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Comparison of Vitamin D3 Supplementation Doses of 1,000, 2,000, 4,000 and 8,000 IU in Young Healthy Individuals

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Abstract. *Background/Aim: Low levels of vitamin D are a widespread global issue. This study aimed to determine the optimal vitamin D3 supplementation dose for healthy young adults by comparing the effectiveness of gradually increasing cholecalciferol doses over two years. Patients and Methods: Thirty-five volunteers participated in a two-season pilot study conducted from October to April to avoid sunlight-induced vitamin D3 synthesis. The participants used oil-based drops of cholecalciferol, increasing their dose from 1,000 to 2,000, 4,000, and then 8,000 IU daily for 60 days with a 30-day break. Results: Supplementing with 1,000 IU/day raised vitamin D levels to the recommended range (above 75 nmol/l), but levels dropped below this range after a 30-day break. A dose of 2,000 IU/day maintained vitamin D levels within the recommended range, even after the break. Increasing the dose to 4,000 IU/day produced a rapid rise, though levels dropped more significantly after stopping supplementation. With 8,000 IU/day, both the rise and subsequent decline in vitamin D levels were more pronounced. Conclusion: Effective vitamin D supplementation in healthy young adults can be achieved with a daily dose of 2,000 IU during winter. However, 4,000 IU/day was more effective for maintaining levels above 100 nmol/l, supporting broader health benefits. Regular monitoring of [25(OH)D], calcium, and phosphorus levels is essential.*

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Vitamin D is one of the oldest hormones; it has existed since the earliest forms of life evolved. Most plants and animals that are exposed to sunlight have the ability to create vitamin D. Vitamin D is classified as a fat-soluble vitamin. There are two primary forms of vitamin D: ergocalciferol and cholecalciferol. Ergocalciferol (vitamin D2) is formed via UV radiation from its precursor ergosterol, mainly in fungi, plants and yeast (1). The dominant form of vitamin D in the animal kingdom is cholecalciferol (vitamin D3), which is synthesized from 7-dehydrocholesterol as a result of the action of UVB radiation (280-315 nm) in the skin. The amount of UVB radiation that reaches the Earth's surface is significantly affected by the seasons. During the fall and the winter, human skin can only synthesize a minimal amount of vitamin D at higher latitudes (above 33˚) (2). The synthesis of vitamin D is influenced by a number of other factors, such as cloudiness, environmental pollution, layer of clothing, use of sunscreens, genetic polymorphisms, age, or skin color (3).

Vitamin D3 formed in the skin is transported to the liver bound to the vitamin D binding protein (VDBP). Hydroxylation takes place in the liver, and vitamin D3 is converted to [25(OH)D3], or calcidiol. The biologically inactive form [25(OH)D3] is transported to the kidneys, where it is further hydroxylated to the active form [1,25(OH)2D3], or calcitriol. It can also be formed directly in target tissues, where the biological effect of [1,25(OH)2D3] is manifested by regulation of gene expression through binding to the vitamin D receptor

Table I. *Participant characteristics.*

Characteristic	Value/Status
Males	14 (40%)
Females	21 (60%)
All	35 (100%)
Median of age (years)	23 (21-26)
Median of BMI	21.8 (18.3-26.8)
Vegetarian	4
Hormonal contraception	10
Chronic medication	no
Metabolic disorders	no
Endocrine disorders	no
Autoimmune disorders	no

Table II. *Dosage schedule for vitamin D3 supplementation in study participants.*

Period	Dose/day	Number of days
October 2021	1,000 IU	60
November 2021	1,000 IU	
December 2021	Break in use	30
January 2022	2,000 IU	60
February 2022	2,000 IU	
March 2022	Break in use	30
October 2022	4,000 IU	60
November 2022	4,000 IU	
December 2022	Break in use	30
January 2023	8,000 IU	60
February 2023	8,000 IU	
March 2023	Break in use	30

(VDR). The VDR is present in nearly all cells and tissues in the body, leading to a wide range of effects of vitamin D. While the role of vitamin D in regulating calcium and phosphorus levels is well-established, recent studies have highlighted its additional effects on cell proliferation, differentiation, and immune regulation (4-6).

Since relying solely on our own synthesis of vitamin D throughout the year is not feasible, external sources of vitamin D, such as food, are crucial for maintaining adequate levels. Foods rich in vitamin D3 include fish oil and eggs, while vitamin D2 can be found in various mushrooms and fortified foods like milk and cereals. Both vitamins D2 and D3 from food are incorporated into chylomicrons and transported in the blood, where they undergo hydroxylation reactions, resulting in the active form (calcitriol), similar to the process that creates vitamin D3 in the skin. Another option for ensuring sufficient vitamin D levels is through supplementation. The most commonly used form of vitamin D for supplementation is cholecalciferol (vitamin D3). The content of vitamin D3 in commercial preparations is given in international units (IU) or in micrograms (μg), with 1 IU equaling 0.025 μg of crystalline vitamin D3. Vitamin D supplementation is generally well tolerated, and there is a wide therapeutic window for its use.

The determination of vitamin D levels is based on measuring the concentration of [25(OH)D] in the blood serum, as it is the major form of circulating vitamin D. Currently, there is no global consensus on a cut-off value for the concentration of [25(OH)D] that would define vitamin D deficiency and help set the optimal daily supplementation dose.

In our pilot study, conducted in collaboration with Charles University, the Faculty of Medicine in Pilsen, and the Pilsen University Hospital, we aimed to determine the optimal supplemental dose of vitamin D. The study compared the effectiveness of supplementation by gradually increasing doses of cholecalciferol over a two-year period.

Table III. *Blood sampling schedule for each study participant to assess serum levels of vitamin D, calcium, phosphate, and parathyroid hormone.*

Blood draw number	Date	Blood draw description
1	14.10.2021	Before starting supplementation
2	15.12.2021	After 60 days of use 1,000 IU/day
3	19.01.2022	After a break in use for 30 days
4	24.03.2022	After 60 days of use 2,000 IU/day
5	25.04.2022	After a break in use for 30 days
6	13.10.2022	Before starting supplementation
7	14.12.2022	After 60 days of use 4,000 IU/day
8	18.01.2023	After a break in use for 30 days
9	22.03.2023	After 60 days of use 8,000 IU/day
10	26.04.2023	After a break in use for 30 days

Patients and Methods

Participants. Thirty-five volunteers participated in this pilot study between October 2021 and April 2023. All participants filled out a questionnaire about their health status, medications, and dietary habits during the last six months before being included in the study. These factors are known to affect serum vitamin D levels. The basic characteristics of participants are summarized in Table I. Study participants were not allowed to take any additional vitamin D supplementation in the form of drugs or food supplements. The participants were furthermore prohibited from intentionally increasing their calcium intake or using any calcium supplements.

The study was conducted between October and April to prevent the results from being distorted by the body's own production of vitamin D3 (cholecalciferol) in response to exposure to solar UVB radiation. It is well known that from October to April in our region, the production of vitamin D3 in the skin is minimal or zero. Informed consent was obtained from all the participants involved in the study. The study was approved by the Ethics Committee of University Hospital Pilsen and the Faculty of Medicine in Pilsen, Charles University, under the number 374/2020, August 6, 2020.

Table IV. *Summary statistics of serum vitamin D concentration in relation to supplementation in all study participants.*

Blood draw description	Mean	Median	Min.	Max.	*p*-Value of increase	*p*-Value of decrease
Before starting supplementation	72.68	73.52	45.59	104.4	<0.0001	-
After 60 days of use 1,000 IU/day	83.87	80.19	57.29	117.1		<0.0001
After a break in use for 30 days	65.49	61.50	46.20	88.59	<0.0001	
After 60 days of use 2,000 IU/day	90.29	89.22	67.01	126.9		<0.0001
After a break in use for 30 days	81.35	81.16	54.21	109.3	-	
Before starting supplementation	74.27	72.92	40.14	130.9	<0.0001	-
After 60 days of use 4,000 IU/day	109.7	108.4	73.95	181.6		<0.0001
After a break in use for 30 days	87.00	84.55	52.48	131.5	<0.0001	
After 60 days of use 8,000 IU/day	144.10	151.1	80.04	202.6		<0.0001
After a break in use for 30 days	94.99	92.50	55.41	148.4	-	

All values are given in nmol/l.

Dosage schedule. For supplementation, an over-the-counter form of cholecalciferol drops in an oil solution was chosen. Participants were supplemented with vitamin D according to the dosage schedule shown in Table II.

Sample collection. Blood sampling was designed in relation to the dosing regimen. The blood sampling schedule is shown in Table III. A total of ten blood samplings were performed over two supplementation seasons. Peripheral blood samples were collected in VACUETTE® CAT Serum Separator Clot Activator tubes (Greiner Bio-One, Kremsmünster, Austria). Within two hours of collection, the test tubes were centrifuged at 1,700 rpm for ten minutes to separate the serum. Each serum sample was then divided into three aliquots (two that remained available for analysis and one archived) of equal volume of 500 µl. The samples were processed on the same day (ion analysis) or stored at –80˚C before further analysis.

Vitamin D measurement. Total vitamin D levels were measured using the chemiluminescent kit ACCESS 25(OH) Vitamin D Total, and the parathormone (PTH) levels were determined using the chemiluminescent kit ACCESS Intact PTH on the Unicel® DxI 800 Analyzer (Beckman Coulter, Brea, CA, USA). All samples were thawed simultaneously and analyzed in one go. Calcium (Ca) and phosphorus (P) concentrations were determined using the Cobas system (Cobas 8000, Cobas c702, Roche Diagnostics, Basel, Switzerland). Samples for ion determination were processed on the day of collection.

Statistical analysis. Statistical analysis was performed using the SAS SW, v. 9.4. (SAS Institute Inc., Cary, NC, USA). Discrete characteristics are expressed as frequencies and percentages; continuous characteristics are expressed as mean, median, minimum, maximum, lower, and upper quartile of serum vitamin D levels. Vitamin D levels are also displayed using a box-plot graph. The Wilcoxon Signed-Rank Test was used for the evaluation of the changes in vitamin D levels, and a p-value <0.05 was considered to be statistically significant. To determine the significance levels of vitamin D changes, we compared each participant's vitamin D levels at each dosage increment to their previous measurement values.

Table V. *Overall calcium, phosphorus, and parathyroid hormone concentrations across all study samples.*

Analyte (units)	Mean	Min.	Max.	Reference values
Ca (nmol/l)	2.31	2.26	2.59	2.20-2.60
P (nmol/l)	1.12	0.69	1.56	0.70-1.70
PTH (pmol/l)	7.4	1.4	6.9	1.3-9.3

Results

A summary of the measured levels of vitamin D in our group of volunteers is presented in Table IV and Figure 1. All increases in levels following supplementation and decreases after discontinuation of supplementation were found to be statistically significant (p<0.0001). The mean initial serum [25(OH)D] concentration was 72.68 nmol/l, ranging from 45.59 nmol/l to 104.4 nmol/l. Following supplementation with 1,000 IU of vitamin D, the average concentration increased to 83.87 nmol/l.

Following a 30-day break from supplementation, the average concentration dropped to 65.49 nmol/l, with the lowest recorded value being 46.20 nmol/l. Subsequently, 60 days of 2,000 IU vitamin D supplementation resulted in an increase in the average serum concentration to 90.29 nmol/l. After a second 30-day break, the average concentration fell to 81.35 nmol/l, with a minimum recorded value of 54.21 nmol/l. Before starting the second supplementation season, the average serum [25(OH)D] concentration was 74.27 nmol/l, ranging from 40.14 nmol/l to 130.9 nmol/l.

With 4,000 IU vitamin D supplementation, the average concentration rose to 109.70 nmol/l, with values ranging from a minimum of 73.95 nmol/l to a maximum of 181.6 nmol/l. After another 30-day break, the average concentration decreased to 87.00 nmol/l, with a range from 52.48 nmol/l to 131.5 nmol/l.

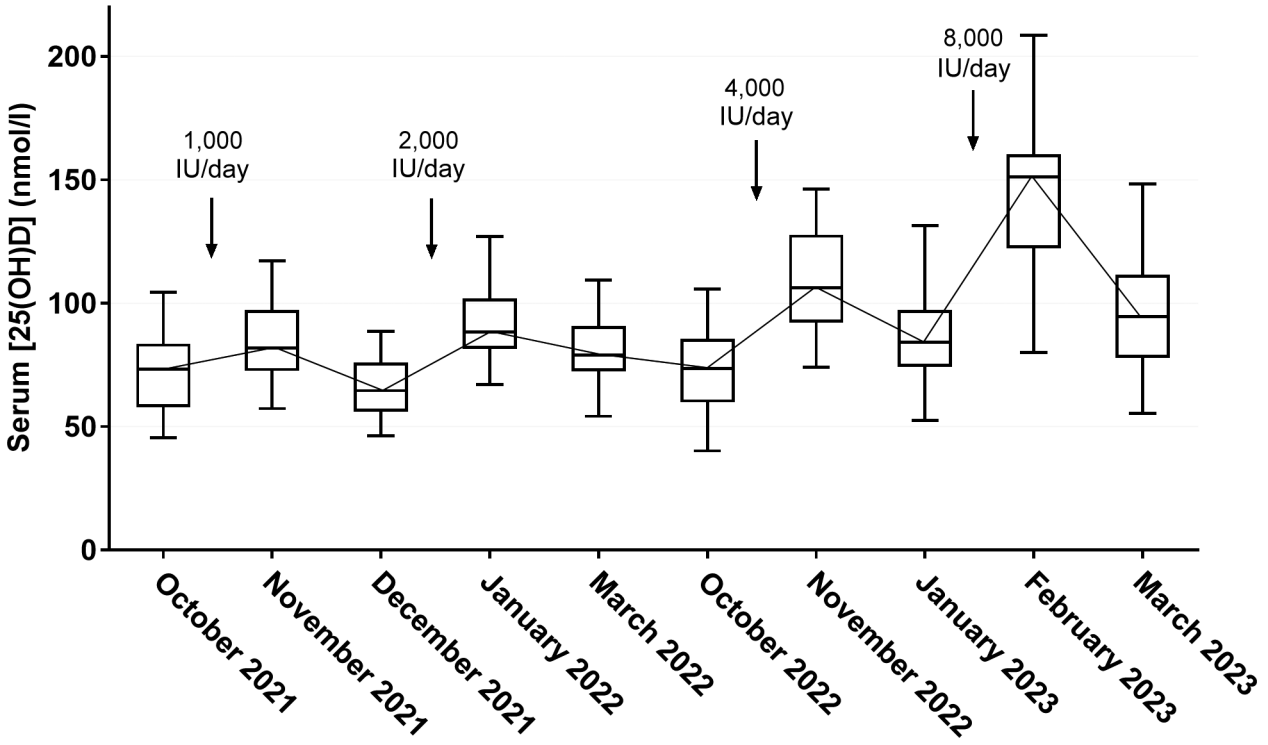

Figure 1. *Distribution of serum vitamin D levels during the supplementation study.*

Finally, supplementation with 8,000 IU of vitamin D increased the average serum [25(OH)D] concentration to 144.10 nmol/l. The concentrations ranged from 80.04 nmol/l to 202.6 nmol/l. After a 30-day break, the average concentration dropped to 94.99 nmol/l, with the lowest and highest values recorded at 55.41 nmol/l and 148.4 nmol/l, respectively.

For the safety of the study participants, calcium (Ca), phosphorus (P), and parathyroid hormone (PTH) levels were monitored throughout the study. These levels remained stable and within the reference ranges during the entire supplementation period. Table V presents an overview of the measured concentrations.

Discussion

Vitamin D plays a vital role in various physiological processes. Despite numerous recommendations from professional societies and research groups, there is still no global consensus on optimal vitamin D levels or the necessary supplemental doses for overall health. While a minimum serum [25(OH)D] concentration of 50 nmol/l is generally regarded as necessary for maintaining skeletal health (7, 8), the optimal level of vitamin D for other health benefits remains a topic of debate.

In individuals with high sunlight exposure, such as outdoor workers and those living in tropical and subtropical regions, [25(OH)D] levels often exceed 120 nmol/l (9). In Europe, serum concentrations of less than 25 nmol/l have long been considered critically low, significantly increasing the risk of metabolic bone diseases. The American Institute of Medicine classifies vitamin D deficiency as serum levels below 30 nmol/l, with levels between 30-50 nmol/l indicating deficiency, 50-75 nmol/l considered insufficient, and levels above 75 nmol/l generally seen as sufficient by most experts (10).

Research suggests that [25(OH)D] concentrations of 75 nmol/l and higher can effectively reduce parathyroid hormone (PTH) levels and enhance intestinal calcium absorption, thereby lowering the risk of secondary hyperparathyroidism and promoting optimal musculoskeletal health (7, 8, 11, 12). Despite these insights, low [25(OH)D] levels are still widespread in the global population, posing a significant public health challenge (13).

We chose to investigate a group of participants aged 20-25 years to monitor changes in serum vitamin D levels in healthy individuals. This age group was chosen because older populations are more prone to vitamin D deficiency, largely irrespective of latitude. Age-related changes in vitamin D metabolism, such as reduced production capacity of the skin, a lower number of VDRs, and diminished renal

hydroxylation of [25(OH)D] due to declining kidney function, can significantly affect vitamin D status (14, 15). We furthermore chose to supplement with cholecalciferol in oil-based drops for its presumed higher bioavailability compared to solid dosage forms (16).

Recommended daily doses of vitamin D vary depending on age and the presence of comorbid conditions. The goal of effective supplementation is to achieve serum [25(OH)D] concentrations greater than 75 nmol/l (17). In this study, supplementation with doses of 1,000, 2,000, 4,000, and 8,000 IU/day over 60 days resulted in significant increases in serum vitamin D levels ($p<0.0001$). A clear dose-response relationship was observed, with higher doses leading to greater increases in serum [25(OH)D] levels.

A daily dose of 1,000 IU was sufficient to raise serum vitamin D to the target range (above 75 nmol/l) during the winter months. However, 30 days after discontinuing supplementation, average levels dropped below this range. Slightly higher levels were achieved with a daily dose of 2,000 IU. Notably, 30 days after stopping supplementation, the average serum concentration remained within the recommended range, and this dose resulted in the smallest decline compared to the other doses. Rupprecht et al. recommend doses of approximately 2,575.69 IU/daily of vitamin D to maintain serum [25(OH)D] level above 75 nmol/l in young healthy individuals (18). In our study, doses of 1,000 IU and 2,000 IU daily were sufficient.

Supplementation with 4,000 IU/day led to a more significant increase in [25(OH)D] serum levels, but the decrease 30 days post-supplementation was more pronounced than with the 2,000 IU dose. This dose was able to raise the average serum [25(OH)D] level above 100 nmol/l – a threshold considered optimal for supporting normal physiology, as it aligns with levels commonly observed in outdoor workers and residents of sunny regions (19). Research by Heaney et al. and Kimball et al. has suggested that maintaining 25(OH)D concentrations above this level is associated with beneficial effects on both bone health and broader extraskeletal functions (20, 21). With the highest dose of 8,000 IU/day, both the rise in serum [25(OH)D] and the subsequent decline after discontinuation were dramatic.

The rapid declines in serum observed in supplementation regimens of 4,000 and 8,000 IU may be attributed to the induction of the CYP24A1 (25OHD-24 hydroxylase) enzyme. CYP24A1 plays a key role in vitamin D metabolism by converting [25(OH)D] to its inactive form, [24,25$(OH)_2$D] (22). This enzymatic regulation helps maintain homeostasis but can also lead to a more significant decrease in serum [25(OH)D] once supplementation is discontinued. This feedback mechanism could explain why higher doses result in a sharper decline in vitamin D levels post-supplementation compared to lower doses.

Vitamin D toxicity can occur when doses exceeding 10,000 IU are taken daily for several weeks to months, leading to an accumulation in the body and resulting in long-term serum concentrations above 300 to 375 nmol/l (21, 23). Symptoms of overdose include loss of appetite, nausea, fatigue, headache, excessive thirst, increased urination, diarrhea, sweating, and paresthesias. Laboratory findings often show hypercalcemia, hyperphosphatemia, and increased urinary excretion of calcium and phosphorus (24). The most serious complication is the formation of calcium phosphate crystals in the kidneys, which can lead to kidney failure (25).

We monitored not only the clinical symptoms of potential overdose but also the laboratory values of calcium and phosphorus, as elevated levels of these ions are critical markers for serious adverse effects of supplementation. Elevated ion levels are often associated with a decrease in PTH levels (26). Throughout the study, both ion and PTH levels remained stable. No participant experienced an increase in serum ion levels beyond the reference range, nor did they experience a significant drop in PTH levels. In one participant, we recorded a serum [25(OH)D] level of 202.6 nmol/l after supplementation with 8,000 IU/day. Despite this high vitamin D level, their calcium (2.43 mmol/l), phosphorus (1.29 mmol/l), and PTH (3.2 pmol/l) levels were all within normal ranges, and no clinical symptoms of overdose were observed. It is noteworthy that this participant was a young adult with fully functioning feedback mechanisms, which likely contributed to the maintenance of normal ion homeostasis despite elevated [25(OH)D] levels. These findings should, therefore, be generalized to the broader public with caution, as individual responses to vitamin D supplementation can vary significantly.

In conclusion, a supplemental dose of 1,000 IU/day was sufficient to raise the average [25(OH)D] serum levels in the monitored group to the recommended range (avobe 75 nmol/l) after 60 days of supplementation. However, 30 days after discontinuing supplementation, levels had already fallen below the recommended lower limit. In contrast, a dose of 2,000 IU/day maintained average serum vitamin D levels within the recommended range even after a 30-day break. Supplementation with higher doses of 4,000 IU/day and 8,000 IU/day resulted in a rapid increase in serum levels above 100 nmol/l. However, the rate of decline in [25(OH)D] serum levels after a 30-day break was significantly greater with these higher doses compared to 1,000 IU/day and 2,000 IU/day. The most effective supplementation model for young, healthy adults during the winter months in the Central European region appears to be a regular dose of 2,000 IU/day from October through April, which effectively raises and maintains vitamin D levels above 75 nmol/l. An alternative regimen that considers the extraskeletal effects of vitamin D and raises average levels above 100 nmol/l involves a dose of 4,000 IU/day. For

individuals with laboratory-confirmed vitamin D deficiency, an initial dose of 4,000 IU/day (or 8,000 IU/day in cases of severe deficiency) for 30 to 60 days may be followed by a maintenance dose of 2,000 IU/day. Both the alternative and intensive dosing regimens are recommended only with regular monitoring of serum [25(OH)D], calcium, and phosphorus levels, particularly in individuals without an increased calcium intake.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, M.K.; methodology, R.K, M.K.; investigation, M.K., H.H., E.D., P.B.; writing original draft preparation, M.K., M.J., H.H, E.D., P.B.; writing, review, and editing, L.P., V.S., M.J.; supervision, R.K. All Authors have read and agreed to the published version of the manuscript.

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