Journal of Steroid Biochemistry and Molecular Biology 189 (2019) 228–239

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

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]

[a] Department of Psychiatry, Wright State University School of Medicine, Dayton, OH, 45435, United States
[b] Summit Behavioral Healthcare, Cincinnati, OH, 45237, United States

ARTICLE INFO

Keywords:
Intact parathyroid hormone
Long-term supplementation
Adverse events

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.

1. 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 [1,6–10]. 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 [10–12]. 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 [19–24]. 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 [19–24].

* Corresponding author at: Summit Behavioral Healthcare, Cincinnati, OH, 45237, USA.
E-mail address: pmccullough1@cinci.rr.com (P.J. McCullough).

https://doi.org/10.1016/j.jsbmb.2018.12.010
Received 2 October 2018; Received in revised form 23 December 2018; Accepted 31 December 2018
Available online 04 January 2019
0960-0760/

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 [25–27], 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 [17,29–32]. 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 [19–24].

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).

2. 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 IU/d (attending doctor's choice) of over-the counter vitamin D3 as a standard of care since July 2011 for the treatment and prevention of vitamin D deficiency. This is done due to the many risks associated with vitamin D deficiency, and because the majority of our patients are deficient in 25-hydroxyvitamin D3 (25OHD) at the time of admission, and receive minimal sun-exposure to their skin during the course of their admission. The vendor used during this entire time frame was Major Pharmaceuticals, and 5000 IU capsules were used in all patients, with the exception of one patient with psoriasis, who was treated daily with a 50,000 IU gel capsule of vitamin D2.

After observing a number of patients on long-term supplementation developing 25OHD blood levels > 100 ng/ml, a research proposal requesting permission to do a retrospective chart review of this data was submitted to and approved by the Institutional Review Boards of the Ohio Department of Mental Health and Addiction Services and Wright State University.

Study material consisted of pharmacy and laboratory records of patients at Summit Behavioral Healthcare who received oral vitamin D supplements between July 2011 and July 2018. All clinical procedures and laboratory assessments were done in the context of clinical care and without intention to perform research.

The main risk related to excessive vitamin D supplementation is hypercalcemia, which has only been shown to occur after ingestion of supra-physiological doses of vitamin D for extended periods of time. Over the counter supplements are not regulated by the Food and Drug Administration (FDA), and therefore their quality cannot be assured. Thus, monitoring of appropriate dose response to vitamin D3 supplementation and signs and symptoms of possible toxicity related to hypercalcemia is warranted.

All new admissions to the hospital are asked to consent to admission blood work, and the majority comply. This will typically include a complete blood count, complete metabolic profile, lipid profile, thyroid profile, glycosylated hemoglobin, acute hepatitis panel, 25OHD, and intact PTH. Follow-up blood levels are obtained periodically thereafter, at the discretion of the unit primary care physician, but at least once a year. All blood samples were sent to Laboratory Corporation of America (LabCorp) for analysis during this time period.

None of the patients in this report were on calcium supplements, and only a small percentage were on a daily multivitamin or fish oil capsules. Depending on the patient's legal status, lengths of stay may last for greater than a year, thus permitting confident assessment of clinical and laboratory parameters associated with vitamin D3 utilization over long intervals.

Medication treatment for severe mental illness depends on the diagnosis and typically includes an antipsychotic for psychosis, a mood stabilizer, a benzodiazepine for agitation, anxiety, or extrapyramidal side effects (eps), or an anticholinergic medication or a beta blocker for the treatment of associated iatrogenic movement disorders.

Many of our patients are relatively young and healthy with few comorbid conditions. Patients with other non-psychiatric medical problems are maintained or started on medications appropriate for their medical problems, with the most commonly encountered problems being asthma, diabetes, dyslipidemia, heart disease, hypertension, hypothyroidism and obesity.

3. Results

3.1. 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 the 2 groups, no cases of vitamin D-induced hypercalcemia or any other adverse events related to vitamin D supplementation were noted in any patient.

There were 2 cases of non-vitamin D related hypercalcemia observed during this time frame. One was due to previously undiagnosed primary hyperparathyroidism. The second was found to be due to hydrochlorothiazide treatment for hypertension, which resolved with cessation of the hydrochlorothiazide.

3.1.1. 25OHD levels

Baseline mean 25OHD levels were 24 ng/ml and 25 ng/ml. At 12months these increased to 68 ng/ml (n = 9) in the 5000 IU/d group, and 96 ng/ml (n = 49) in the 10,000 IU/d group. At 16months the mean 25OHD levels were essentially unchanged, with values of 60 ng/ml (n = 11) in group 1 and 97 ng/ml (n = 11) in group 2.

The range of 25OHD values at months 12 and 16 were also very similar in the 2 groups. At 12months the ranges were 41–95 ng/ml in group 1 and 53–148 ng/ml in group 2. At 16months the ranges were 43–86 ng/ml in group 1, and 81–139 ng/ml in group 2 at 16 months.

The changes in individual and mean monthly 25OHD blood levels over time are depicted graphically in Fig. 1.

3.1.2. Calcium levels

The mean monthly serum calcium levels ranged from 9 to 10 mg/dl in patients on 5000 IU/d (n = 225 values), and from 9.4 to 10 mg/dl in patients on 10,000 IU/d (n = 515 values). The highest serum calcium level observed in both groups was 10.9 mg/dl. The mean monthly serum calcium values are plotted in Fig. 2.

3.1.3. Intact parathyroid hormone levels

Intact parathyroid hormone (iPTH) levels were measured in a much smaller number of patients. A total of 26 and 61 serum iPTH levels were obtained in groups 1 and 2, respectively, with very few levels obtained in the first 9 months in either group.

Although there were relatively few measurements of iPTH, the monthly mean and range of values was very similar between the 2 groups between months 10 to 29. In particular, the range of monthly mean values from months 23 to 29 is very similar between the 2 groups. In group 1 it was 16 to 24 pg/ml (n = 10), and 15 to 26 pg/ml in group 2 (n = 16) (normal range 15–60 pg/ml). Many more data points for iPTH levels will be discussed in data set 2.

Plots of the mean monthly serum iPTH values (pg/ml) with standard deviation bars for patients taking 5000 IU/d and 10,000 IU/d of oral vitamin D3 are shown in Fig. 3.

3.2. Comparison of 25OHD3, calcium and iPTH blood levels in patients not on vitamin D3 (n = 777) vs patients on D3 with 25OHD3 blood levels of at least 74.4 ng/ml in the past 2 years (n = 418)

There were no cases of vitamin D-induced hypercalcemia or any other adverse events related to vitamin D supplementation observed in any patient.

There were 7 cases of non-vitamin D related hypercalcemia observed during this time frame. Five were due to previously undiagnosed primary hyperparathyroidism. One was found to be due to treatment with lithium and hydrochlorothiazide, which resolved with change in medications. The last case occurred in association with a bout of acute pancreatitis, which resolved with resolution of the pancreatitis.

3.2.1. Demographics & Number of 25OHD measurements at each vitamin D3 dose (Table 1)

A total of 777 measurements of 25OHD made in patients over the past 2 years who were not on D3 supplementation are included in this analysis. This includes new admissions, long term patients who declined vitamin D supplementation, and baseline levels in patients who were on D3 long enough to have a 25OHD level > 74.4 ng/ml.

Of this total, 568 measurements (73%) were made in male patients, and 210 measurements (27%) in female patients. This is reflective of the male to female patient ratio in the hospital. The age range was from 18 to 90 years old, and by race, 49.9% were black, 47.3% were white, and 2.8% were other races.

A total of 418 measurements of 25OHD greater than 74.4 ng/ml were identified in the past 2 years in patients who were on daily vitamin D supplementation.

This includes 377 measurements in male patients (90%) and 41 measurements (10%) in female patients. The age range was from 19 to 76 years old, and by race, 60.3% were black, 38.3% white, and 1.4%

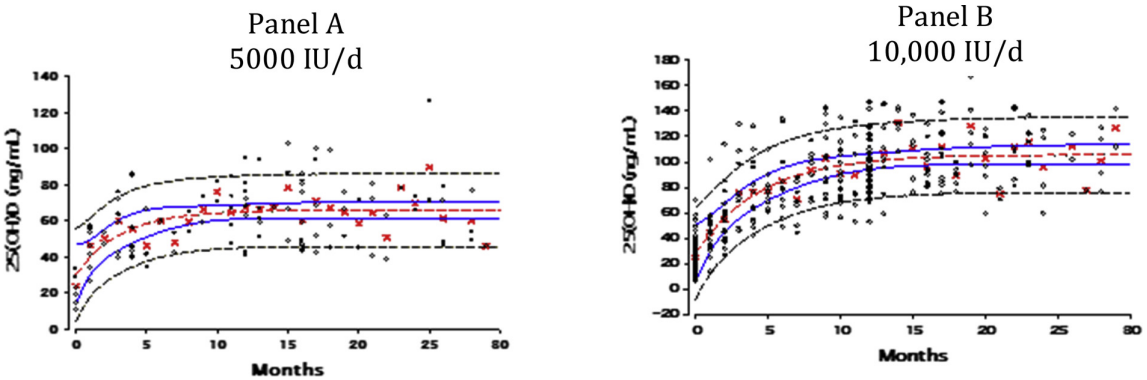

Fig. 1. Panel A: Plot of individual monthly 25OHD3 values (o) and mean monthly 25OHD3 values (x) for 36 patients taking 5000 IU of vitamin D3 daily (n = 125 values). **Panel B:** Plot of individual monthly 25OHD3 values (o) and mean monthly 25OHD3 values (x) for 78 patients taking 10,000 IU of vitamin D3 daily (n = 344 values).
The curve (—) represents a rising exponential curve of the mean monthly values. The middle curves (—) represent the 95% confidence band, and the outer curves (—) represent the 95% prediction band. Units are ng/ml. (Figs. 1 to 3 are courtesy of the late Dr. Robert P. Heaney, Creighton University.)

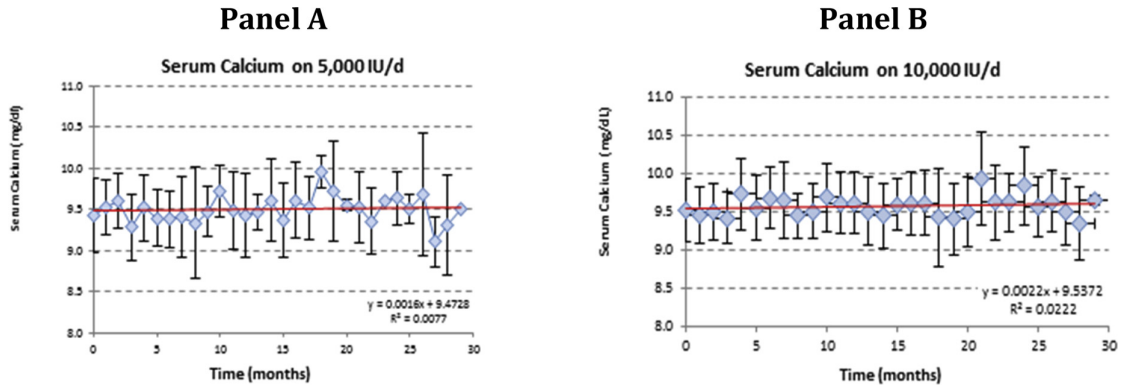

Fig. 2. Panel A: Plot of mean monthly serum calcium values (mg/dl) with standard deviation bar in 36 patients on 5000 IUs of vitamin D3 daily. **Panel B:** Plot of mean monthly serum calcium values (mg/dl) with standard deviation bar in 78 patients on 10,000 IUs of vitamin D3 daily. The red lines are weighted mean values.

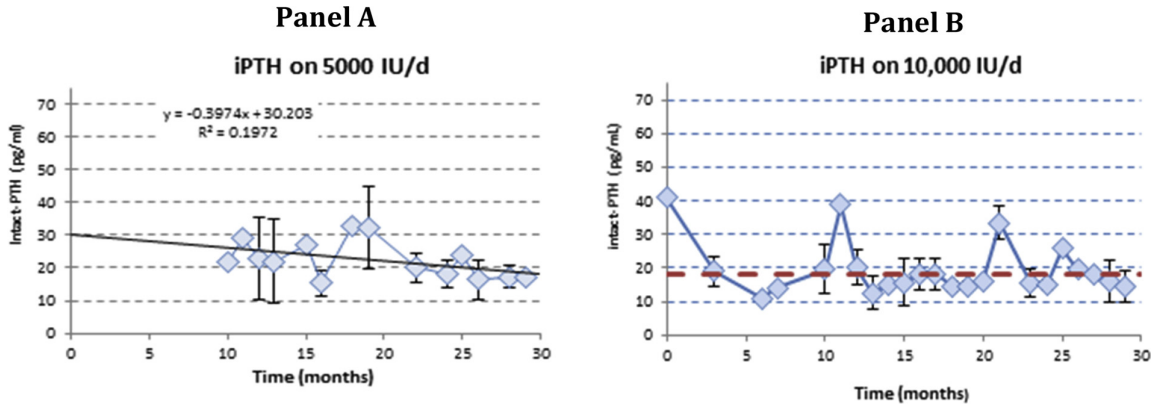

Fig. 3. Panel A: Plot of mean monthly serum iPTH levels (pg/ml) with standard deviation bars in patients on 5000 IU of vitamin D3 daily. **Panel B:** Plot of mean monthly serum iPTH levels (pg/ml) with standard deviation bars in patients on 10,000 IU of vitamin D3 daily. The red line is the weighted mean value.

other. This variance in more measurements in black males is likely a reflection of differences in length of stay between the populations.

The majority of 25OHD3 values > 74.4 ng/ml, i.e. 79%, were obtained on patients taking 10,000 IU/d, with 17% in patients on 5000 IU/d, and 4% on doses higher than 10,000 IU/d. There was one patient with psoriasis who was on 50,000 IU of vitamin D2 daily for more than 2 years. There were 2 other patients with psoriasis who were taking doses ranging from 20,000 IU to 45,000 IU of vitamin D3 daily. All 3 patients showed marked improvement in their psoriasis within 3 to 4 months without developing any complications.

The breakdown of the actual numbers of 25OHD blood levels above 74.4 ng/ml obtained at varying doses of vitamin D3 is shown in Table 1.

Table 1
Number of 25OHD levels at each D3 dose.

D3 Dose	No D3	D3	Total
0	777	0	777
5000	x	70	70
10,000	x	331	331
20,000	x	5	5
40,000	x	4	4
45,000	x	1	1
50,000	x	7	7
total	777	418	1195

Note: baseline labs for patients on D3 are included in the no D3 group, and were not analyzed separately from patients who did not take D3.

3.2.2. Comparison of the mean and range of serum 25OHD, calcium and iPTH levels in patients not on D3 vs on oral D3 long enough to achieve 25OHD blood levels > 74.4 ng/ml

The mean 25OHD blood level in patients on D3 supplementation was 118.9 ng/ml, vs. 27.1 ng/ml in patients not on D3 supplementation, for a difference of 91.8 ng/ml between the groups, as shown in Table 2.

With the exception of one patient in the No D3 group, there was no overlap in the range of 25OHD values between the 2 groups. The distribution of serum 25OHD values is discussed in Section 3.2.3, and is shown in Table 3.

In spite of the large difference between mean 25OHD values between the 2 groups, the mean and range of calcium levels were almost identical in the D3 group vs the no D3 group, also shown in Table 2.

The mean serum calcium level in the D3 group was 9.6 mg/dl, vs 9.5 mg/dl in the no D3 group. The range of serum calcium levels was 8.7–10.7 mg/dl in the D3 group, vs 8.4–10.7 mg/dl in the No D3 group.

A total of 7 patients with elevated calcium levels due to causes other than vitamin D were excluded, as discussed in Section 3.2.

The distribution of serum calcium values was also very similar

Table 2
Summary of D3 vs No D3 Supplementation - Mean, Range, N.

Test	D3 Mean	No D3 Mean	D3 Range	No D3 Range	D3 N	No D3 N
25OHD	118.9	27.1	74.4 - 384.8	4.9 - 74.8	418	777
Calcium	9.6	9.5	8.7 - 10.7	8.4 - 10.7	381	728
iPTH	24.2	30.2	5 - 54	8.0 - 77.0	261	650

Table 3
Distribution of Serum 25OHD Concentrations (ng/ml) - D3 vs. No D3.

	N	74 to 79	80 to 89	90 to 99	100 to 199	200 to 299	> 300
D3	418	29	52	54	270	9	4
	%	6.9%	12.4%	12.9%	64.6%	2.2%	1.0%
	N	**0 to 9**	**10 to 19**	**20 to 29**	**30 to 39**	**40 to 49**	**> 50**
No D3	777	26	196	278	177	74	26
	%	3.3%	25.2%	35.8%	22.8%	9.5%	3.3%

between the 2 groups, and are discussed in Section 3.2.4, and shown in Table 4.

The mean iPTH level in patients on D3 was 24.2 pg/ml, vs 30.2 pg/ml in those not on D3. The range of values was also narrower in the D3 group, at 5–54 pg/ml, vs 8–77 pg/ml in the no D3 group, as shown in Table 2.

The distribution of serum iPTH values is discussed in Section 3.2.5, and is shown in Table 5.

Beginning in January 2017, intact PTH blood levels were routinely obtained on all new admissions to the hospital, and with all follow-up 25OHD blood levels. For this reason, there are significantly more iPTH blood levels in both groups of patients compared to those available in Data Set 1.

This was done as an additional measure to monitor for toxicity from vitamin D supplementation, as blood levels of iPTH have been shown to be undetectable in cases of vitamin D toxicity secondary to hypercalcemia [33]. There were no undetectable blood levels of iPTH in any patient.

Note: The mean and range of serum 25OHD, calcium and iPTH levels was also evaluated separately for patients on 5000 IU, 10,000 IU or > 10,000 IU per day (see table in the supplementary data section).

The mean serum 25OHD levels were 102.9, 115.8, and 234.6 ng/ml in the 3 groups, while the mean serum calcium values were 9.5, 9.6, and 9.6, and the mean serum iPTH levels were 25.6, 24.2, and 21.5. The distribution and range of serum calcium and iPTH values was also very similar in all 3 groups

Hypercalcemia is the main risk from excessive vitamin D intake. Because there was no difference in the mean and range of serum calcium levels between the 3 groups, and because there were relatively few data points in the > 10,000 IU/d group, the data was reported with the results of all 3 vitamin D doses combined when compared to patients not taking vitamin D.

3.2.3. Distribution of serum 25OHD Concentrations (ng/ml)

The distribution of serum 25OHD levels in each group is shown in Table 3.

Vitamin D deficiency was present in a significant percentage of the patients not on vitamin D3 supplementation, depending on the reference range used. A total of 28.5% had 25OHD levels < 20 ng/ml, while 64.3% were < 30 ng/ml (Table 3).

A 25OHD level < 20 ng/ml is currently considered deficient by the Institute of Medicine [47,48], while a level < 30 ng/ml is considered insufficient by the Endocrine Society [27]. A 25OHD level of 100 ng/ml is currently considered the upper limit of normal [27,38], while the IOM warns of caution with 25OHD levels > 50 ng/ml.

A majority of the patients (67.8%) on vitamin D supplementation had 25OHD blood levels above 100 ng/ml. There were 9 blood levels above 200 ng/ml, and 4 above 300 ng/ml.

A total of 6 of these thirteen 25OHD levels > 200 ng/ml were in the patient with psoriasis who was taking 50,000 IU/day of vitamin D2. His serum calcium has been measured 13 times, and has ranged from 9.4 to 9.8 mg/dl. His iPTH levels were 40, 38, 29, and 32 pg/ml. His data is presented in Table 6, and his case is discussed in more detail in Section 3.3.

A total of 4 of these levels above 200 ng/ml, 263, 384, 316 and 347 ng/ml, were observed in a second psoriasis patient taking 40,000 IU/d on 3 occasions, and 45,000 IU/d on the fourth. Corresponding calcium levels were 8.9, 9.5, 9.1, and 10.2 mg/dl, while iPTH levels were 6, 5, 9, and 5 pg/ml.

There was one patient on 50,000 IU/d who had a 25OHD level of 263 ng/ml. Her calcium was 9.0 mg/dl, and iPTH was 24 pg/ml.

There were 2 patients on 10,000 IU/d with 25OHD levels over 200 ng/ml. Both had levels of 202 ng/ml, and these were the highest 25OHD levels observed in patients taking 10,000 IU/d. The serum calcium was 9.8 mg/dl in one, not measured in the other, and the iPTH levels were 18 and 24 pg/ml.

3.2.4. Distribution of serum calcium concentrations (mg/dl)

The distribution of serum calcium levels is shown in Table 4.

The distribution of serum calcium levels was very similar between the 2 groups.

A total of 59.8% of the values were < 9.7 mg/dl in the D3 group, and 58.5% were < 9.7 mg/dl in the No D3 group.

A total of 12.8% of the values were above 10.0 in both groups, and there were no patients with a calcium level above 10.7 in either group. The normal range in our reference laboratory is 8.7–10.2 mg/dl.

In the group of patients with calcium levels above 10.2 mg/dl, there were no patients who exhibited any signs or symptoms associated with hypercalcemia in either group. There was also a lack of persistence of elevation of calcium levels above 10.2 in these patients on repeat testing.

Because of the lack of signs or symptoms of hypercalcemia, the lack of persistence of elevation of the calcium levels on repeat resting, and the same rate of occurrence in both groups of patients, no one was classified as having developed hypercalcemia who had calcium levels above 10.2 in these 2 groups of patients.

3.2.5. Distribution of serum intact parathyroid hormone concentrations (pg/ml)

The distribution of serum iPTH levels is shown in Table 5.

The distribution of serum intact PTH values is distinctly different between the two groups. There is a shift to lower values in the D3 group compared to the no D3 group. The percentage of iPTH values < 30 pg/ml is 79.7% in the D3 group, vs. 55.5% in the no D3 group. There were no undetectable blood levels of iPTH in any patient. The lowest level in the D3 group was 5, and in the No D3 group was 8.

3.3. Changes in 25OHD3, calcium and iPTH blood levels in 3 individuals who have been taking daily doses of vitamin D ranging from 25,000 IU to 60,000 IU a day for 2 to 8 years

Three patients with psoriasis agreed to take vitamin D in doses

Table 4
Distribution of Serum Calcium Concentrations (mg/dl) - D3 vs. No D3.

	N	< 9	9 to 9.3	9.4 to 9.6	9.7 to 9.9	10 to 10.3	10.4 to 10.7	> 10.7
D3	**381**	**24**	**84**	**120**	**104**	**39**	**10**	**0**
NoD3	**728**	**34**	**196**	**219**	**186**	**83**	**10**	**0**
D3	**%**	**6.3%**	**22.0%**	**31.5%**	**27.3%**	**10.2%**	**2.6%**	**0.0%**
NoD3	**%**	**4.7%**	**26.9%**	**26.9%**	**25.5%**	**11.4%**	**1.4%**	**0.0%**

Table 5
Distribution of Serum intact Parathyroid Hormone Concentrations (pg/ml) - D3 vs No D3.

	N	0 to 10	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	> 59
D3	261	4	72	132	37	12	4	0
No D3	650	1	79	282	192	57	29	10
D3	%	1.5%	27.6%	50.6%	14.2%	4.6%	1.5%	0.0%
No D3	%	0.2%	12.2%	43.4%	29.5%	8.8%	4.5%	1.5%

Table 6
Patient with Severe Psoriasis Completely Cleared on 50,000 IU D2 for > 2 years (Vitamin D2 50,000 IU capsule started daily on 2/25/16).

Date	25OHD	iPTH	Calcium	Comments
2/27/2016	70.5	40	9.5	severe
5/27/2016			9.5	marked improvement
10/20/2016			9.6	mild
12/3/2016			9.6	
12/15/2016			9.7	
1/12/2017			9.4	
1/28/2017	262		9.5	
3/6/2017	297.6		9.6	
4/13/2017	290.8	38	9.6	dermatology clinic visits stopped
6/10/2017	296.4		9.8	no signs
9/6/2017			9.4	no signs
12/6/2017	249.6	29	9.5	
3/2/2018	308.4	32	9.6	no signs

24 hour Urine Calcium with Creatinine on 6/9/17

test	value	range
calcium	14.4	Not est.
24 hr calcium	316.8	100 to 300
creatinine	69.6	Not est.
ca/cr ratio	207	0 to 260

ranging from 20,000 IU/d to 50,000 IU/d while hospitalized, and each showed marked clinical improvement in their skin within 3 to 4 months without the development of hypercalcemia or any other adverse events related to supplementation with vitamin D. The data from 2 of these patients was discussed earlier in data set 2, and one will be reviewed in more detail in this section.

One of the psoriasis patients was a 29-year-old obese black male who started on 50,000 IU of vitamin D2 po daily on the day of admission, and has now been taking this dose for 29 consecutive months without complication.

On admission, his psoriasis was poorly controlled, in spite of being followed in the dermatology clinic at the local medical school. He had extensive plaques on his scalp, forehead, and ears, and scattered plaques on his chest, abdomen, elbows and thighs. He was being treated with topical steroid creams and medicated shampoos at the time of admission. He was not on a vitamin D supplement. PASI scores were not routinely calculated, but it was approximately 7 at the time of admission.

His skin began improving shortly after starting on vitamin D2, was markedly improved within a few months, eventually cleared completely, and has remained clear for many months. He is no longer using topical steroids or medicated shampoos, and is no longer being seen in the dermatology clinic.

The patient chose to leave the dose of vitamin D2 at 50,000 IU/d, which is provided in a single capsule, rather than titrate the dose down using multiple 5000 IU vitamin D3 capsules. His serum calcium and iPTH levels have been checked numerous times, and have remained normal. His 25OHD blood level has been ranging from 250 ng/ml to 308 ng/ml, 13 calcium levels have ranged from 9.4 mg/dl to 9.8 mg/dl, and four iPTH levels have ranged from 29 pg/ml to 40 pg/ml.

He has never developed any adverse reactions to the vitamin D2. A 24-hour urine calcium and creatinine was obtained in July 2017, which was unremarkable.

His data is shown in Table 6.

The other 2 cases to be discussed involve two of the authors, who previously reported in 2017 on their experience in taking 20,000–60,000 IU of vitamin D3 daily for 2–6 years without complication [49].

One (JA) has experienced marked clinical improvement in his asthma since starting on vitamin D3 in 2011. His asthma was previously poorly controlled on usual medical care. Prior to taking vitamin D3, he would have 5 to 6 severe asthma exacerbations a year, requiring bedrest, time off from work, and treatment with antibiotics and oral steroids. He was on usual care for asthma during this time, and saw a pulmonologist and primary care physician on a regular basis.

Since starting on the vitamin D3 in 2011, he has only had one serious exacerbation, which occurred when he inadvertently lowered his dose from 10,000 IU/d to 5000 IU/d early in the course of therapy with vitamin D. He originally started on 10,000 IU/d, and has since titrated the dose to 30,000 IU/d. He has discontinued most of his other asthma medications. During this time period his labs were measured several times. He has had 25OHD levels 96.6, 161.1, and 106.9 ng/ml, calcium levels of 9.2, 10.0, 9.9, and 9.9 mg/dl, and iPTH of 25 pg/ml (most recent calcium and iPTH from May 2018). All lab results were obtained through his primary care office.

The second (PM) experienced marked clinical improvement in an ulcerated skin lesion on his hand after titrating his daily vitamin D3 dose from 20,000 IU/d to 60,000 IU/d over the course of 4 years. The ulceration was dime-sized, developed while taking 20,000 IU/d, and slowly shrank in size as the dose of vitamin D3 was increased.

The ulceration was presumed to be a non-melanoma skin cancer. It was eventually excised, and showed no cancer cells after reviewed by pathology. It has never recurred since excision approximately 2 years ago. His 25OHD levels have been measured every 6 months since

starting on 60,000 IU/d in 2014 with home test kits from Grassroots Health (www.grassrootshealth.net). His last 7 measurements on this dose were 225, 166, 218, 247, 187, 236, 219, and 194 ng/ml, averaging 212 ng/ml (most recent 25OHD in July 2018). Calcium levels have been monitored less frequently, and were normal at 9.4 and 9.7 mg/dl. He has never experienced any adverse events while taking vitamin D.

None of the 3 individuals have ever developed hypercalcemia or any other signs or symptoms of vitamin D toxicity while taking daily oral doses of D3 ranging from 25,000 IU/d to 60,000 IU/d for several years. All 3 have shown marked clinical improvement in their chronic medical problems.

3.4. Comparison of the results of 3.1 with the results from four previously discussed studies reporting changes in 25OHD3 blood levels after daily oral supplementation with varying doses of vitamin D for 4 to 12 months, and one study reporting changes in 25OHD levels after successful use of phototherapy in treating patients with psoriasis after 1 to 4 months

Data comparisons were made at several time points, including baseline, and after 1–4 months, 5 months or 12 months of treatment, based on the data reported in the comparison study. (**Note**: this data comparison is presented in Tables 7–10 in the supplemental data section.)

3.4.1. Brief summary of each of the comparison studies

3.4.1.1. Stamp [25]. A 4 month study with 164 healthy volunteers using 10 different oral doses of vitamin D. Equilibrium 25OHD blood levels were obtained after 4 months or longer of daily oral dosing. Baseline values were not reported. The data provided by Stamp are graphical, plotting individual equilibrium 25OHD blood levels for each patient against the oral dose of vitamin D. For this report, all 25OHD blood levels were estimated from the graphical data presented in the manuscript (Table 8, supplemental data section). 25OHD blood levels from a one month UVB phototherapy treated group was also presented. These patients were found to develop 25OHD blood levels that were in between those in observed in individuals taking 10,000 IU/d and 20,000 IU/d.

3.4.1.2. Heaney [37]. a 5month study with 67 healthy volunteers using 3 different oral doses of vitamin D vs placebo. Baseline 25OHD ranges were not reported (Table 9, supplemental data section).

3.4.1.3. Ryan [43]. a 4month phototherapy study in 29 patients with chronic plaque psoriasis, who were treated until complete clearing of psoriasis skin lesions occurred. Clearing of the plaques was observed after 1–4 months of treatment with NB-UVB phototherapy, at which time follow-up 25OHD blood levels were obtained, and compared to baseline levels (Table 8, supplemental data section). An untreated age-matched control group of psoriasis patients was also included for comparison.

3.4.1.4. Garrett-Mayer [45]. a 12month study comparing the 25OHD response to a daily oral dose of 4000 IU of vitamin D3 in African American vs white men (Table 10, supplemental data section).

3.4.1.5. Marshall [46]. a 12month study examining the safety and clinical efficacy of using an oral dose of 4000 IU/d of vitamin D3 in 52 low-risk prostate cancer patients (Table 10, supplemental data section).

Table 7 shows the similarity in the median, mean and range of 25OHD blood levels observed at baseline between the current and comparison studies.

Table 8 shows the remarkable similarity between the median and range of 25OHD blood levels observed by Ryan after using NB-UVB phototherapy in the treatment of psoriasis in 2010, versus after the administration of daily 10,000 IU oral doses of vitamin D reported by Stamp in 1977, and as observed in the current report in our patients who took 10,000 IU/d of D3 after 1–4 months.

Table 9 shows that our 5 month mean 25OHD blood levels in both the 5000 IU/d and 10,000 IU/d treatment groups are very similar to those reported by Heaney in 2003 [38].

Table 10 shows the mean and range of 25OHD blood level in our patients on 5000 IU/d (n = 9) and 10,000 IU/d (n = 49) at 12 months, and how the 5000 IU/d data are very similar to those reported in patients taking 4000 IU/d of vitamin D3 for 12 months by both Garrett-Mayer [44] and Marshall [45].

4. 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 1602 vitamin D trials registered on the Clinicaltrials.gov website (August 2018).

Since 2009, we have been offering hospitalized patients daily supplementation with 5000 IU to 10,000 IU of vitamin D3 to both correct and prevent vitamin D deficiency. This was first shown to be safe and effective in a 5-month study reported by Dr Robert Heaney in 2003 [37]. Our data shows that this protocol continues to be safe and effective, even when used for extended periods of time, and with 25OHD blood levels reaching as high as 202 ng/ml on 10,000 IU/d. Many of our patients have prolonged hospital stays, and remain on supplementation for many months. A total of 43% of our current patients have been hospitalized for a year or longer, and a significant percentage were found to be either deficient or insufficient in vitamin D at the time of admission.

We previously reported that in a random sampling of 425 patients admitted in 2009 to a post-acute care hospital, a total of 58% were < 20 ng/ml, with 84% being < 30 ng/ml at the time of admission [50]. This continues to be a significant problem in our patients, as the sampling of 777 recently admitted and long-term patients reported in this study showed similar results, with 28.5% below 20 ng/ml, and 64.3% below 30 ng/ml.

Before making the decision to follow this protocol in 2009, an extensive review of the literature on vitamin D dosing, toxicity, and clinical efficacy was done as discussed earlier. During this review, hypercalcemia and its attendant symptoms was identified as the main adverse reaction, but it was only associated with prolonged intake of supra-physiologic doses of vitamin D, as noted in many reports and reviews [16,17,20,24,29–33,36,38–40,42].

Several reviews on vitamin D toxicity and safety between 1999 and 2008 found no evidence of toxicity associated with daily intakes of 5000 IU to 10,000 IU a day [36,38–40,42]. And there were at least 2 reports in 2007 advocating that intakes of 10,000 IU should be recognized as the tolerable upper intake level (UL), an intake that “is likely to pose no risk of adverse events in almost all individuals in the general population [39,39,40].

The reasoning for choosing 10,000 IU/d for the UL was two-fold. The first was that rigorous review of published studies involving cases of hypercalcemia related to vitamin D intake found it to be safe. The second was due to the discovery, first reported in 1977 and later confirmed and extended by others, that the body will make up to 10,000–25,000 IU a day in response to adequate sun exposure to the skin [1–3,25–28,36,38–40]. It was reasoned that if the body makes 10,000 IU of vitamin D a day in response to whole body exposure for a sufficient period of time, then it should be safe to take this dose on a daily basis [39,39,40].

The data we present in this report support this hypothesis, as we observed no adverse events in any patient taking 10,000 IU/d for an

extended period of time. Some of our patients have been on this dose for 7 years. Our data also suggests that even higher doses are safe to take for prolonged periods of time, and are associated with the same clinical benefits observed by others in the 1930s and 1940s.

We found intakes of 20,000 IU/d to 60,000 IU/d, associated with 25OHD blood levels ranging as high as 384 mg/dl, safe when taken on an extended daily basis. Many of the 25OHD blood levels we have observed are much higher than the currently defined upper limit of normal of 100 ng/ml [27,38], yet we found no evidence of toxicity in any individual who achieved these blood levels after taking these doses for extended periods of time.

There were no differences in mean serum calcium levels, the distribution of serum calcium levels, or any cases of vitamin D induced hypercalcemia in patients on vitamin D vs those not on vitamin D in any of our data sets. This is in spite of marked differences in the mean 25OHD levels (118.9 ng/ml vs 27.1 ng/ml), and in the ranges of 25OHD blood levels (74.4–384.8 ng/ml vs 4.9–74.8 ng/ml) observed.

We also found that the mean and range of 25OHD levels from our patients on 10,000 IU/d for 1 to 4 months (54 ng/ml, range 14–130 ng/ml) were strikingly similar to the results observed in patients on 10,000 IU/d for at least 4-months reported in 1977 by Stamp (median 55 ng/ml, range 40–110 ng/ml) [25], and to those obtained after 1 to 4-months of phototherapy in patients with psoriasis reported in 2010 by Ryan (median 59 ng/ml, 32–112 ng/ml) [43].

This lends strong support to the observations that the body makes at least 10,000 IU of vitamin D in response to UVB radiation, and that 10,000 IU of vitamin D should be safe to take on a daily basis. This is a very important finding, and lends more support to the recommendation of increasing the UL to at least 10,000 IU/d.

It is important to note that the baseline median 25OHD level (23 ng/ml) and range of 25OHD levels (9–46 ng/ml) in the Ryan study were much lower than the values observed after phototherapy. This calls into question the accuracy of considering a 25OHD blood level of at least 20 ng/ml as sufficient [47,48]. Other phototherapy studies in patients with psoriasis have shown similar changes in 25OHD levels before and after treatment [51]. No cases of hypercalcemia were observed in any of the phototherapy reports.

As discussed earlier, phototherapy has been known to be effective in treating rickets [5,13], tuberculosis [6–12] and psoriasis [14,43,51–53] dating back to the 1890s, 1920s, 1930s and 1940s. Phototherapy and sunshine are both currently recommended as treatments for psoriasis by the National Psoriasis Foundation [52], and phototherapy is also recommended for treating psoriasis by the American Academy of Dermatology [53].

Unfortunately, we were unable to find any literature on 25OHD blood levels with extended phototherapy for disease control in patients with psoriasis. It is not currently known how high 25OHD blood levels will become with prolonged phototherapy used to maintain remission in psoriasis. This is an important void in the literature that needs to be filled, as maintenance phototherapy administered 2–3 times a week is required to maintain control in psoriasis [52,53]. If the phototherapy is stopped, the disease will recur, unlike with TB or rickets.

It would be informative to know just how high 25OHD blood levels can be with phototherapy, as it would give us more insight into what the “normal range” of 25OHD blood levels might be. Our data on extended daily dosing with 5000 IU/d and 10,000 IU/d show that the 25OHD curves don’t plateau until about 12 months, which was not evident in the 5-month report from Heaney in 2003 [37]. It is not clear if the same will be true with phototherapy.

Interestingly, also like TB and rickets, psoriasis has also been shown to improve with oral vitamin D3. This was not only shown in the 1930s [14], but again in the 1980s, 1990s and 2000s [54–58]. Topically applied vitamin D has also been known to be an effective treatment for psoriasis since the 1980s [59].

The fact that sunshine, phototherapy, and vitamin D are all effective in treating these 3 diseases, and because vitamin D is produced in the skin by the action of UVB radiation on 7-dehydeocholesterol, makes it very likely that correction of vitamin D deficiency induced by sunshine and phototherapy is responsible for their clinical effects. This is what motivated physicians to start using oral vitamin D to treat disease in the 1930s and 1940s [14–17,19–24], and which they ultimately found to be quite effective.

In support of this hypothesis, it was shown in 2006 that the mechanism by which vitamin D is able to kill tuberculosis is by turning on a gene in the nucleus of white blood cells that makes an antibiotic called cathelicidin [60]. The gene is unable to be turned on in a state of vitamin D deficiency. Once the vitamin D deficiency is corrected, the gene can be turned on and the disease cured, regardless of the method used to correct the underlying state of vitamin D deficiency [24].

The decision to treat our psoriasis patients with vitamin D was made due to the multiple reports cited earlier showing its clinical efficacy and safety [14,54–59]. This includes the previous success of one of the authors (PM) in treating psoriasis using oral vitamin D3 in doses ranging up to 40,000 IU/d [57]. We were also confident that the doses we used would be safe and effective due to the recent experience of two of the authors (JA, PM) in safely using comparable doses of vitamin D in treating asthma and skin cancer.

The reason one of the authors (PM) made the decision to titrate the dose of vitamin D3 to see its effect on the skin cancer was due to a number of factors. This included reports from 1980 to 2006, and again in 2018, showing a strong relationship between vitamin D deficiency and increased risk for a number of cancers [61–65], others reports from the 1990s, and again in 2011, describing the ability of vitamin D to kill human tumor cells in-vitro, including melanoma and basal cell cancers [66–70], reports detailing the cellular mechanisms by which vitamin D is able to arrest cancer cell growth from 2008 and 2012 [71,72], and a clinical trial from 2007 that showed a decrease risk for a number of cancers in individuals receiving daily oral vitamin D vs placebo [73].

There are also now reports from 2016 [74] and 2018 [75] showing evidence of clinical efficacy of vitamin D in preventing cancer growth. One is a case report on advanced pancreatic cancer [74], in which an elderly patient, who was unable to tolerate chemotherapy, radiation, or surgery, took 50,000 IU/d of D3 for 9 months and was found to have a remarkable period of disease free progression, far beyond what would have been expected with chemotherapy. The authors were so impressed by this finding that they issued a call for more research in cancer patients with vitamin D using doses in this range.

Consistent with data from the 1930′s, 1940s, 1980s and 1990s discussed earlier, the three patients with psoriasis and the author with asthma all safely showed marked clinical improvement on oral vitamin D supplementation. However, they were able to do this using much lower doses of vitamin D than were used in the 1930′s and 1940s. The doses these individuals used, 20,000 IU/d to 50,000 IU/d, are an order of magnitude lower than the doses of 60,000 IU/d to 300,000 IU/d used for asthma, 150,000 IU/d to 600,000IU/d for RA, and 100,000 IU/d to 150,000IU/d for TB. They were also within or much closer to the range of vitamin D estimated to be produced in the skin from sunshine, i.e. 10,000 IU/d to 25,000 IU/d, which likely explains why they were clinically effective, but without causing toxicity from hypercalcemia.

There appears to be a dose response relationship between the clinical effectiveness of vitamin D and its toxicity. In the case of the individual with asthma, the only time he has had an exacerbation is when he dropped the dose of vitamin D3 to 5000 IU/d.

His experience is also consistent with the results of a recent clinical trial in which vitamin D3 supplementation was found to be ineffective in treating patients with asthma [76]. In this trial, 100,000 IU of vitamin D3 was given once, followed by 4000 IU/d of vitamin D3 given for 28 weeks, and was found to be ineffective in reducing the rate of first treatment failure or exacerbation in 201 adults with persistent asthma and vitamin D insufficiency, as compared to 207 control patients treated with placebo. The authors concluded that “These findings do not support a strategy of therapeutic vitamin D3 supplementation in

patients with symptomatic asthma."

A follow-up clinical trial using vitamin D3 with higher daily doses, in the range of at least 10,000 IU/d to 25,000 IU/d, is clearly needed before this conclusion can be reached. Their results only prove that 4000 IU/d is ineffective in treating patients with asthma, not that vitamin D is ineffective in treating asthma.

We have consistently found that supplementing individuals with vitamin D using daily dosing equivalent to 100% to 200% of the estimates of daily production from sunshine to not only be safe, but also effective in treating diseases strongly linked to vitamin D deficiency.

The 4000 IU/d vitamin D3 dose used in this asthma study is the maximum daily dose currently recommended by the Institute of Medicine [47,48,77], but only represents 16% to 40% of the amount of vitamin D estimated to be produced from sun exposure to the skin, i.e. 10,000 IU/d to 25,000 IU/d. The patients in the asthma study were clearly deficient, with mean baseline 25OHD levels of 18.8 ng/ml. These values increased to a 25OHD mean of 42 ng/ml (range, 6.3–97.3 ng/mL) by week 12 in the treatment group, and persisted at this mean level through week 28, but remained less than 20 ng/ml in the placebo group.

These on treatment values are less than the median and range observed by Ryan in the phototherapy study after 1–4 weeks (median 59 ng/ml, range 32–112 ng/ml), and in our 10,000 IU/d group at 5 months (mean 77 ng/ml, range 63–110 ng/ml) and 12 months (mean 96 ng/ml, range 53–148 ng/ml). They are also much lower than the 25OHD levels observed in the author (JA) with asthma (96.6, 161.1, and 106.9 ng/ml).

Similar remarkable clinical benefits using doses in this range have previously been reported in a patient with Parkinson's disease treated with 4000 IU/d of 25OHD3 (roughly equivalent to 40,000 IU/d of D3 (25)) for a year in 1997 [78], and in a pancreatic cancer patient treated with 50,000 IU/d for 9 months reported in 2016 [74]. Based on these case reports, our experience, and the reports from the 1930s and 1940s discussed earlier, the failure of many clinical trials involving vitamin D3, that have been reported in the last few decades appear to be related to the use of insufficient dosing of vitamin D, which have typically ranged from 800 IU to 2000 IU/d.

It is interesting to note that both Dowling [79] and Howard [17] in the 1940s observed random calcifications occur at times in patients treated with large doses of vitamin D, with both also observing that the calcifications resolved over time along with the hypercalcemia with cessation of vitamin D intake. The main treatment for vitamin D induced hypercalcemia appears to be stopping the vitamin D intake, and supportive care if necessary. Once the vitamin D levels fall, the hypercalcemia improves, calcifications will dissolve if present, symptoms abate, and patients recover uneventfully [17,33,79]. See an expanded discussion of these references in the supplemental data section.

It was with this broad background of information on dosing, safety, and toxicity, recommendations for the new UL of 10,000 IU/d, the clinical trial evidence on the effectiveness of vitamin D in treating asthma in the 1930s, psoriasis in the 1930s, 1980s and 1990s, rickets in the 1920s, RA in the 1940s, TB in the 1940s, epilepsy in 1974 and 2012 [80,81], Parkinson's disease in 1997 [78,82], estimates of vitamin D production in the skin made in the 1970s and 1980s ranging from 10,000 IU/d to 25,000 IU/d, and the strong link between vitamin D and cancer discussed earlier, that we began to supplement hospitalized patients in 2009 with 5000 IU/d to 10,000 IU/d of vitamin D3, and have safely continued to do so through today.

A few years after implementing this protocol, a national debate over vitamin D dosing, safety, clinical efficacy and toxicity erupted in 2011 with the publication of 2 contrasting sets of recommendations, one from the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) [47,48,77], and the other from the Endocrine Society [27]. This debate remains unsettled and continues today [83].

In 2011, the IOM defined vitamin D deficiency as < 20 ng/ml [47,48,77], while the Endocrine Society considered levels < 30 ng/ml to be insufficient [27]. The IOM warned against achieving 25OHD levels > 50 ng/ml due to concerns for increased mortality risk, while the Endocrine Society maintained a 25OHD blood level of 100 ng/ml as the upper limit of normal. The IOM stated that a 25OHD blood level of 20 ng/ml or above was sufficient for the majority of the population, and that an intake of 600 IU/d would achieve this result in most people. They also assumed that all the vitamin D that a person gets is obtained from the diet, and recommended avoidance of sunshine due to the risk of developing skin cancer [48].

However, several reports have shown that prolonged sun exposure or phototherapy results in mean and median 25OHD blood levels 2–3 times higher than the IOMs estimate for sufficiency [25,41,43,51,85], and can result in complete control of a disease, as has been shown for psoriasis, tuberculosis and rickets. See an expanded discussion of the issues surrounding this debate in the supplemental data section.

There is also a discussion in the supplemental section of the 25OHD blood levels obtained in 1971 when the first accurate measurements of 25OHD were made [41]. They measured 25OHD blood levels in several groups of people. In a group of 8 lifeguards, mean 25OHD blood levels were 64.4 ± 8.7 ng/ml, with a range of range 53–79 ng/ml.

Several more recent studies also support the safety of 25OHD blood levels > 50 ng/ml [85–93]. These are discussed in detail in the supplemental data section.

We have not observed any cases of hypercalcemia, nephrolithiasis, or any other signs or symptoms of toxicity in any of our patients who achieved 25OHD blood levels ranging from 100 ng/ml to 384 ng/ml while taking daily supplemental doses of vitamin D ranging from 5000 IU/d to 60,000 IU/d.

Several other groups of investigators have also recently reported no increased risk for the development of kidney stones with vitamin D supplementation [94–100].

5. 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 50% higher than those observed in our patients taking 5000 IU/d for the same period of time.

Serum 25OHD levels above 100 ng/ml, ranging to as high as 202 ng/ml, were commonly observed in patients on prolonged daily oral dosing with 10,000 IU. Serum 25OHD blood levels over 200 ng/ml, ranging as high as 384 ng/ml, were also observed in several individuals taking vitamin D doses > 10,000 IU/d. However none of these 25OHD blood levels were associated with hypercalcemia, nephrolithiasis, or any other adverse health effects in our study population.

Estimates of 25OHD blood levels associated with toxicity from hypercalcemia have varied over time [1,27,33,36,38,40,42,48], with recent evidence suggesting that 25OHD blood levels up to 400 ng/ml are safe [33]. Our data are consistent with this value.

The use of doses ranging from 25,000 IU/d to 60,000 IU/d was associated with remarkable clinical benefits in several individuals with psoriasis, asthma and skin cancer, without the development of hypercalcemia or clinical toxicity.

These case findings are consistent with case reports on pancreatic cancer in 2016 [74], Parkinson's disease in 1997 [78,82], and psoriasis in the 2000s [57], and clinical trials with psoriasis in the 1930s [14], 1980s [54,55], and 1990s [56,58], asthma in the 1930s [15], rheumatoid arthritis in the 1930s and 1940s [16,17], tuberculosis in the 1940s [19–24,79], rickets [5,18], and epilepsy in the 1970s [80] and 2000s [81].

Both the baseline, and on treatment median and range of 25OHD

blood levels in our 10,000 IU/d group of patients after 1–4 months were very similar to those observed in both the NB-UVB phototherapy study reported by Ryan in 2010 [43], which were obtained at the time of complete clearing of psoriasis skin lesions, as well as in the 10,000 IU/d group of patients reported by Stamp in 1977 [25], who were supplemented daily for at least 4 months before a follow-up 25OHD level was obtained.

Contrary of the assertions of the Institute of Medicine that sunshine should be avoided due to the risk of developing skin cancer [47,48,77], sunshine and phototherapy have been shown to be safe and effective treatments for rickets [5,13], tuberculosis [6–12,24], and psoriasis [43,51], and are currently recommended for the treatment of psoriasis [52,53].

Clinical trials using doses of vitamin D within the range of amounts estimated to be made in the body from sun exposure to the skin, i.e. 10,000 IU/d to 25,000 IU/d [1–3,25–28,36,38–40], and up to 50,000 IU/d appear to be warranted. These studies are likely to be both safe and clinically effective for a number of disease states. If toxicity from hypercalcemia were to occur, it is not life threatening, and is easily reversible with cessation of vitamin D supplementation [17,33,79].

Consideration should also be given to revising the UL to 10,000 IU/d, as has been previously advocated [39,40].

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Funding

This research was performed without external funding.

References

[1] L.E. Tavera-Mendoza, J. White, Cell defenses and the sunshine vitamin, Sci. Am. (November) (2007) 62–72.
[2] A. Norman, Minireview: vitamin d receptor: new assignments for an already busy receptor, Endocrinology 147 (12) (2006) 5542–5548.
[3] A. Norman, R. Bouillon, Vitamin D nutritional policy needs a vision for the future, Exp. Biol. Med. 235 (2010) 1034–1045.
[4] C.J.B. Williams, On the use and administration of cod-liver oil in pulmonary consumption, Lond. J. Med. (January(1)) (1849) 1–14.
[5] K. Rajakumar, Vitamin d, cod-liver oil, sunlight, and rickets: a historical perspective, Pediatrics 112 (August (2)) (2003) e132–e135.
[6] K.A.H. Morner, Nobel Prize for Physiology or Medicine Award Ceremony Speech, December 10, 1903. Available at (1903) http://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/press.html.
[7] Biography of Dr Neils Ryberg-Finsen. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/finsen-bio.html.
[8] A. Masten, Tuberculosis of the Lungs (A Booklet for the Patient), Colorado State Board of Health Bulletin, 1936, pp. 1–14 December.
[9] A. Masten, Good climate – an asset in the treatment of tuberculosis, Chest 3 (7) (1937) 20–21.
[10] R. Aitken, Lupus vulgaris* with special reference to its treatment with the finsen-lomholt lamp, Br. Med. J. 23 (January) (1937) 160–163.
[11] L. Van Der Lugt, P.B. Rottier, Finsen therapy and vitamin D, Acta Dermato-Venerologica 38 (1958) 264–273.
[12] P.C. Gotzsche, Niels Finsen's treatment for lupus vulgaris, J. R. Soc. Med. 104 (2011) 41–42.
[13] A.F. Hess, L.J. Unger, The cure of infantile rickets by sunshine, JAMA 77 (1) (1921) 39.
[14] J. Krafka, A simple treatment for psoriasis, J. Clin. Lab. Med. 21 (1936) 1147–1148.
[15] B.Z. Rappaport, C.I. Reed, M.L. Hathaway, H.C. Struck, The treatment of hay fever and Asthma with viosterol of high potency, J. Allergy 5 (September (6)) (1934) 541–553.
[16] I. Dreyer, C. Reed, The treatment of arthritis with massive doses of vitamin D, Arch. Phys. Ther. 16 (September) (1935) 537–543.
[17] J.E. Howard, R.J. Meyer, Intoxication with vitamin D, J. Clin. Endocrinol. 8 (11) (1948) 895–910.
[18] E.A. Parks, The therapy of rickets, JAMA 115 (5) (1940) 370–379.
[19] G.B. Dowling, E.W. Prosser Thomas, Lupus vulgaris treated with calciferol, Proc. R. Soc. Med. 39 (December) (1945) 96–99.
[20] G.B. Dowling, E.W. Prosser Thomas, H.J. Wallace, Lupus vulgaris treated with calciferol, Proc. R. Soc. Med. 39 (March) (1946) 225–227.
[21] H.E. Michelson, R.J. Steves, Treatment of cutaneous tuberculosis with large doses of vitamin D, Arch. Derm. Syphilol. 56 (3) (1947) 317–324.
[22] K.M. Tomlinson, Calcium content of skin in lupus vulgaris treated with Calciferol, Lancet 251 (1948) 327–328.
[23] W. Raab, Vitamin D – its bactericidal action, Chest 12 (1946) 409–415.
[24] P.J. McCullough, D.S. Lehrer, Vitamin D, cod liver oil, sunshine and phototherapy: safe, effective and forgotten tools for treating and curing tuberculosis infections – a comprehensive review, J. Steroid Biochem. Mol. Biol. 177 (2018) 21–29.
[25] T.C.B. Stamp, J.G. Haddad, C.A. Twigg, Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D, Lancet (June) (1977) 1341–1343.
[26] M. Holick, Environmental factors that influence the cutaneous production of vitamin D, Am. J. Clin. Nutr. 61 (suppl) (1995) 638S-45S.
[27] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, et al., Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (July (7)) (2011) 1911–1930.
[28] M. Holick, Vitamin d deficiency, New Engl. J. Med. 357 (2007) 266–281.
[29] C.I. Reed, Symptoms of viosterol overdosage in human subjects, JAMA 102 (May (21)) (1934) 1745–1748.
[30] C.D. Leake, Vitamin d toxicity, Cal. West. Med. 44 (March (3)) (1936) 149–150.
[31] B. Bevans, H. Taylor, Lesions following the use of Ertron in rheumatoid arthritis, Am. J. Pathol. 23 (May (3)) (1947) 367–387.
[32] J. Cannell, Gary Null and Vitamin D Toxicity, August 15 Available at (2010) www.vitamindcouncil.org/newsletters/newsletters-gary-null-and-vitamin-d-toxicity/.
[33] T. Araki, M.F. Holick, B.D. Alfonso, et al., Vitamin d intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States, J. Clin. Endocrinol. Metab. 96 (December (12)) (2011) 3603–3608.
[34] S.V. Ramagopalan, A. Heger, A.J. Berlanga, et al., A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution, Genome Res. 20 (2010) 1352–1360.
[35] A. Hossein-nezhad, M.F. Holick, Vitamin d for health; a global perspective, Mayo Clin. Proc. 88 (July (7)) (2013) 720–755.
[36] R. Vieth, Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety, Am. J. Clin. Nutr. 69 (1999) 842–856.
[37] R.P. Heaney, K.M. Davies, T.C. Chen, M.F. Holick, M.J. Barger-Lux, Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol, Am. J. Clin. Nutr. (77) (2003) 204–210.
[38] B.W. Hollis, Circulating 25-hydroxyvitamin d levels indicative of vitamin d sufficiency: implications for establishing a new effective dietary intake. Recommendation for vitamin D, J. Nutr. 135 (2005) 317–322.
[39] R. Vieth, Vitamin D toxicity, policy, and science, J. Bone Miner. Res. 22 (S2) (2007) V64–V68, https://doi.org/10.1359/JBMR.07S221.
[40] J.N. Hathcock, A. Shao, R. Vieth, R. Heaney, Risk assessment for vitamin D, Am. J. Clin. Nutr. 85 (2007) 6–18.
[41] J.G. Haddad, K.J. Chyu, Competitive protein-binding radioassay for 25-hydroxycholecalciferol, J. Clin. Endocr. 33 (1971) 992–995.
[42] G. Jones, Pharmacokinectics of vitamin D toxicity, Am. J. Clin. Nutr. 88 (suppl) (2008) 582S-6S.
[43] C. Ryan, B. Moran, M.J. McKenna, et al., The effect of narrowband UV-B treatment for psoriasis on vitamin d status during wintertime in Ireland, Arch. Dermatol. 146 (8) (2010) 836–842.
[44] C.F. Garland, C.B. French, L.L. Baggerly, R.P. Heaney, Vitamin d supplement doses and serum 25-Hydroxyvitamin d in the range associated with Cancer prevention, Anticancer Res. 31 (2011) 617–622.
[45] Garrett-Mayer E, Wagner CL, Hollis BW, Kindy MS, Gattoni-Celli S. Vitamin D3 supplementation (4000 IU/d for 1 y) eliminates differences in circulating 25-hydorxyvitamin D between African American and white men. Am J Clin Nutr doi: 10.3945/ajcn.112.034256.
[46] D.T. Marshall, S.J. Savage, E.G. Garrett-Mayer, et al., Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate Cancer under active surveillance, J. Clin. Endocrinol. Metab. 97 (July (7)) (2012) 2315–2324.
[47] Dietary Reference Intakes for Calcium and Vitamin D. Report Brief, Institute of Medicine, 2010 Nov.
[48] IOM (Institute of Medicine), Dietary Reference Intakes for Calcium and Vitamin D, The National Academies Press, Washington, DC, 2011.
[49] P.J. McCullough, J.A. Amend, Results of daily oral dosing with up to 60,000 international units (iu) of vitamin D3 for 2 to 6 years in 3 adult males, J. Steroid Biochem. Mol. Biol. (2017), https://doi.org/10.1016/j.jsbmb.2016.12.009.
[50] P.J. McCullough, R.P. Heaney, Correction of vitamin D deficiency using sublingually administered vitamin D2 in a Crohn's disease patient with mal-absorption and a new ileostomy, J. Ster. Biochem. Mol. Biol. 173 (2017) 211–214.
[51] A. Osmancevic, K. Landin-Wilhelmsen, O. Larko, A.L. Krogstad, Vitamin D status in psoriasis patients during different treatments with phototherapy, J. Photochem. Photobiol. B: Biol. 101 (2010) 117–123.
[52] Light Therapy. National Psoriasis Foundation. http://www.psoriasis.org/about-psoriasis/treatments/phototherapy.
[53] A. Menter, N.J. Korman, C.A. Elmets, et al., Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy, J. Am. Acad. Dermatol. 62 (2010) 114–135.
[54] S. Morimoto, K. Yoshikawa, T. Kozuka, et al., An open study of vitamin D3 treatment in psoriasis vulgaris, Br. J. Dermatol. 115 (1986) 421–429.
[55] E.L. Smith, S.H. Pincus, L. Donovan, M.F. Holick, A novel approach for the evaluation and treatment of psoriasis, J. Am. Acad. Dermatol. 19 (1988) 516–528.
[56] A. Perez, R. Raab, T.C. Chen, A. Turner, M.F. Holick, Safety and efficacy of oral calcitriol (1,25-dihydorxyvitamin D3) for the treatment of psoriasis, Br. J.

Dermatol. 134 (1996) 1070–1078.
[57] P.J. McCullough, M. Arnold-Long, Marked Improvement in Psoriasis Skin Lesions Within 5 Months in Two Patients After Treatment With Oral Vitamin D3 in Doses Ranging From 10,000 International Units (IU's) to 40,000 IUs Daily. Poster Presentation, 15th Vitamin D Workshop, Houston, Texas, 2012.
[58] D. Huckins, D.T. Felson, M. Holick, Treatment of psoriatic arthritis with oral 1,25-dihydroxyvitamin D3: a pilot study, Arthritis Rheum. 33 (November (11)) (1990).
[59] L. Barrea, M.C. Savanelli, C. Somma, Napolitano, M. Megna, A. Colao, S. Savastano, Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist, Rev. Endocr. Metab. Disord. 18 (2017) 195–205, https://doi.org/10.1007/s11154-017-9411-6.
[60] P.T. Liu, S. Stenger, H. Li, et al., Toll-like receptor triggering of a vitamin D-Mediated human antimicrobial response, Science 311 (2006) 1770–1773.
[61] C. Garland, F. Garland, Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidemiol. 9 (1980) 227–231 [PubMed].
[62] W.B. Grant, An estimate of premature cancer mortality in the US because of inadequate doses of solar ultraviolet-B radiation, Cancer 94 (6) (2002) 1867–1875 [PubMed].
[63] E. Giovannucci, The epidemiology of vitamin D and cancer incidence and mortality: a review (United States), Cancer Causes Control 16 (March (2)) (2005) 83–95.
[64] C.F. Garland, F.C. Garland, E.D. Gorham, M. Lipkin, H. Newmark, S.B. Mohr, M.F. Holick, The role of vitamin d in Cancer prevention, Am. J. Public Health 96 (February (2)) (2006) 252–261, https://doi.org/10.2105/AJPH.2004.045260 PMCID: PMC1470481 PMID: 16380576.
[65] S.L. McDonnell, C.A. Baggerly, C.B. French, L.L. Baggerly, C.F. Garland, E.D. Gorham, B.W. Hollis, D.L. Trump, J.M. Lappe, Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations > 60 vs < 20ng/ml (150 vs 50 nmol/L): pooled analysis of two randomized trials and a prospective cohort, PLoS One 13 (June (6)) (2018) e0199265, , https://doi.org/10.1371/journal.pone.0199265.
[66] M. Shabahang, R.R. Buras, F. Davoodi, L.M. Schumaker, R.J. Nauta, S.R. Evans, 1,25-Dihydroxyvitamin D3 receptor as a marker of human colon carcinoma cell line differentiation and growth inhibition, Cancer Res. 53 (August (16)) (1993) 3712–3718.
[67] M. Shabahang, R.R. Buras, F. Davoodi, L.M. Schumaker, R.J. Nauta, M.R. Uskokovic, R.V. Brenner, S.R. Evans, Growth inhibition of HT-29 human colon cancer cells by analogues of 1,25-dihydroxyvitamin D3, Cancer Res. 54 (August (15)) (1994) 4057–4064.
[68] M. Shabahang, A.E. Buffan, J.M. Nolla, L.M. Schumaker, R.V. Brenner, R.R. Buras, R.J. Nauta, S.R. Evans, The effect of 1, 25-dihydroxyvitamin D3 on the growth of soft-tissue sarcoma cells as mediated by the vitamin D receptor, Ann. Surg. Oncol. 3 (March (2)) (1996) 144–149.
[69] S.R. Evans, A.M. Houghton, L. Schumaker, R.V. Brenner, R.R. Buras, F. Davoodi, R.J. Nauta, M. Shabahang, Vitamin D receptor and growth inhibition by 1,25-dihydroxyvitamin D3 in human malignant melanoma cell lines, J. Surg. Res. 61 (February (1)) (1996) 127–133.
[70] A. Uhmann, H. Niemann, B. Lammering, et al., Antitumoral effects of calcitriol in basal cell carcinomas involve inhibition of hedgehog signaling and induction of vitamin d receptor signaling and differentiation, Mol. Cancer Ther. 10 (2011) 2179–2188.
[71] J.C. Fleet, Molecular actions of vitamin D contributing to cancer prevention, Mol. Aspects Med. 29 (December (6)) (2008) 388–396, https://doi.org/10.1016/j.mam.2008.07.003 Epub 2008 Aug 8.
[72] J.C. Fleet, M. Desmet, R. Johnson, Vitamin D and cancer: a review of molecular mechanisms, Biochem. J. 441 (2012) 61–75.
[73] J.M. Lappe, D. Travers-Gustafson, K.M. Davies, R.R. Recker, R.P. Heaney, Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial, Am. J. Clin. Nutr. 85 (June (6)) (2007) 1586–1591.
[74] T.L. Cannon, J. Ford, D. Hester, D.L. Trump, The incidental use of high-dose vitamin D3 in pancreatic Cancer, Case Rep. Pancreat. Cancer 2 (1) (2016), https://doi.org/10.1089/crpc.2016.0003.
[75] J.M. Madden, L. Murphy, L. Zgaga, K. Bennett, De novo vitamin D supplement use post-diagnosis is associated with breast cancer survival, Breast Cancer Res. Treat. (2018), https://doi.org/10.1007/s10549-018-4896-6 Published online: 23 July 2018.
[76] M. Castro, T.S. King, S.J. Kunselman, et al., for the National Heart, Lung, and Blood Institute's Asthma Net. Effect of Vitamin D_3on Asthma Treatment Failures in Adults with Symptomatic Asthma and Lower Vitamin D Levels. The VIDA Randomized Clinical Trial, JAMA 311 (20) (2014) 2083–2091, https://doi.org/10.1001/jama.2014.5052.
[77] The 2011 report on dietary reference intake for vitamin d: where do we go from Here? John F. Aloia, J. Clin. Endocrinol. Metab. 96 (October (10)) (2011) 2987–2996, https://doi.org/10.1210/jc.2011-0090.
[78] L. Derex, P. Trouillas, Reversible parkinsonism, hypophosphoremia, and hypocalcemia under vitamin D therapy, Mov. Disord. 12 (July (4)) (1997) 612–613.
[79] G.B. Dowling, E.W. Prosser, Treatment of lupus vulgaris with calciferol, Lancet 22 (June) (1946) 919–922.
[80] C. Christiansen, P. Rodbro, O. Sjö, "Anticonvulsant action" of vitamin D in epileptic patients. A controlled pilot study, Br. Med. J. 2 (1974) 258–259.
[81] A. Holló, Z. Clemens, A. Kamondi, P. Lakatos, A. Szűcs, Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study, Epilepsy Behav. (2012), https://doi.org/10.1016/j.yebeh.2012.03.011.
[82] H.L. Newmark, J. Newmark, Vitamin d and Parkinson's disease—a hypothesis, Mov. Disord. 22 (4) (2007).
[83] L. Szabo. Vitamin D, the Sunshine Supplement, has Shadowy Money Behind It. https://www.nytimes.com/2018/08/18/business/vitamin-d-michael-holick.html.
[84] Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, National Academies Press (US), Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington (DC), 1997.
[85] M.F. Luxwolda, R.S. Kuipers, I.P. Kema, E. van der Veer, D.A. Dijck-Brouwer, F.A. Muskiet, Vitamin D status indicators in indigenous populations in East Africa, Eur. J. Nutr. 52 (April (3)) (2013) 1115–1125, https://doi.org/10.1007/s00394-012-0421-6 Epub 2012 Aug 10.
[86] J.P. Ekwaru, J.D. Zwicker, M.F. Holick, E. Giovannucci, P.J. Veugelers, 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 9 (11) (2014) e111265, , https://doi.org/10.1371/journal.pone.0111265.
[87] C.F. Garland, J.J. Kim, Burgette Mohr, Gorham SB, Grant ED, W.B. Giovannucci, Baggerly EL, Hofflich L, Ramsdell H, Zeng JW, Heaney K, RP meta-analysis of all-cause mortality according to serum 25-Hydroxyvitamin d, Am. J. Public Health 104 (2014) e43–e50, https://doi.org/10.2105/AJPH.2014.302034.
[88] D.V. Dudenkov, B.P. Yawn, S.S. Oberelman, P.R. Fischer, R.J. Singh, S.S. Cha, J.A. Maxson, S.M. Quigg, T.D. Thacher, Changing incidence of serum 25-Hydroxyvitamin d values above 50 ng/ml: a 10-Year population-based study, Mayo Clin. Proc. 90 (May (5)) (2015) 577–586.
[89] M.F. Holick, Vitamin d is not as toxic as was once thought: a historical and an up-to date perspective, Mayo Clin. Proc. 90 (May (5)) (2015) 561–564.
[90] D.V. Dudenkov, K.C. Mara, T.M. Petterson, J.A. Maxson, T.D. Thacher, Serum 25-Hydroxyvitamin d values and risk of all cause and cause-specific mortality: a population-based cohort study, Mayo Clin. Proc. 93 (June (6)) (2018) 721–730.
[91] M.F. Holick, The death D-fying vitamin, Mayo Clin. Proc. 93 (June (6)) (2018) 679–681.
[92] S.M. Kimball, N. Mirhosseini, M.F. Holick, Evaluation of vitamin D3 intakes up to 15,000 international units/day and serum 25-hydroxyvitamin D concentrations up to 300 nmol/L on calcium metabolism in a community setting, Dermato-Endocrinology 9 (1) (2017) e1300213, , https://doi.org/10.1080/19381980.2017.1300213.
[93] S.L. McDonnell, K.A. Baggerly, C.A. Baggerly, J.L. Aliano, C.B. French, et al., Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center, PLoS One 12 (7) (2017) e0180483, , https://doi.org/10.1371/journal.pone.0180483.
[94] S. Nguyen, L. Baggerly, C. French, R.P. Heaney, E.D. Gorham, C.F. Garland, 25Hydroxyvitamin D in the range of 20 to 100 ng/ml and Incidence of Kidney Stones, Am. J. Public Health 104 (2014) 1783-1718.
[95] B. Nygaad, N.E. Frandsen, L. Brandi, et al., Effects of high doses of cholecalciferol in normal subjects: a randomized double-blinded, placebo-controlled trial, PLoS One 9 (8) (2014) e102965.
[96] A. Haghighi, H. Samimagham, G. Gahardehi, Calcium and vitamin d supplementation and risk of kidney stone formation in postmenopausal women, IJKD 7 (2013) 210–213.
[97] C. Pipili, D.G. Oreopoulos, Vitamin d status in patients with recurrent kidney stones, Nephron Clin. Pract. 122 (2012) 134–138.
[98] J. Tang, K.K. McFann, M.B. Chonchol, Association between serum 25-hydroxyvitamin d and nephrolithiasis: the national health and nutrition examination survey III, 1988-94, Nephrol. Dial. Transplant. 27 (2012) 4385–4389.
[99] K.L. Penniston, A.N. Jones, S.Y. Nakada, K.E. Hansen, Vitamin D repletion does not alter urinary calcium excretion in healthy postmenopausal women, BJU Int. 104 (2009) 1512–1516.
[100] P.M. Ferraro, E.N. Taylor, G. Gambaro, G.C. Curhan, Vitamin d intake and the risk of incident kidney stones, J. Urol. 197 (February (2)) (2017) 405–410, https://doi.org/10.1016/j.juro.2016.08.084.