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Safety of 5000 International Units Daily Oral Dosing of Vitamin D3 for Four Years in Various Diseases

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Abstract— Studies have found that daily oral 5000 IU vitamin D3 is safe to avoid insufficiency, recover from insufficiency, and avoid toxicity. Thus, this study would like to support the findings that daily oral dose of vitamin D3 for 5000 IU is still safe by following up patients who take daily oral 5000 IU vitamin D3 for four years in various diseases. 14 subjects with various diseases were recruited for this study. Subjects were administered oral vitamin D3 5000 IU daily with informed consent and blood vitamin D level was tested on study entry and follow-up. Subjects were divided into 2 groups based on their blood vitamin D level test follow-up time. The first group consisted of 12 subjects who were followed up once in the range of 1-4 years. The second group consisted of 3 subjects who were followed up every year for 4 years. One subject was included in both groups. The first group who were followed up once in the range of 1-4 years did not have a significant increase in 25(OH)D serum concentration and did not reach toxicity level. The second group which was followed up every year for 4 years had their 25(OH)D serum concentration increased but the increase was also affected by the disease they had. Daily oral 5000 IU vitamin D3 dose is safe proven by 25(OH)D serum concentration not passing 100 ng/ml which is still below 150 ng/ml, where adverse effects are usually present.

Keywords— vitamin D3 supplementation, 5000 IU, safety

Background

Vitamin D is important for calcium homeostasis and skeletal health. It promotes bone remodeling and bone growth. Another role of vitamin D is to modulate cell growth, neuromuscular and immune function, and inflammation. [1,2]One form of vitamin D is vitamin D3 or cholecalciferol which is the more potent form of vitamin D.[1,3] Vitamin D3 can be synthesized by human skin when exposed to UVB. Another way of obtaining vitamin D3 is from oil-rich fish such as herring, mackerel, and salmon. Like any other vitamins, vitamin D3 can also be found in oral supplements.[3]However, vitamin D3 is still biologically inactive. It should be hydroxylated in the liver to 25-hydroxyvitamin D_3 [$25(OH)D_3$]. A second hydroxylation in the kidney is required to convert [25(OH)D] to the biologically active form of vitamin D $1,25(OH)_2D_3$ which will later be catabolized to carry out its functions. [3,4]

The result of the first vitamin D3 hydroxylation in the liver, $25(OH)D_3$, which can be found in serum is the best indicator of vitamin D status. Vitamin D insufficiency is indicated when serum concentration of $25(OH)D_3$ is below 50 nmol/L.[1,5]Although skin can synthesize vitamin D3 through UVB exposure, prevalence of vitamin D insufficiency is still high and even increasing in tropical countries where sun exposure is abundant.In Indonesia, a tropical country, a high prevalence of over 50% vitamin D insufficiency was reported.This have made oral vitamin D3 supplementation a choice to be considered in Indonesia.[5,6]

Studies have found that daily oral 5000 IU vitamin D3 is safe to avoid insufficiency, recover from insufficiency, and avoid toxicity. [7-13] This daily oral 5000 IU vitamin D3 intake is recommended to avoid vitamin D toxicity and its adverse effects which are usually present at $25(OH)D_3$ serum concentration greater than 150 ng/ml. [14,15]Thus, this study would like to support the findings that daily oral dose of vitamin D3 for 5000 IU is still safe by following up patients who take daily oral 5000 IU vitamin D3 for four years in various diseases.

Methodology

Study Subjects

This was a retrospective study involving patients that were treated with oral vitamin D3 5000 IU daily. Ethical clearance was obtained from Health Research Ethics Committee, University of Indonesia, and CiptoMangunkusumo Hospital (HREC-FMUI/CMH) with letter of approval no. 0249/UN2.F1/ETIK/2018. Adult subjects >30 years old who were KlinikHayandra's patients were recruited for study.

Follow-up and Collecting Data

14 subjects with various diseases, including diabetes mellitus (DM) type 2, post cardiac stenting, chronic obstructive pulmonary disease (COPD), osteoarthritis, osteoporosis, hypertension, post colon cancer, parkinson, preventive, and vitamin D deficiency, were recruited for this study. Subjects were administered oral vitamin D3 5000 IU daily with informed consent and blood vitamin D level was tested on study entry and follow-up. Subjects were divided into 2 groups based on their blood vitamin D level test follow-up time. The first group consisted of 12 subjects who were followed up once in the range of 1-4 years. The second group consisted of 3 subjects who were followed up every year for 4 years. One subject was included in both groups.

Statistical Analysis

Statistical analysis to show the significance of age between male and female was done using Mann-Whitney U test with $p<0.05$ showing a significant difference. Statistical analysis to compare between before and after of the follow-up was done using paired T-test with $p<0.05$ showing a significant difference.

Results

Daily oral dose of vitamin D3 5000 IU for four years was found to be safe shown by 25(OH)D serum concentration less than 100 ng/ml which does not reach its toxicity level of 25(OH)D serum concentration. After a certain period of time, $25(OH)D_3$ serum concentration also seems to stabilize at a certain concentration.

Demography of 12 patients in this study can be seen in table 1. Four male patients and eight female patients took part in this study. Male patients' average age was 66 years old and female patients' average age was 56 years old. Statistical analysis has shown that there were no significant difference ($p=0.734$) between male and female's age which suggests that the male and female patients' age were not a confounding variable for this study.

Table 1.Demography of Patients

Patient No.	Sex	Age	Disease	Before		Follow up (years)	After	
1	F	74	DM type 2, Post Cardiac Stenting, History of breast cancer	Normal	36.7	1	Normal	33.1
2	M	78	Chronic Obstructive Pulmonary Disease (COPD)	Insufficient	21.4	1	Normal	30.6
3	M	63	Osteoarthritis Genu bilateral & DM type 2*	Insufficient	27.1	1	Insufficient	27.1
4	M	63	Post cardiac stenting	Normal	40.5	2	Normal	45.5
5	F	60	Osteoporosis, hypertension, post cardiac stenting	Insufficient	23.9	2	Normal	45.0
6	F	62	Hypertension	Normal	35.5	2	Normal	59.8
7	F	71	Post colon cancer	Normal	30.0	3	Normal	59.4
8	M	57	Parkinson#	Insufficient	28.9	3	Deficiency	18.3
9	F	75	Hypertension	Normal	30.3	3	Normal	48.7
10	F	31	Preventive	Insufficient	20.1	4	Normal	67.8
11	F	30	Preventive	Normal	58.9	4	Normal	59.1
12	F	72	Vitamin D Deficiency	Deficient	11.1	4	Normal	68.2

* patient's 25(OH)D serum concentration remained insufficient after 1 year of administration
# patient's 25(OH)D serum concentration decreased into deficiency from insufficiency after 3 years of administration

The 12 patients' mean 25(OH)D serum concentration can be seen in figure 1. Before indicates the mean 25(OH)D baseline serum concentration of the patients who were followed up for a certain year. After indicates mean 25(OH)D serum concentration after a certain year of daily 5000 IU vitamin D3 supplementation.

For the 1 year follow-up group, the average of 25(OH)D serum concentration at study entry was 28.4 ng/ml and after 1 year it increased to 30.267 ng/ml. Statistic analysis have shown that there were no significant difference (p=0.673) for the 1 year follow-up group.

For the 2 year follow-up group, the average of 25(OH)D serum concentration at study entry was 33.3 ng/ml and after 2 years it increased to 50.1 ng/ml. Statistic analysis have shown that there were no significant difference (p=0.107) for the 2 years follow-up group.

For the 3 years follow-up group, the average of 25(OH)D serum concentration at study entry was 29.73 ng/ml and after 3 years it increased to 42.1 ng/ml. Statistic analysis have shown that there were no significant difference (p=0.408) for the 3 years follow-up group.

For the 4 years follow-up group, the average of 25(OH)D serum concentration at study entry was 30.03 ng/ml and after 4 years it increased to 65.03 ng/ml. Statistic analysis have shown that there were no significant difference (p=0.185) for the 4 years follow-up group.

Two interesting findings were found in this study. One of the patients who had Parkinson disease. At study entry, patient's 25(OH)D level was 28.9 ng/ml. Intriguingly, 3 years after the study entry, patient's 25(OH)D serum concentration worsened into deficiency (18.3 ng/ml). The other one is the patient who had osteoarthritis genu bilateral and diabetes mellitus type 2. At study entry, patient's 25(OH)D level was insufficient (27.1 ng/ml). After 1 year of supplementation, patient's 25(OH)D level stayed insufficient (27.1 ng/ml).

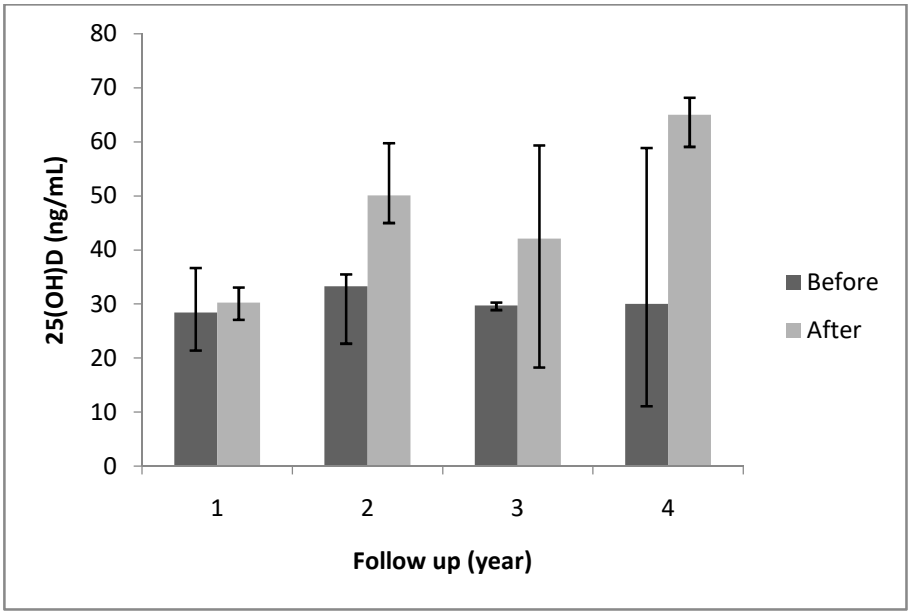

Figure 1. The mean concentration of 25(OH)D after 1-4 years of vitamin D intake

Two patients who suffer from autoimmune disease were excluded from the table and shown in figure 2 to emphasize their 25(OH)D serum concentration compared to patient with deficiency. One patient had psoriasis and the other had vasculitis.

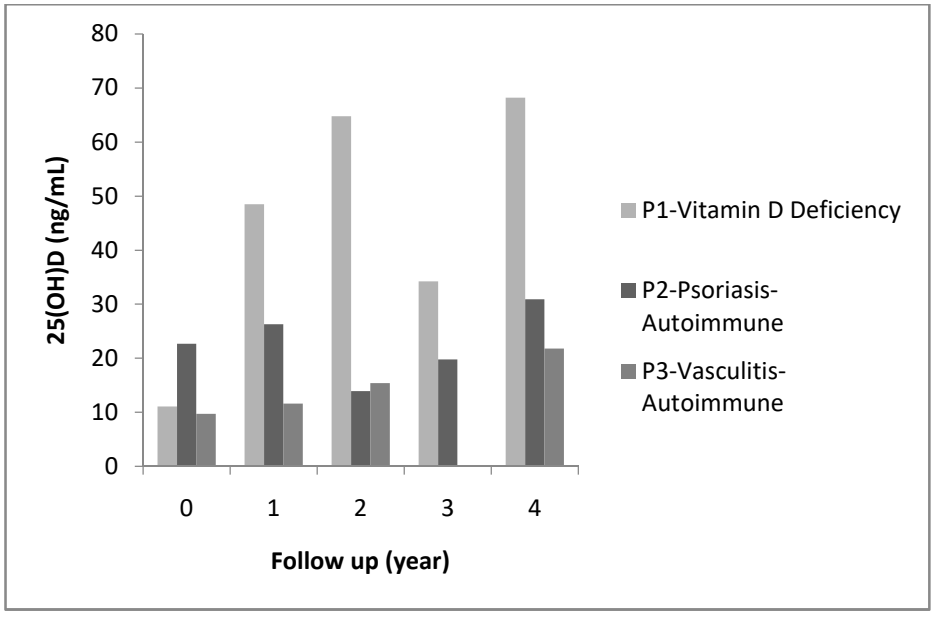

Figure 2. 25(OH)D serum concentration of 2 autoimmune patients compared to patient with vitamin D deficiency;P1/P2/P3: patient-1/patient-2/patient-3

Daily 5000 IU vitamin D3 supplementation in vitamin D deficient patient increased 25(OH)D serum concentration from 11.1 ng/ml to 68.2 ng/ml after 4 years. The increase of 25(OH)D serum concentration was not as significant as vitamin D deficient patient in autoimmune patients. The autoimmune patient who was vitamin D3 deficient with 25(OH)D serum concentration of 9.7 ng/ml did not reach sufficiency after 4 years of supplementation. As for the autoimmune patient who had a higher baseline 25(OH)D serum concentration reached sufficiency after 4 years of supplementation from 22.7 ng/ml to 30.9 ng/ml.

Discussion

Normal adequate vitamin D is indicated by 25(OH)D serum concentration around 50-125 nmol/L or 20-50 ng/ml.[1] Vitamin D toxicity and its adverse effects are usually present when 25(OH)D serum concentration is 150 ng/ml.[14] Results obtained were still within the range of normal 25(OH)D serum concentration which implies that 5000 IU daily oral dose of vitamin D3 is still safe.

Results obtained were still align with other studies' results. A study of vitamin D3 5000 IU/day in epilepsy found that daily supplementation of 5000 IU vitamin D3 for 12 weeks in epilepsy patients never exceeded potentially toxic levels of 25(OH)D serum concentrations greater than 100 ng/ml.[7]Another study of oral vitamin D3 5000 IU/day for 2 years in long-term hospitalized patients showed that 25(OH)D serum concentrations were still below 100 ng/ml for the first year and stayed the same in the second year. [8]Vitamin D3 5000 IU/day for 1 year in vitamin D-deficient nursing home patients also increased their serum 25(OH)D concentrations to normal range. [9]Sufficient serum 25(OH)D concentrations were also reached with daily 5000 IU vitamin D3 in insufficient serum 25(OH)D concentrations athletes. [10]

Daily dose of 5000 IU vitamin D3 has also shown promising results. Significant improvement in children in autism has been proven. [11]Daily 5000 IU vitamin D3 can also be used to prevent influenza and COVID-19 after one month of daily 10,000 IU vitamin D3. It can also help treat COVID-19 patients due to its ability to reduce cytokine storm which usually happen in COVID-19 patients. [12]A study had also found that this dose for 6 months can increase peripheral insulin sensitivity and beta-cell function in individuals at risk of diabetes or newly diagnosed type 2 diabetes. [13]

Another interesting result obtained in this study was $25(OH)D_3$ serum concentration became constant after a certain period of time. This result is aligned with studies that have suggested that $1,25(OH)_2D_3$ inhibits the conversion of vitamin D3 to $25(OH)D_3$. Therefore, in subjects who have reached sufficiency of vitamin D3, their $25(OH)D_3$ serum concentration is constant. [16]

The time needed for the patients with psoriasis and vasculitis to reach its normal level from insufficiency was 4 years, this suggests that daily vitamin D3 supplementation of 5000 IU was not enough to reach normal level in a short period of time. Studies have also found that increased vitamin D levels improved outcomes of patients with psoriasis and vasculitis. [17,18] This result is still align with a study that showed that 100,000 IU/month vitamin D3 supplementation is not enough to improve the outcome of patients with psoriasis. [18]

Two autoimmune patients were followed up every year for 4 years. Results suggested that daily dose of 5000 IU vitamin D3 increased 25(OH)D serum concentration. However, these results suggested that daily dose of 5000 IU vitamin D3 took longer time to reach sufficiency even one of the autoimmune patient hadn't reach sufficiency by the end of the 4 year study. Several studies have suggested that increasing the dose of vitamin D3 supplementation will reduce the time taken to reach sufficiency and may improve the outcome of the patients. [19]

The higher dose of vitamin D3 supplementation in autoimmune patients is needed due to the ability of vitamin D to regulate immune function. Autoimmune patients suffer from the defect of T cells and B cells tolerance which produces self-reactive lymphocytes and result in tissue injury. Vitamin D is able to regulate autoimmunity by suppressing the activation of self-reactive lymphocytes by binding with vitamin D receptors (VDRs) which result in the inactivation of antigen-presenting cells (APCs) and suppression by theactivated regulatory B and regulatory T cells. [20,21]

The decrease of 25(OH)D serum concentration in subject with Parkinson disease suggested that the dose of 5000 IU/day for 3 years is still not enough to reach sufficiency. A randomized controlled trial found that an increase of 25(OH)D serum concentration in subjects with Parkinson disease requires 10,000 IU/day. Another important factor in determining the effectiveness of vitamin D3 supplementation in patients with Parkinson disease is the severity of their Parkinson disease. [22]

Conclusion

Daily oral 5000 IU vitamin D3 dose is safe proven by 25(OH)D serum concentration not passing 100 ng/ml which is still below 150 ng/ml, where adverse effects are usually present. Higher daily dose of vitamin D3 is needed to reduce the time of patients with autoimmune and Parkinson disease to reach sufficiency.

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References

[1] National Institutes of Health [Internet]. Bethesda: US Department of Health & Human Services; 2018. Vitamin D [update 2020 Mar 24; cited 2020 Jul 8]. Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en1

[2] Tannous P, Fiscaletti M, Wood N, Gunasekera H, Zurynski Y, Biggin A, et al. Safety and effectiveness of stoss therapy in children with vitamin D deficiency. J Paediatr Child Health. 2020 Jan;56(1):81-9.

[3] Nair R, Maseeh A. Vitamin D: the "sunshine" vitamin. J PharmacolPharmacother. 2012 Apr;3(2):118-26.

[4] Hassan AB, Hozayen RF, Alotaibi RA, Tayem YI. Therapeutic and maintenance regimens of vitamin D3 supplementation in healthy adults: a systematic review. Cell Mol Biol. 2018 Nov 30;64(14):8-14.

[5] Poh BK, Rojroongwasinkul N, Nguyen BKL, Sandjaja, Ruzita AT, Yamborisut U, et al. 25-hydroxy-vitamin D demography and the risk of vitamin D insufficiency in the South East Asian Nutrition Surveys (SEANUTS). Asia Pac J ClinNutr. 2016;25(3):538-48.

[6] Aji AS, Erwinda E, Yusrawati Y, Malik SG, Lipoeto NI. Vitamin D deficiency status and its related risk factors during early pregnancy: a cross-sectional study of pregnant Minangkabau Women, Indonesia. BMC Pregnancy Childbirth. 2019;19:183.

[7] DeGiorgio CM, Hertling D, Curtis A, Murray D, Markovic D. Safety and tolerability of Vitamin D3 5000 IU/day in epilepsy. Epilepsy Behav. 2019 May 1;94:195-7.

[8] McCullough PJ, Lehrer DS, Amend J. Daily oral dosing of vitamin D3 using 5000 to 50,000 international units a day in long-term hospitalized patients: insights from a seven year experience. J Steroid BiochemMol Biol. 2019 May;189:228-39.

[9] Mocanu V, Stitt PA, Costan AR, Voroniuc O, Zbranca E, Luca V, et al. Long-term effects of giving nursing home residents bread fortified with 125 microg (5000 IU) vitamin D(3) per daily serving. Am J ClinNutr. 2009 Apr;89(4):1132-7.

[10] Han Q, Li X, Tan Q, Shao J, Yi M. Effects of vitamin D3 supplementation on serum 25 (OH) D concentration and strength in athletes: a systematic review and meta-analysis of randomized controlled trials. J IntSoc Sports Nutr. 2019 Nov 26;16(1):55.

[11] Saad K, Abdel-Rahman AA, Elserogy YM, Al-Atram AA, Cannell JJ, Bjørklund G, et al. Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children. NutrNeurosci. 2016 Sep 13;19(8):346-51.

[12] Grant WB, Lahore H, McDonell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020 Apr 2;12(4):988.

[13] Lemieux P, Weisnagel SJ, Caron AZ, Julien AS, Morisset AS, Carreau AM, Poirier J, Tchernof A, Robitaille J, Bergeron J, Marette A. Effects of 6-month vitamin D supplementation on insulin sensitivity and secretion: a randomised, placebo-controlled trial. Eur J Endocrinol. 2019 Sep 1;181(3):287-99.

[14] Haines ST, Park SK. Vitamin D supplementation: what's known, what to do, and what's needed. Pharmacotherapy. 2012 Apr;32(4):354-82.

[15] Osborn J, Germann A, St Anna L. Which regimen treats vitamin D deficiency most effectively?. J FamPract. 2011 Nov;60(11):682-3.

[16] Schmidt-Gayk H, Armbruster FP, Bouillon R. Calcium regulating hormones, vitamin D metabolites, and cyclic AMP assays and their clinical application [Internet]. Berlin: Springer-Verlag Berlin Heidelberg; 1990. [cited 2020 Jul 8]. Available from: https://www.springer.com/gp/book/9783662004081

[17] Pitukweerakul S, Thavaraputta S, Prachuapthunyachart S, Karnchanasorn R. Hypovitaminosis D is associated with psoriasis: a systematic review and meta-analysis. Kans J Med. 2019 Nov;12(4):103-8.

[18] Adeeb F, Khan MU, Li X, Stack AG, Devlin J, Fraser AD. High vitamin D levels may downregulate inflammation in patients with Behçet's disease. Int J Inflamm. 2017 Jun 4;2017.

[19] Jarrett P, Camargo Jr CA, Coomarasamy C, Scragg R. A randomized, double-blind, placebo-controlled trial of the effect of monthly vitamin D supplementation in mild psoriasis. J Dermatolog Treat. 2018 May 19;29(4):324-8.

[20] Vanherwegen AS, Gysemans C, Mathieu C. Regulation of immune function by vitamin D and its use in diseases of immunity. EndocrinMetabClin North Am. 2017 Dec 1;46(4):1061-94.

[21] Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. Front Immunol. 2017 Jan 20;7:697.

[22] Hiller AL, Murchison CF, Lobb BM, O'Connor S, O'Connor M, Quinn JF. A randomized, controlled pilot study of the effects of vitamin D supplementation on balance in Parkinson's disease: does age matter?.PloS one. 2018 Sep 26;13(9):e0203637.