ScienceDirect

The Journal of Steroid Biochemistry and Molecular Biology

Volume 189, May 2019, Pages 228-239

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

Patrick J. McCullough [a b], Douglas S. Lehrer [a b], Jeffrey Amend [b]

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https://doi.org/10.1016/j.jsbmb.2018.12.010

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Abstract

Vitamin D3 is a secosteroid hormone produced in the skin in amounts estimated up to 25,000 international units (IUs) a day by the action of UVB radiation on 7-dehydrocholesterol. Vitamin D deficiency is common due to both lack of adequate sun exposure to the skin, and because vitamin D is present in very few food sources. Deficiency is strongly linked to increased risk for a multitude of diseases, several of which have historically been shown to improve dramatically with either adequate UVB exposure to the skin, or to oral or topical supplementation with vitamin D. These diseases include asthma, psoriasis, rheumatoid arthritis, rickets and tuberculosis. All patients in our hospital have been routinely screened on admission for vitamin D deficiency since July 2011, and offered supplementation to either correct or prevent deficiency. During this time, we have admitted over 4700 patients, the vast majority of whom agreed to supplementation with either 5000 or 10,000 IUs/day. Due to disease concerns, a few agreed to larger amounts, ranging from 20,000 to 50,000 IUs/day. There have been no cases of vitamin D3 induced hypercalcemia or any adverse events attributable to vitamin D3 supplementation in any patient. Three patients with psoriasis showed marked clinical improvement in their skin using 20,000 to 50,000 IUs/day. Analysis of 777 recently tested patients (new and long-term) not on D3 revealed 28.7% with 25-hydroxyvitaminD3 (25OHD3) blood levels < 20 ng/ml, 64.1% < 30 ng/ml, a mean 25OHD3 level of 27.1 ng/ml, with a range from 4.9 to 74.8 ng/ml. Analysis of 418 inpatients on D3 long enough to develop 25OHD3 blood levels > 74.4 ng/ml showed a mean 25OHD3 level of 118.9 ng/ml, with a range from 74.4 to 384.8 ng/ml. The average serum calcium level in these 2 groups was 9.5 (no D3) vs 9.6 (D3), with ranges of 8.4 to 10.7 (no D3) vs 8.6 to 10.7 mg/dl (D3), after excluding patients with other causes of hypercalcemia. The average intact parathyroid hormone levels were 24.2 pg/ml (D3) vs. 30.2 pg/ml (no D3). In summary, long-term supplementation with vitamin D3 in doses ranging from 5000 to 50,000 IUs/day appears to be safe.

Introduction

Vitamin D was misnamed in 1922, when it was isolated from both cod liver oil and the skin of laboratory animals subjected to UVB radiation [1]. Its chemical structure was determined in the 1930s, and it was discovered to be a secosteroid hormone made by the action of UVB radiation present in sunshine on 7-dehydrocholesterol in the skin [2,3].

By the 1930′s, cod liver oil, sunshine and phototherapy were known to be effective treatments for several diseases. Cod liver oil had been used to cure both rickets and tuberculosis in the 1800′s [1,4,5]. Sunshine and phototherapy were used to cure tuberculosis in the 1890′s and 1930′s [1,[6], [7], [8], [9], [10]]. In fact, the Nobel prize in medicine was awarded to Dr. Neils Ryberg Finsen in 1903 for curing hundreds of long-standing cases of TB with refracted light rays from an electric arc lamp [6,7], and this method of treatment became the standard of care for treating TB until the discovery of antibiotics in the 1940′s [[10], [11], [12]]. In addition, both rickets [5,13] and psoriasis [14] were also reported to improve dramatically with sun exposure.

Because of the link between sunshine and vitamin D formation, physicians in that era also began treating diseases with vitamin D alone, and found much success. In the 1930s and 1940s reports were published describing the successful use of vitamin D in treating psoriasis [14], asthma [15], rheumatoid arthritis [16,17], rickets [1,5,18] and tuberculosis [[19], [20], [21], [22], [23], [24]]. Doses ranging from 60,000 to 300,000 IUs were shown to control asthma [15], 150,000 to 600,000 IUs a day ameliorated the signs and symptoms of rheumatoid arthritis [16,17], and 100,000 to 150,000 IU per day for 2 to 3 months completely cured many long-standing cases of tuberculosis infections [[19], [20], [21], [22], [23], [24]].

It is not clear why such high daily doses of vitamin D were chosen, but the vitamin D doses used at that time were remarkably high based on today's standards. Estimates of the amount of vitamin D made in the skin from sun exposure were unknown at that time, and would not be made until the 1970s and 1980s.

When these estimates were made, which range from 10,000 to 25,000 IU per day [[25], [26], [27]], it became apparent that the daily doses of vitamin D selected by clinicians during the 1930s and 1940s were about an order of magnitude higher than what the body actually produces from sun exposure. We now know that our bodies are designed to produce vitamin D3 in the skin from the action of sunshine on the precursor molecule 7-dehydrocholesterol, and very little is obtained from the diet [28].

Unfortunately, reports soon surfaced in the 1930s and 1940s describing complications from vitamin D induced hypercalcemia after prolonged daily intake of these supra-physiologic daily doses of vitamin D [17,[29], [30], [31], [32]]. It was thought at the time that vitamin D induced hypercalcemia led to several patient deaths, and as a result, the use of vitamin D in these high doses for treating disease fell out of favor.

However, it is not clear from the literature how many people may have actually died from vitamin D toxicity, as there were also remarkable reports describing patients who recovered without long-term complications after ingesting massive amounts of vitamin D for long periods of time.

One such report was published in 1948, describing in detail patients who recovered uneventfully after taking 150,000 to 600,000 IU a day for 2 to 18 months for rheumatoid arthritis [17]. A more recent toxicity report from 2011 confirms that this is still possible, as an individual who inadvertently took 970,000 IUs daily for one month, and another who took 1,864,000 IUs of vitamin D daily for 2 months, both recovered uneventfully within a few months after stopping the vitamin D and receiving supportive care [33]. Both individuals became symptomatic from the hypercalcemia. The first had a serum 25OHD level of 645 ng/ml, and a calcium of 13.2 mg/dl, and the second had a serum 25OHD level of 1220 ng/ml, and a calcium of 15.0 mg/dl. However, the hypercalcemia resolved in both patients over time after cessation of the vitamin D supplement. Both the symptoms abated and the calcium levels became normal after the 25OHD level dropped below 400 ng/ml.

In addition, with the relatively short course of treatment for tuberculosis, many patients were able to safely ingest 100,000 to 150,000 IU/d for several months and achieve complete cures without developing complications related to hypercalcemia or withdrawing from therapy [[19], [20], [21], [22], [23], [24]].

Unfortunately, instead of titrating down the dose of vitamin D to see if a lower dose range might exist that would still be clinically effective but without causing hypercalcemia in treating patients with these diseases, vitamin D was labeled as toxic, and the use of these high doses for treating disease stopped. The recommended daily dose of vitamin D was then reduced to the amounts present in a teaspoon of cod liver oil, or approximately 400 IU/day [18], and has remained there for several decades. This is in spite of the fact we now know that the body will make much more than this amount with exposure to sunshine or phototherapy.

It wasn't until the late 1960's that the active steroid hormone form of vitamin D3, namely 1,25-dihydroxyvitamin D3, was discovered, and the vitamin D receptor (VDR) was characterized [2]. It is now recognized that vitamin D3 exerts significant control over normal cellular metabolism in many different cells and tissues throughout the body [3]. Vitamin D3 has been found to control cellular metabolism in 2 distinct ways: a) via rapid reactions which occur at the plasma membrane by interacting with the VDR and opening or closing ion channels, and b) by binding to the VDR in the nucleus of the cell, where it is then able to act as a gene switch and turn on and off gene transcription [3].

The exact number of gene products controlled by vitamin D3 is unknown, but the active hormone form of vitamin D3 was recently found to bind via its receptor to 2776 distinct binding sites in a human cell line, many of which were located near autoimmune and cancer associated genes [34].

This may help to explain the strong association that has been found between vitamin D deficiency and increased risk for a multitude of diseases, including Alzheimer's disease, asthma, several autoimmune diseases such as Crohn's disease, multiple sclerosis, psoriasis, rheumatoid arthritis and ulcerative colitis, many cancers including breast, colon, prostate, sarcomas and skin cancer, chronic pain, dementia, depression, diabetes mellitus, epilepsy, fibromyalgia, falls, fractures and muscle weakness, osteoporosis, osteomalacia, Parkinson's disease, pregnancy complications including premature birth and death, rickets, schizophrenia and seasonal affective disorder [1,28,35].

We have also learned much more about toxicity and safety with oral dosing of vitamin D3 over the past 20 years. In 1999, a comprehensive review article on vitamin D supplementation, 25OHD blood levels, and safety was published, and found that toxicity from hypercalcemia appeared to involve intake of daily doses of vitamin D greater than 40,000 IU/day [36].

In 2003, a study was published evaluating the safety and dose response of daily supplementation with three oral doses of vitamin D3. This study compared placebo versus supplementation with 836 IU, 5500 IU or 11,000 IU a day in 67 healthy adult male volunteers over a 5-month period. Mean baseline 25OHD blood levels were 28.1 ng/ml, rising to a mean level of 64 ng/ml in the 5500 IU/day group, and 88 ng/ml in the 11,000 IU/day group after 5 months. No adverse events related to vitamin D3 supplementation were reported [37].

In 2005, a report defining "Circulating levels of vitamin D indicative of sufficiency" was published [38]. Based on analysis of specific biomarkers that appropriately increase or decrease with changes in 25(OH)D levels, it was determined that a 25OHD blood level of <32 ng/ml was indicative of insufficiency. A blood level >100 ng/ml was set as the upper limit of normal, but the author noted that based on evidence available at that time, that it may actually be higher. It was also noted that "The current adult recommendations for vitamin D, 200–600 IU/d, are very inadequate when one considers that a 10–15 min whole-body exposure to peak summer sun will generate and release up to 20,000 IU vitaminD-3 into the circulation. "

In 2007, a publication on Vitamin D Toxicity, Policy, and Science noted that "hypercalcemia is the hazard criterion for vitamin D", and argued that "because sunshine can provide an adult with vitamin D in an amount equivalent to daily

oral consumption of 250ug (10,000 IU)/d, this is intuitively a safe dose." The point was also made that because "clinical trial evidence shows that a prolonged intake of 250ug (10,000 IU)/d of vitamin D is likely to pose no risk of adverse events in almost all individuals in the general population; this meets the risk for a tolerable upper intake level [39]."

A comprehensive review also published in 2007 on the risk of daily dosing with vitamin D also concluded that 10,000 IU/day should be the safe tolerable upper intake level, and estimated that 25OHD blood levels above 240 ng/ml were required to result in clinically significant hypercalcemia [40]. It should be noted that 25OHD blood levels were unable to be measured until the 1970's [41], which explains why 25OHD blood levels associated with hypercalcemia in the 1930s and 1940s are unknown.

In 2008, a report on the pharmacokinetics of vitamin D toxicity was published, in which the author concluded that "although current data support the viewpoint that the biomarker plasma 25(OH)D concentration must rise above 750 nmol/l (300 ng/ml) to produce vitamin D toxicity, the more prudent upper limit of 250 nmol/L (100 ng/ml) might be retained to ensure a wide safety margin" [42].

In 2010, a study from Ireland reported 25OHD blood levels measured before and after using narrow band UVB phototherapy to treat 29 patients with psoriasis in the wintertime in Ireland, and were compared to 29 age-matched untreated control patients with psoriasis [43].

The median baseline 25OHD level was 23 ng/ml, with a range of 9–46 ng/ml in the treatment group. All patients responded to treatment with phototherapy within 25–118 days with essentially complete clearing of their skin, at which time 25OHD blood levels were again measured. The median 25OHD blood level increased to 59 ng/ml in the treated group, with a range of 32–112 ng/ml, while no change in either disease severity or 25OHD blood levels were observed in the control group. These 25OHD blood levels were remarkably similar to those reported in 1977 in a dose response study in which healthy volunteers received 10,000 IU of vitamin D a day for at least 4 months [25].

In 2011, a community-based cohort study involving 3667 subjects also found daily dosing with 10,000 IU a day or lower to be safe, with no reported adverse events or 25OHD blood levels above 200 ng/ml, and concluded that "universal intake of up to 40,000 IU of vitamin D per day is unlikely to result in vitamin D toxicity" [44].

In 2012, no adverse events were reported due to vitamin D supplementation over the course of a year in two separate reports in which oral vitamin D3 was given at a dose of 4000 IU a day. In these studies, mean 25OHD blood levels after 12 months were 66 ng/ml and 67 ng/ml, with a range of 35 ng/ml to 95 ng/ml [45,46].

At our institution, we have found the majority of patients admitted for care to be vitamin D deficient at the time of admission (<30 ng/ml 25OHD). They also receive little to no direct sun exposure during their hospital stay, which often lasts for 12 months or longer. For these reasons, as well as those discussed above, we offered daily supplementation with oral vitamin D3 as a standard of care in July of 2011.

Our goal was to supplement our patients with an amount of vitamin D3 at the low end of the range of amounts that the body has been shown to make on a daily basis with adequate sun exposure to the skin, and which have been shown in previous oral dosing studies and reviews to be safe and effective at raising serum 25OHD levels. One of the authors (PM) started this practice in April 2009 while working at a post-acute care hospital for the same reasons, and found that long-term daily supplementation with 5000 to 10,000 IU of vitamin D3 was safe in several hundred patients (unpublished data). This practice was then continued after changing hospitals in 2011.

In this report, we will present 4 sets of data. The first will be a review of changes in 25OHD3, calcium and iPTH blood levels over time in patients who were on daily supplementation with either 5000 IU/d or 10,000 IU/d of vitamin D3 for at least 12–29 months. This is basically an extension of the work previously discussed published by Dr. Robert Heaney in 2003, who showed that this was safe over a period of 5 months [37].

The second data set will compare 25OHD3, calcium and iPTH blood levels obtained in patients not on vitamin D3 supplementation (new admissions and long-term patients declining supplementation) vs those obtained in patients on D3 supplementation long enough to have achieved a 25OHD3 blood level of at least 74.4 ng/ml.

The third data set will show changes in 25OHD3, calcium and iPTH blood levels in 3 people who have been taking daily doses of vitamin D ranging from 25,000 IU/d to 60,000 IU/d for 2 to 8 years.

The first is a patient who has been on 50,000 IU/d of vitamin D2 for over 2 years for treatment of psoriasis. The second is a staff member who has been on 25,000 IU/d for several years for treatment of asthma (author JA), and the third is a staff member who has been on 60,000 IU/d of vitamin D3 for the past 4 years for the treatment of an ulcerated skin lesion (author PM). All 3 individuals experienced marked clinical improvement in their chronic medical problems on vitamin D supplementation without complications.

The fourth data set will be a comparison of data set 1 with results from reports in the literature previously discussed which published data showing changes in 25OHD3 blood levels after either daily oral supplementation with varying doses of vitamin D, or phototherapy [25,37,43,45,46], after varying lengths of time. (The data tables from this discussion are available in the supplemental data section).

Section snippets

Materials and methods

Summit Behavioral Healthcare (SBH) is a 291-bed state psychiatric hospital in Cincinnati, Ohio. The patient population consists of male and female adults age 18 and over. The majority of the patients have a diagnosis of severe mental illness at the time of admission, usually schizophrenia, schizoaffective disorder, or bipolar disorder. Many of the patients also have coexisting substance abuse issues.

All patients at our facility have been offered supplementation with either 5000 IU/d or 10,000…

Changes in 25OHD3, calcium and iPTH blood levels over time in patients who have been on daily supplementation with either 5000 IU or 10,000 IU a day of vitamin D3 for at least 12–29 months

Between July 2011 and Feb 2014, a total of 36 patients were identified who received 5000 IU of vitamin D3 once daily for 12 months or longer (group 1), and 78 patients who received 5000 IU of vitamin D3 twice daily for 12 months or longer (group 2). A total of 125 and 344 serum levels of 25OHD, 225 and 515 serum calcium levels, and 26 and 61 serum iPTH levels were obtained in groups 1 and 2, respectively.

While significant differences were observed over time in mean 25OHD blood levels between…

Discussion

The possibility that oral vitamin D may be safe and effective in treating the numerous medical problems found to be strongly linked to vitamin D deficiency remains an area of great interest in medicine. A 2010 review of publications that use the term “vitamin D” in either the title or abstract revealed an exponential increase in the publication rate of peer-reviewed papers on the topic of vitamin D over the last 40 years [3]. And at the time of the writing of this manuscript, there were a total …

Conclusion

Daily oral intake of vitamin D3 ranging from 5000 IU/d to 60,000 IU/d for several years was well tolerated and safe in both our patients and staff. The mean 25OHD blood levels in our patients appear to take around 12 months to plateau on 5000 IU/d and 10,000 IU/d.

The average 25OHD values we observed in patients taking 10,000 IU/d at 12 months (96 ng/ml) and 16 months (97 ng/ml) are almost identical to what is currently considered to be the upper limit of normal (100 ng/ml) and are approximately …

Conflicts of Interest

The authors have no conflicts of interest to disclose.…

Funding

This research was performed without external funding.…

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Normal 24-hour urine calcium concentrations after long-term daily oral intake of vitamin D in doses ranging from 5000 to 50,000 international units in 14 adult hospitalized psychiatric patients
2023, Journal of Steroid Biochemistry and Molecular Biology

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The peculiar role of vitamin D in the pathophysiology of cardiovascular and neurodegenerative diseases
2022, Life Sciences

> *Citation Excerpt :*
> …Grant et al., tried to explain the possible reasons for this confusing issue, pointing out that U-shape relationship could be result of a certain lifestyle or the appearance of a disease due to the vitamin D deficiency masked by supplementation that started too late to affect the progression of undergoing disease [83]. In support of these claims, a 7-year-old study by McCullough et al. pointed out that several years of daily vitamin D supplementation in the range of 5000 IU/d to 60,000 IU/d were safe for participants indicating that high doses of vitamin D can be tolerated [84]. This imposes the hypothesis that in only cases of severe overdose, vitamin D supplementation can lead to disastrous consequences.…

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Treatment With 25-Hydroxyvitamin D<inf>3</inf> (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial
2021, Endocrine Practice

> *Citation Excerpt :*
> …The analysis of this pilot study showed that this dose of 25(OH)D3 only had effect on decreasing the NLR that has been related to improved clinical outcomes.29,30 Although we did not observe that the significant decrease in the NLR in the patients who ingested

> 25(OH)D3 was related to improved clinical outcomes compared with that in the control group, this could be due to the need to more rapidly improve serum 25(OH)D3 concentrations by administering a higher dose of 25(OH)D3, as has been recently reported.9,33,37 This pilot study was performed on 53 patients in each group.…

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The VDR FokI (rs2228570) polymorphism is involved in Parkinson's disease

2021, Journal of the Neurological Sciences

> *Citation Excerpt :*
>
> …Vitamin D was initially believed to have an exclusive role in calcium homeostasis and in the modulation of metabolism. Starting from the 30s, though, Vitamin D was also observed to improve conditions like rheumatoid arthritis, asthma and psoriasis [46,47]; this vitamin is nowadays known to play a role in many other processes and in different health conditions, including autoimmune diseases, cancer, cardiovascular diseases, diabetes, infections and neurodegenerative diseases PD [48]. Vitamin D is a fat-soluble hormone that can cross the blood-brain barrier, an observation that justifies which supports its role in the central nervous system (CNS) [49].…

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Revisiting vitamin D status and supplementation for in-patients with intellectual and developmental disability in the North of England, UK ↗

2022, BJPsych Bulletin

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2021, Irish Journal of Psychological Medicine

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