (30,000 IU vs 50,000 IU) comparing the different dosing in the context of effectiveness of obtaining the concentrations of 25(OH)D to expected values (> 30 ng/mL), especially in high risk groups chosen by us in this review. We realize that in some medical conditions a coinciding status of vitamin D deficiency has been reported, as it was for obesity, malabsorption, liver diseases or polypharmacy, despite the discussion of correlation or association. However, the role of professional medical care and doctors is to fight against deficiency, whatever it is, including vitamin D, with the use of proper doses, with safety. In case of high risk groups the doses proposed by us for consideration are higher than normal but still lower than upper limit value of 10,000 IU/d, even for 30,000 IU twice per week (7 days X 8600 IU, approximately), and safe, at least according to published data and our medical

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

experience. Of course we are aware that *CYP24A1* and *SLC34A1* mutations, hypercalciuria, hypercalcemia, nephrolithiasis, nephrocalcinosis, or history of other types of vitamin D hypersensitivity in an individual or family members should be always excluded before the start of using high dosing, as offered by us for consideration by medical doctors. The basis of this suggested approach is the understanding that the potential benefits of vitamin D in proposed dosing in the treatment and/or prophylactic or maintenance during a specific health condition course significantly outweigh the risk of vitamin D intoxication and need for regular monitoring of 25(OH)D.

5. Conclusions

This study provides data on safety and efficacy of 7000 IU per day or 30,000 IU/week or twice weekly or 50,000 IU per week for patients at high risk of vitamin D deficiency, including those with absorption disorders, liver diseases, with obesity, and multi-morbidity and multi-treatment patients requiring polypharmacy. Without monitoring of 25(OH)D and keeping in mind the safety, despite the lack of adverse events reported, the treatment of possible vitamin D deficiency with the intermittent doses of 30,000 IU twice weekly or 50,000 IU per week of cholecalciferol should be considered for 6-8 weeks of initial treatment and then a lower doses, i.e. 7,000 IU/day or 30,000 IU/week, should be introduced and considered for prolonged time as prophylactic or maintenance doses. With these clear and simple vitamin D dosage suggestions, we can contribute to the overall reduction of vitamin D deficiency rates and, consequently, strive to improve public health outcomes.

Author Contributions: Writing—original draft preparation, P.P.; Z.B.; W.B.G.; S.P.; M.F.H. Writing the final review and final editing, P.P.; W.B.G.; E.M-S.; G.T.; Z.B; S.P.; M.F.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: W.B.G. has received funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA). The other authors have no conflicts of interest to declare.

References

1. Płudowski P, Kos-Kudła B, Walczak M, Fal A, Zozulińska-Ziółkiewicz D, Sieroszewski P, Peregud-Pogorzelski J, Lauterbach R, Targowski T, Lewiński A, Spaczyński R, Wielgoś M, Pinkas J, Jackowska T, Helwich E, Mazur A, Ruchała M, Zygmunt A, Szalecki M, Bossowski A, Czech-Kowalska J, Wójcik M, Pyrżak B, Żmijewski MA, Abramowicz P, Konstantynowicz J, Marcinowska-Suchowierska E, Bleizgys A, Karras SN, Grant WB, Carlberg C, Pilz S, Holick MF, Misiorowski W. Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland. Nutrients. 2023 Jan 30;15(3):695. doi: 10.3390/nu15030695.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab. 2012 Apr;97(4):1153-8. doi: 10.1210/jc.2011-2601.
3. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, Lips P, Mitchell DM, Murad MH, Powers S, Rao SD, Scragg R, Tayek JA, Valent AM, Walsh JME, McCartney CR. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2024 Jun 3:dgae290. doi: 10.1210/clinem/dgae290. Online ahead of print.
4. Pludowski P, Takacs I, Boyanov M, Belaya Z, Diaconu CC, Mokhort T, Zherdova N, Rasa I, Payer J, Pilz S. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement. Nutrients. 2022 Apr 2;14(7):1483. doi: 10.3390/nu14071483
5. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024 Mar 16;403(10431):1027-1050.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

6. World Health Organization: Obesity and overweight. 9.06.2021. https://www.who.int/ news room/fact sheets/detail/obesity and overweight.
7. Stepaniak U, Micek A, Waśkiewicz A, et al. Prevalence of general and abdominal obesity and overweight among adults in Poland Results of the WOBASZ II study (2013–2014) and comparison with the WOBASZ study (2003–2005). Pol. Arch. Med. Wewn. 2016; 126:662–671.
8. OECD Health Policy Studies The Heavy Burden of Obesity THE ECONOMICS OF PREVENTION Technical Country Notes. https://www.oecd.org/health/health systems/ Heavy burden of obesity Technical Country Notes.pdf
9. Daniel D, Hardigan P, Bray N, Penzell D, Savu C. The incidence of vitamin D deficiency in the obese: a retrospective chart review. J Community Hosp Intern Med Perspect. 2015;5(1):26069. Published 2015 Feb 3. doi:10.3402/jchimp.v5.26069
10. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-349. doi:10.1111/obr.12239
11. Vranić L, Mikolašević I, Milić S. Vitamin D Deficiency: Consequence or Cause of Obesity?. Medicina (Kaunas). 2019;55(9):541. Published 2019 Aug 28. doi:10.3390/medicina55090541
12. Contreras-Bolívar V, García-Fontana B, García-Fontana C, Muñoz-Torres M. Mechanisms Involved in the Relationship between Vitamin D and Insulin Resistance: Impact on Clinical Practice. Nutrients. 2021;13(10):3491. Published 2021 Oct 1. doi:10.3390/nu13103491
13. Heath AK, Williamson EJ, Hodge AM, et al. Vitamin D status and the risk of type 2 diabetes: The Melbourne Collaborative Cohort Study. Diabetes Res Clin Pract. 2019;149:179-187. doi:10.1016/j.diabres.2018.05.007
14. Kjalarsdottir L, Tersey SA, Vishwanath M, et al. 1,25-Dihydroxyvitamin D3 enhances glucose-stimulated insulin secretion in mouse and human islets: a role for transcriptional regulation of voltage-gated calcium channels by the vitamin D receptor. J Steroid Biochem Mol Biol. 2019;185:17-26. doi:10.1016/j.jsbmb.2018.07.004
15. Cefalo CMA, Conte C, Sorice GP, et al. Effect of Vitamin D Supplementation on Obesity-Induced Insulin Resistance: A Double-Blind, Randomized, Placebo-Controlled Trial. Obesity (Silver Spring). 2018;26(4):651-657. doi:10.1002/oby.22132
16. Zhang Y, Xue Y, Zhang D, et al. Effect of Vitamin D Supplementation on Glycemic Control in Prediabetes: A Meta-Analysis. Nutrients. 2021;13(12):4464. Published 2021 Dec 14. doi:10.3390/nu13124464
17. Sadat-Ali M, AlTabash KW, Al-Turki HA, AlMousa SA, AlSayed HN. Time out: should vitamin D dosing be based on patient's body mass index (BMI): a prospective controlled study. J Nutr Sci. 2021;10:e106. Published 2021 Dec 13. doi:10.1017/jns.2021.100
18. Tobias DK, Luttmann-Gibson H, Mora S, et al. Association of Body Weight With Response to Vitamin D Supplementation and Metabolism. JAMA Netw Open. 2023;6(1):e2250681. Published 2023 Jan 3. doi:10.1001/jamanetworkopen.2022.50681
19. Elkhwanky MS, Kummu O, Piltonen TT, et al. Obesity Represses CYP2R1, the Vitamin D 25-Hydroxylase, in the Liver and Extrahepatic Tissues. JBMR Plus. 2020;4(11):e10397. Published 2020 Aug 26. doi:10.1002/jbm4.10397op3
20. Brancatella A, Cappellani D, Vignali E, Canale D, Marcocci C. Calcifediol Rather Than Cholecalciferol for a Patient Submitted to Malabsortive Bariatric Surgery: A Case Report. J Endocr Soc. 2017 Jul 14;1(8):1079-1084. doi: 10.1210/js.2017-00114. PMID: 29264560; PMCID: PMC5686642.
21. Jetter A, Egli A, Dawson-Hughes B, Staehelin HB, Stoecklin E, Goessl R, Henschkowski J, Bischoff-Ferrari HA. Pharmacokinetics of oral vitamin D(3) and calcifediol. Bone. 2014 Feb;59:14-9. PMID: 24516879.
22. Jodar E, Campusano C, de Jongh RT, Holick MF. Calcifediol: a review of its pharmacological characteristics and clinical use in correcting vitamin D deficiency. Eur J Nutr. 2023 Jun;62(4):1579-1597. doi: 10.1007/s00394-023-03103-1. Epub 2023 Mar 2. PMID: 36862209; PMCID: PMC9979899.
23. Charoenngam N, Kalajian TA, Shirvani A, Yoon GH, Desai S, McCarthy A, Apovian CM, Holick MF. A pilot-randomized, double-blind crossover trial to evaluate the pharmacokinetics of orally administered 25-hydroxyvitamin D3 and vitamin D3 in healthy adults with differing BMI and in adults with intestinal malabsorption. Am J Clin Nutr. 2021 Sep 1;114(3):1189-1199. doi: 10.1093/ajcn/nqab123. PMID: 34008842; PMCID: PMC8408845.
24. Lo CW, Paris PW, Clemens TL, Nolan J, Holick MF. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. Am J Clin Nutr. 1985 Oct;42(4):644-9. doi: 10.1093/ajcn/42.4.644.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

25. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000 Sep;72(3):690-3. doi: 10.1093/ajcn/72.3.690.
26. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014;21(3):319-329.3.
27. Kupisz-Urbańska M, Płudowski P, Marcinowska-Suchowierska E. Vitamin D Deficiency in Older Patients—Problems of Sarcopenia, Drug Interactions, Management in Deficiency. Nutrients 13.4 (2021): 1247.
28. Marcinowska – Suchowierska E, Kupisz- Urbańska M. Osteoporoza u starszych kobiet i mężczyzn - diagnostyka i leczenie farmakologiczne. Terapia. 2020;(6): 86-111.
29. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P, Jones G. Vitamin D Toxicity-A Clinical Perspective. Front Endocrinol (Lausanne). 2018 Sep 20;9:550. doi: 10.3389/fendo.2018.00550. eCollection 2018.
30. Wamberg L, Kampmann U, Stødkilde-Jørgensen H, Rejnmark L, Pedersen SB, Richelsen B. Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - Results from a randomized trial. Eur J Intern Med. 2013 Apr 5. pii: S0953-6205(13)00089-7. doi: 10.1016/j.ejim.2013.03.005.
31. Wamberg L, Pedersen SB, Richelsen B, Rejnmark L. The Effect of High-Dose Vitamin D Supplementation on Calciotropic Hormones and Bone Mineral Density in Obese Subjects with Low Levels of Circulating 25-Hydroxyvitamin D: Results from a Randomized Controlled Study. Calcif. Tissue Int. 2013; 93:69–77.
32. Stallings VA, Schall JI, Hediger ML, Zemel BS, Tuluc F, Dougherty KA, Samuel JL, Rutstein RM. High-Dose Vitamin D3 Supplementation in Children and Young Adults with HIV: A Randomized, Placebo-Controlled Trial. Pediatr Infect Dis J. 2015 Feb;34(2):e32-40.
33. Alvarez N, Aguilar-Jimenez W, Rugeles MT. The Potential Protective Role of Vitamin D Supplementation on HIV-1 Infection. Front Immunol. 2019 Sep 25;10:2291. doi: 10.3389/fimmu.2019.02291.
34. Faria ACC, Moreira CL, Cunha MRD, Mattos S, Oigman W, Neves MF. Effects of Vitamin D Supplementation on Central Hemodynamic Parameters and Autonomic Nervous System in Obese or Overweight Individuals. Arq Bras Cardiol. 2024 Apr;121(5):e20230678. doi: 10.36660/abc.20230678.
35. Khan QJ, Kimler BF, Reddy PS, Sharma P, Klemp JR, Nydegger JL, Yeh HW, Fabian CJ. Randomized trial of vitamin D3 to prevent worsening of musculoskeletal symptoms in women with breast cancer receiving adjuvant letrozole. The VITAL trial. Breast Cancer Res Treat. 2017 Nov;166(2):491-500.
36. Takacs I, Bakos B, Nemeth Z, Toth BE, Szili B, Lakatos P. Controlled randomized open label clinical study comparing the safety and efficacy of loading schedules in vitamin D deficient patients. J Steroid Biochem Mol Biol. 2023 Jul:231:106330. doi: 10.1016/j.jsbmb.2023.106330.
37. Lotfi-Dizaji L, Mahboob S, Aliashrafi S, Vaghef-Mehrabany E, Ebrahimi-Mameghani M, Morovati A. Effect of vitamin D supplementation along with weight loss diet on meta-inflammation and fat mass in obese subjects with vitamin D deficiency: a double-blind placebo-controlled randomized clinical trial. Clin Endocrinol (Oxf). 2019 Jan;90(1):94-101. doi: 10.1111/cen.13861.
38. Subih HS, Zueter Z, Obeidat BM, Al-Qudah MA, Janakat S, Hammoh F, Sharkas G, Bawadi HA. A high weekly dose of cholecalciferol and calcium supplement enhances weight loss and improves health biomarkers in obese women. Nutr Res. 2018 Nov;59:53-64. doi: 10.1016/j.nutres.2018.07.011.
39. Sayadi Shahraki M, Khalili N, Yousefvand S, Sheikhbahaei E, Shahabi Shahmiri S. Severe obesity and vitamin D deficiency treatment options before bariatric surgery: a randomized clinical trial. Surg Obes Relat Dis. 2019 Jun 12. pii: S1550-7289(19)30259-X. doi: 10.1016/j.soard.2019.05.033
40. Brian O'Sullivan B, Ounpraseuth S, James L, Majure M, Lang J, Hu Z, Simon A, Bickel S, Ely B, Faricy LE, Garza M, Greer M, Hsia D, Jefferson A, Knight L, Lee J, Liptzin D, Abul MH, Perry TT, Prior F, SanGiovanni C, Tam-Williams J, Wu B, Snowden J; ECHO IDeA States Pediatric Clinical Trial Network. Vitamin D Oral Replacement in Children With Obesity Related Asthma: VDORA1 Randomized Clinical Trial. Clin Pharmacol Ther 2024 Feb;115(2):231-238. doi: 10.1002/cpt.3086
41. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007 Nov 1;357(18):1799-809. doi: 10.1056/NEJMoa07494.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 July 2024 doi:10.20944/preprints202407.1527.v1

42. Grant WB, Al Anouti F, Boucher BJ, Dursun E, Gezen-Ak D, Jude EB, Karonova T, Pludowski P. A Narrative Review of the Evidence for Variations in Serum 25-Hydroxyvitamin D Concentration Thresholds for Optimal Health. Nutrients. 2022 Feb 2;14(3):639. doi: 10.3390/nu14030639.
43. Grant WB, Boucher BJ, Pludowski P, Wimalawansa SJ. The emerging evidence for non-skeletal health benefits of vitamin D supplementation in adults. Nat Rev Endocrinol. 2022 May;18(5):323. doi: 10.1038/s41574-022-00646-x.
44. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, Shoenfeld Y, Lerchbaum E, Llewellyn DJ, Kienreich K, Soni M. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev. 2013 Aug;12(10):976-89. doi: 10.1016/j.autrev.2013.02.004.
45. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS One. 2014 Nov 5;9(11):e111265. doi: 10.1371/journal.pone.0111265. eCollection 2014.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.