Review

Oral and Topical Vitamin D, Sunshine, and UVB Phototherapy Safely Control Psoriasis in Patients with Normal Pretreatment Serum 25-hydroxyvitamin D Concentrations: A Literature Review and Discussion of Health Implications

Patrick J McCullough[1,3]*, William P McCullough[2], Douglas Lehrer[3] and Jeffrey B Travers[4] (ORCID 0000-0001-7232-1039), **Steven J Repas[5]**

[1]   Medical Services Department, Summit Behavioral Healthcare, Ohio Department of Mental Health and Addiction Services, 1101 Summit Rd, Cincinnati, OH 45237

[2]   Rose-Hulman Institute of Technology, 5500 Wabash Ave, Terre Haute, IN 47803

[3]   Department of Psychiatry, Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435

[4]   Department of Pharmacology & Toxicology, Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435

[5]   Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435,

*Correspondence: Patrick.mccullough@mha.ohio.gov Tel: 1-513-948-3600

Abstract: Vitamin D, sunshine and UVB phototherapy were first reported in the early 1900s to control psoriasis, cure rickets and cure tuberculosis (TB). Vitamin D also controlled asthma and rheumatoid arthritis with intakes ranging from 60,000 to 600,000 International Units (IU)/day. In the 1980s interest in treating psoriasis with vitamin D rekindled. Since 1985 four different oral forms of vitamin D (D_2, D_3, 1-hydroxyvitaminD$_3$ (1(OH)D$_3$) and 1,25-dihydroxyvitaminD$_3$ (calcitriol)) and several topical formulations have been reported safe and effective treatments for psoriasis—as has UVB phototherapy and sunshine. In this review we show that many pre-treatment serum 25(OH)D concentrations fall within the current range of normal, while many post-treatment concentrations fall outside the upper limit of this normal (100 ng/ml). Yet, psoriasis patients showed significant clinical improvement without complications using these treatments. Current estimates of vitamin D sufficiency appear to underestimate serum 25(OH)D concentrations required for optimal health in psoriasis patients, while concentrations associated with adverse events appear to be much higher than current estimates of safe serum 25(OH)D concentrations. Based on these observations, the therapeutic index for vitamin D needs to be reexamined in the treatment of psoriasis and other diseases strongly linked to vitamin D deficiency, including COVID-19 infections, which may also improve safely with sufficient vitamin D intake or UVB exposure.

Keywords: vitamin D_3, D_2, calcitriol, oral, topical, serum 25-hydroxyvitamin D, psoriasis, skin diseases, UVB, phototherapy, sunshine, COVID-19, regulatory T lymphocytes

1. Introduction

Psoriasis is the most common autoimmune disease in the United States, estimated to affect over 8 million people [1]. The total cost of health care in the US for psoriasis was estimated to be $135 billion per year in 2013 [2] and is likely much higher today. A wide variety of treatment options are currently available, classified by the National Psoriasis Foundation (NPF) as biologic drugs, bio-similar medicines, oral treatments, traditional systemic medications, UVB phototherapy and sunshine, and topically applied medications (corticosteroids, vitamin D analogues, others), and are summarized on the NPF website [3-9]. In addition, the American Academy of Dermatology (AAD) and the National Psoriasis Foundation released two guidelines in 2019 outlining best practices for managing this inflammatory skin disease [10-11]. One guideline extensively reviews the use of the relatively newly developed

biologic agents that target specific components of the inflammatory process causing psoriasis [10], and the other focuses on the management and treatment of psoriasis with awareness of and attention to comorbidities [11]. Neither of these two references mentions the use of oral vitamin D.

While topical vitamin D is included in the list of recommended treatments by the NPF, oral vitamin D is not discussed, other than a brief comment stating, "Research on the use of vitamin D dietary supplements for treating psoriasis is limited…We recommend speaking with your health care provider about taking a vitamin D supplement" (page 11, 2018 Topical Treatments handbook) [9]. The reason for the exclusion of oral vitamin D as a recommended treatment for psoriasis by both the NPF and AAD is unclear. Four different forms of oral vitamin D have been shown to be safe treatments for psoriasis dating back to the 1930s [12-28], when oral vitamin D_2 was first found to be effective in treating a number of diseases in addition to psoriasis, including asthma [29], rheumatoid arthritis [30-31], rickets [32] and tuberculosis [33-39]. Sunshine, UVB phototherapy and cod liver oil, a concentrated food source of vitamin D, were also noted to be effective treatments for psoriasis [12, 40-44], rickets [45-46] and TB [39, 47-54] during that era.

There is currently much debate as to what constitutes vitamin D deficiency, insufficiency, sufficiency and toxicity, and what diseases are responsive to vitamin D supplementation. A serum 25(OH)D concentration > 20 ng/ml was defined as sufficient for the vast majority of the population by the Institute of Medicine (IOM) in 2011 [55], while serum 25(OH)D concentrations < 30 ng/ml were defined as insufficient by the Endocrine Society in 2011 [56]. A serum 25(OH)D concentration > 50 ng/ml was cited as a cause for concern by the IOM in 2011 [55], while the Endocrine Society set a serum 25(OH)D concentration of 100 ng/ml as the upper limit of normal in 2011 [56]. The risk for toxicity has been variably thought to occur with serum 25(OH)D concentrations above 150 ng/ml in 1999 [57], 240 ng/ml in 2007 [58], 300 ng/ml in 2008 [59] and 400 ng/ml in 2011 [60].

In this report we review clinical research studies that reported serum 25(OH)D concentrations in psoriasis patients who responded safely to treatment with either oral 1-OHD₃ [14], oral or topical calcitriol [14,19,21-22], oral vitamin D_3 [25-26], oral vitamin D_2 [28], UVB phototherapy [61-64] or sunshine [64]. We will summarize the serum 25(OH)D concentrations obtained before and after treatment in each report as they relate to current definitions of vitamin D deficiency, sufficiency and toxicity, as well as the safety and efficacy of the treatments. We will show that psoriasis patients commonly have normal serum 25OHD concentrations prior to treatment with vitamin D yet show significant clinical improvement after treatment, while those treated with UVB phototherapy often have serum 25(OH)D concentrations greater that 100 ng/ml post treatment without complications.

The data reviewed in this report was never mentioned in reports published in 2011 by the IOM [55] and the Endocrine Society [56] when they issued separate recommendations for what constitutes vitamin D deficiency, insufficiency, sufficiency and toxicity. The vitamin D clinical research studies will be reviewed in section 2, and the UVB phototherapy and sunshine clinical research studies in section 3, with a summary of the key findings from these reports in section 4. A discussion of the implications of our findings in this review for the treatment of psoriasis and other diseases strongly linked to vitamin D deficiency using vitamin D, including COVID-19 infections, is included in sections 5 and 6. Numerous recent reports have shown a strong link between adverse outcomes from COVID-19 infections and vitamin D deficiency [65-80], with at least one pilot study showing clinical efficacy in reducing intensive care unit admissions and mortality among patients hospitalized for COVID-19 after treatment with calcitriol [80].

2. Oral vitamin D₂, oral 1 alpha-hydroxyvitaminD₃ (1(OH)D₃), oral calcitriol, topical calcitriol and oral vitamin D₃ safely treat psoriasis – 1930s to 2019

2.1. Sunshine and oral vitamin D₂ (n=3) in the 1930s – Krafka [12]

In 1936, a report documented the use of oral vitamin D_2 to clear psoriasis plaques in three psoriasis patients, two of which were long-standing cases [12]. The author stated that the idea of using oral vitamin D for treating psoriasis came from the realization that "a commonly observed fact in the South concerning this disease is that it generally clears up to some extent in the summer sun." Knowing that vitamin D was made in the skin from the action of sunshine led to the hypothesis that psoriasis might respond to treatment with oral vitamin D_2 (Viosterol). Vitamin D became available commercially shortly after its discovery in the 1920s,

allowing physicians to test this hypothesis. In this 1936 report, the first patient had a 10-year history of psoriasis. A description of the treatment used was given, but it is difficult to determine the exact dosages employed. However, the response noted was relatively quick and complete as the author noted that "Within sixty days from the beginning of the test, the skin of this patient was entirely clear."

The two other patients also responded very well. "The two cases were admirable for the test. The first was of only three weeks' duration; the second had run a course of thirty years." It appears that the patients were given a dose of 20,000 IU a day for 10 days, for a course or two, with a 10-day break in between, and then on a maintenance dose of 4000 IU a day. Both patients showed the same remarkable benefits as observed in the first patient.

The 1936 report closed with a discussion of the 3 cases: "Our experience with these three cases of psoriasis leads us to this preliminary report. We realize the shortcomings of such a limited experience in the light of what is now called "experimental research" that demands at least two hundred cases. If the treatment were at all hazardous or difficult, we would not presume to lay it before the profession. But the treatment is so simple that it should be put to a trial test in the interest of every patient suffering from this obnoxious condition. Certainly, it is worth a fair trial. We leave our results to be tested on a more elaborate scale by the larger clinics."

Other reports describing variable results from the use of vitamin D in treating psoriasis were also published in that era, but unfortunately the use of oral vitamin D to treat psoriasis and other diseases soon fell out of favor due to concerns of toxicity from hypercalcemia which was observed with the supraphysiogical doses of vitamin D then used [29-31, 33-39].

Published reports on the use of vitamin D in the treatment of psoriasis did not resume again until the 1980's, when a serendipitous observation was made in a psoriasis patient who was being treated with oral 1-hydroxyvitamin D_3 (1(OH)D_3) for osteoporosis, whose skin showed remarkable clinical improvement [13]. This observation led to the resurrection of research into the use of vitamin D in treating psoriasis, which continues through today [12-28, 81-109].

2.2. Oral 1 alpha-hydroxyvitaminD$_3$, oral calcitriol and topical calcitriol in the 1980s – Morimoto [14]

The impetus for this study was the chance observation made the year before by two of the investigators when they were using 1(OH)D_3 as a treatment for osteoporosis in a patient who happened to have psoriasis, and whose skin cleared completely [13]. "This observation prompted us to confirm the effect by an open-design study" [14].

In the open-design study, both oral 1(OH)D_3, and oral and topically applied calcitriol were found to be safe and effective in clearing psoriasis skin lesions [14]. A total of 40 patients were studied: a) 17 with oral 1(OH)D_3, b) 4 with oral calcitriol, and c) 19 with topical calcitriol. This report is reviewed in the next 2 sections.

2.3. Oral 1 alpha-hydroxyvitaminD$_3$ (n-17), 6-month study, 1986 – Morimoto [14]

A total of 17 patients with psoriasis vulgaris were treated orally with 1 mcg/d of 1-OHD$_3$ for up to six months. Significant clinical improvement was observed in 13 (76%) by the end of the study period, with complete clearing of the skin lesions noted in 5 (29%). Patients were examined once every two weeks during the course of the study. Serum 25(OH)D, calcium, hepatic function, renal function, inorganic phosphate, parathyroid hormone, and plasma calcitonin concentrations were obtained at baseline and during follow-up visits. Data was presented as baseline versus 3-month levels. It took about 3 months to begin seeing significant clinical improvement in the 13 patients who responded well to treatment. In the remaining 4 patients, one showed slight improvement, 2 showed no change, and one deteriorated.

The baseline mean serum 25(OH)D concentration was 23 ± 12 ng/ml, and 27 ± 18 ng/ml at 3 months, which was not significantly different. It should be noted that 1(OH)D_3 is metabolized directly into calcitriol (1,25-dihydroxyvitamin D_3) and has no effect on serum 25(OH)D_3 concentrations. Mean serum calcium concentrations were 9.2 mg/dl at baseline and 9.6 mg/dl at 3 months. Mean serum calcitriol concentrations increased from 41 pg/ml at baseline to 62 pg/ml at three months. Although a statistically significant increase in serum calcium, phosphate, and calcitriol concentrations were observed after 3 months of treatment, "the

increases were slight and remained within the normal range." It should be noted that no cases of hypercalcemia were observed, and no adverse side effects were noted in any patients. Baseline and on treatment lab values are shown in Table 1.

2.4.   Oral calcitriol 0.5 mcg/day (n=4) and topical calcitriol (n=19), 1986 – Morimoto [14]

One of 4 patients (25%) treated with oral calcitriol showed significant clinical improvement in psoriasis. In the topical calcitriol group 16 of 19 (84%) showed significant clinical improvement within 3 to 4 weeks, with complete clearing noted in 3 (16%). The results with topical calcitriol are very similar to those seen in the patients treated with oral $1(OH)D_3$ but occurred in a much shorter time period.

Mean serum 25OHD concentrations were 17 ± 5 ng/ml and 15 ± 8 ng/ml at baseline and 3 months in the oral calcitriol group, versus 20 ± 10 ng/ml and 20 ± 9 ng/ml in the topical calcitriol group. Calcium levels (mean) were 9.4 mg/dl at baseline and 9.8 mg/dl at 3 months in the oral group (p=<0.05), versus 9.3 mg/dl and 9.2 mg/dl in the topical group. Calcitriol levels (mean) were 40 pg/ml (sd=11) and 47 pg/ml (sd=12) at baseline and 3 months in the oral group, versus 34 pg/ml (sd=11) and 35 pg/ml (sd=12) in the topical group.

Baseline and 3-month mean serum $25(OH)D_3$, calcium and calcitriol concentrations for the 3 treatment groups are shown in Table 1.

Table 1: Baseline and 3-month mean serum $25O(H)D_3$ (ng/ml), calcium (mg/dl) and calcitriol (pg/ml) concentrations in the 3 treatment groups.

	Treatment Group		
	Oral $1(OH)D_3$	Oral Calcitriol	Topical Calcitriol
Blood Test	Mean $\pm$ sd	Mean $\pm$ sd	Mean $\pm$ sd
Baseline $25(OH)D_3$	23 ± 12	17 ± 5	20 ± 10
3 Month $25(OH)D_3$	27 ± 18	15 ± 8	20 ± 9
Baseline Calcium	9.2 ± 0.6*	9.4 ± 0.2*	9.3 ± 0.2
3 Month Calcium	9.6 ± 0.6*	9.8 ± 0.2*	9.2 ± 0.4
Baseline Calcitriol	41 ± 19*	40 ± 11	34 ± 11
3 Month Calcitriol	62 ± 32*	47 ± 12	35 ± 12
# patients/group	17	4	19

Note: No significant differences were observed in baseline versus 3-month $25(OH)D_3$ levels in any group.
*A significant difference between baseline and 3-month calcium levels was noted in the $1(OH)D_3$ and oral calcitriol groups, and for calcitriol in the $1(OH)D_3$ group, but all values were within the normal range.

The baseline and 3 month serum $25(OH)D_3$ concentration ranges and the number of serum $25(OH)D_3$ concentrations > 20, 50 or 100 ng/ml or < 20 ng/ml at each time point were not reported. However, the average serum $25(OH)D_3$ concentration at baseline in the 40 patients in the 3 groups was 21 ± 11 ng/ml, indicating that a significant percentage had baseline serum $25(OH)D_3$ concentrations > 20 ng/ml with active psoriasis, and improved significantly after treatment with oral or topical vitamin D.

There were no adverse reactions noted in any of the 3 groups of patients. "None of the patients in the three groups suffered from any topical or systemic complications or symptoms during these observation periods. Blood and urine analysis showed values within normal limits at all times. Hepatic and renal function, …were within normal ranges and did not change significantly during the observation periods."

Morimoto and colleagues published the results of 3 other clinical trials in the 1980s with similar results [15-16], and a review of their experience in 1989 [17]. In their review, they concluded: "These data suggest that exogenous active forms of vitamin D_3 are effective for the treatment of psoriasis, and that the endogenous 1,25-dihydroxyvitamin D level also may be involved in the development of this disease."

In the 1980s several important discoveries were made regarding vitamin D and the skin leading to the realization that the skin is both the site of production of vitamin D and a target organ for its actions:

a) Calcitriol could be synthesized in the skin

b) Vitamin D receptors are present in the skin

c) vitamin D inhibited the proliferation of cultured keratinocytes and induced them to terminally differentiate [18-20, 83-84, 90].

2.5.   Oral and topical calcitriol in the 1980s and 1990s – Smith, Huckins, Perez and Holick [19, 21-22]

Reports published beginning in 1987 by Holick et al described the safe and effective use of oral calcitriol in treating psoriasis [18-23]. One report also examined the use of topical calcitriol and found it to be safe and effective as well [19]. Three of these reports will be reviewed in the next section.

2.6.   Oral (n=14) and topical (n=3) calcitriol 12-month study, 1988 – Smith [19]

In 1988 [19] calcitriol was tested in three different ways:

a) On cultures of fibroblasts and keratinocytes from patients with psoriasis

b) Orally in 14 patients with moderate to severe psoriasis

c) Topically in 3 patients with psoriasis.

Baseline serum concentrations of $25(OH)D_3$, calcitriol, calcium, phosphorous, total protein, albumin, blood urea nitrogen, creatinine, and a 24-hour urine collection for calcium and creatinine measurements were obtained. The daily oral doses of calcitriol used ranged from 0.5 mcg to 2.0 mcg. Post-treatment labs were not provided. In the oral calcitriol dosing study, all patients had moderate to extensive psoriasis, with large plaques on extensor surfaces. A total of 10 of the 14 patients (71%) showed at least a moderate response, while 77% had > 50% clearing of their skin. Complete clearing occurred in 3 patients (21%) "that was sustained with maintenance therapy."

"Thirteen of the 14 patients improved after < 2 months of oral calcitriol therapy and continued to improve for 6 to 8 months after initial improvement was observed." Four patients withdrew from the study, two for personal reasons, and two due to persistent hypercalciuria. Six of the patients chose to continue on with oral therapy and had been receiving treatment for one year without any complications. Four patients received little to no benefit." Two of the 10 patients showing the most improvement (>75% improved) had baseline serum $25(OH)D_3$ concentrations of 40 ng/ml and 67 ng/ml. One (40 ng/ml) cleared completely within 2 to 3 months of therapy. The patient then stopped taking the calcitriol for 1 to 2 months, and the psoriasis reappeared. Treatment with calcitriol was resumed, and "the lesions cleared but at a slower rate than with the first course of treatment."

The 3 patients treated topically with calcitriol "showed a rapid response with complete clearing after 6 weeks of therapy," consistent with the results of the Morimoto study. No adverse reactions were noted in any of the patients treated with either oral or topical calcitriol. No side effects of hypercalcemia, calcium deposits, renal insufficiency or nephrolithiasis were observed in any of the patients in the study. In their evaluation of cultures of fibroblasts and keratinocytes from patients with psoriasis, the investigators were able to demonstrate the presence of vitamin D receptors in the cells, and a normal response to the anti-proliferative action of the hormone in fibroblasts from 3 of 5 patients and a partial resistance in the other two.

The range and distribution of pre-treatment serum $25(OH)D_3$ concentrations in the combined oral and topical calcitriol treatment groups are shown in Table 2.

Table 2: Range and distribution of pre-treatment serum $25(OH)D_3$ concentrations in the combined group of 15 psoriasis patients treated with oral calcitriol (n=13) and topical calcitriol (n=2).

Pretreatment serum $25(OH)D_3$ values	
$25(OH)D_3$ Range ng/ml	8 to 67
# > 20 ng/ml	11
# > 50 ng/ml	4
# > 100ng/ml	0
# < 20 ng/ml	4
# patients	15

Note: no data was available for 1 patient in each group. Post-treatment serum $25(OH)D_3$ concentrations not provided. N = 15 patients: oral calcitriol (n=13) and topical calcitriol (n=2).

In the combined oral and topical groups a total of 11 of 15 patients (73%) had pre-treatment serum $25(OH)D_3$ concentration > 20 ng/ml, and 4 of 15 patients (27%) were > 50 ng/ml, with a peak serum $25(OH)D_3$ concentration of 67 ng/ml. Four patients had baseline serum $25(OH)D_3$ concentration < 20 ng/ml. In the oral dosing study, pre-treatment serum $25(OH)D_3$ concentrations ranged from 8 ng/ml to 67 ng/ml. A total of 9 of 13 (69%) were > 20 ng/ml (one patient had no value). Post treatment serum $25(OH)D_3$ concentrations were not reported but should have been unaffected by the calcitriol treatment. In the topical dosing study pre-treatment serum $25(OH)D_3$ concentration were available for 2 of the 3 patients. Both were > 20 ng/ml (30 ng/ml and 67 ng/ml). Post treatment serum $25(OH)D_3$ concentration were not reported.

The authors concluded their report stating: "Topical or oral use of $1,25-(OH)_2D_3$ heralds a new mode of treatment that appears to be both safe and effective for the treatment of psoriasis." And as was shown by Morimoto, many patients with active psoriasis had baseline serum $25(OH)D_3$ concentrations > 20 ng/ml and improved significantly after treatment with oral or topical vitamin D_3.

2.7.   Oral calcitriol (n=10) 6-month study in psoriatic arthritis, 1990 – Huckins [21]

In 1990 ten patients with active psoriatic arthritis were treated daily with oral calcitriol for 6 months in an open label trial. The goal of the study was to determine if the treatment would be beneficial for the arthritis, and if so, was there a correlation between the improvement in the skin lesions and the improvement in the arthritis. The dose of calcitriol was titrated from 0.5 mcg/day to a maximum of 2 mcg/day.

Statistically significant improvement was noted in both tender joint count and physician global assessment. Four patients had > 50% improvement in tender joint count, and 3 had > 25% improvement. Two patients were unable to receive therapeutic doses due to hypercalciuria. One patient was lost to follow-up.

In 6 patients who completed the 6-month study, the tender joint count decreased from a mean of 18 to 5, and the mean physician global assessment decreased from 8.4 to 1.8 (estimated from figure one in reference [58]). "It often took 2-3 months for improvement to occur, and improvement never occurred at a dosage < 1.5 ug/day." Five patients chose to stay on the treatment at the end of the study.

A number of labs were drawn at baseline and periodically throughout the study, but the values were not reported. However, the time to improvement was similar to the previous oral dosing studies, and a dose response was noted.

2.8.   Oral calcitriol (n=88) 3-year dose titration safety study, 1996 – Perez [22]

In 1996, a three-year follow-up study of 88 patients with plaque type psoriasis involving at least 15% of their body surface who were treated with oral calcitriol was published. The doses of calcitriol used ranged from 0.5 mcg/day to 4.0 mcg/day. The mean

calcitriol dose was 2.1 mcg/day at 24 months, and 2.4 mcg/day at 36 months. A total of 88% of the patients noted some degree of improvement in their disease. Complete clearing occurred in 26.5%, moderate improvement occurred in 36.2%, and slight improvement occurred in 25.3%. A total of 12% of the patients had no change in their disease severity. The mean PASI score decreased from 18.4 at baseline to 9.7 at 6 months, 7.8 at 24 months and 7.0 at 36 months.

Multiple safety parameters were monitored over the 3-year period in an effort to perform a thorough evaluation of the potential toxicity of oral calcitriol. This included monitoring multiple blood tests, performing bone mineral density tests twice a year, checking for kidney stones with renal ultrasounds, measuring creatinine clearance, and 24-hour urinary excretion of calcium and creatinine.

Serum $25(OH)D_3$ and calcium concentrations were provided at baseline (n=88), 6 months (n=88), 12 months (n=51), 24 months (n=26), and at 36 months (n=20, calcium only). There was no change in bone mineral density. Creatinine clearance decreased 13.4% from baseline in the first 6 months, then remained unchanged for the duration of the study. No cases of hypercalcemia, calcium deposition, nephrolithiasis or renal insufficiency or other adverse events were observed over the 3-year course of the study.

The mean serum $25(OH)D_3$, calcium, PTH, calcitriol, creatinine, and 24-hour urine calcium concentrations at 0, 6, 12, 24 and 36 months in psoriasis patients treated with oral calcitriol are shown in table 3.

Table 3: Mean serum $25(OH)D_3$, calcium, PTH, calcitriol, creatinine, and 24-hour urine calcium concentrations at 0, 6, 12, 24 and 36 months in 88 plaque psoriasis patients treated with oral calcitriol.

Blood Test	Baseline	6 month	12 month	24 month	36 month
$25(OH)D_3$ ng/ml	31.8 ± 18.4	33.8 ± 19.8	32.0 ± 20.8	37.2 ± 16.8	NR
Calcium mg/dl*	9.6 ± 0.5	9.9 ± 0.5	9.9 ± 0.5	9.8 ± 0.5	9.7 ± 0.4
PTH pg/ml	23.0 ± 14.8	NR	NR	12.4 ± 9.7	NR
Calcitriol pg/ml	40.4 ± 16.4	49.1 ± 14.9	50.2 ± 23	44.1 ± 12.2	NR
Creatinine mg/dl	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.3 ± 0.3
24hr urine calcium*	163 ± 95	268 ± 117	291 ± 148	282 ± 135	274 ± 3
# patients	88	88	51	26	20

Note: *The mean 24-hour urine calcium concentrations (mg/24hr) and calcium/creatinine ratios, and the serum calcium levels were significantly increased compared to baseline at 6, 12, 24 and 36 months. NR = not reported. The baseline and on treatment serum $25(OH)D_3$ concentration ranges and the number of serum $25(OH)D_3$ concentrations > 20, 50 or 100 ng/ml or < 20 ng/ml at each time point were not reported.

The mean baseline serum $25(OH)D_3$ concentration was 31.8 ± 14 ng/ml, indicating that many of the 88 patients had pretreatment serum $25(OH)D_3$ concentrations > 20 ng/ml (exact number not provided). The mean serum $25(OH)D_3$ concentration was not affected by calcitriol supplementation and did not change significantly over time, as shown in the table. The mean serum calcium at baseline was 9.6 mg/dl and 9.7 mg/dl at 36 months.

As reported in the previous studies, many patients with active psoriasis had baseline pre-treatment serum $25(OH)D_3$ concentrations > 20 ng/ml, but still improved significantly after treatment with oral vitamin D, in this case calcitriol. The fact that serum $25(OH)D_3$ concentrations did not change was as expected, as calcitriol is the active hormone form of vitamin D and is not metabolized into serum $25(OH)D_3$. At the end of the opening summary paragraph, the authors concluded "Oral calcitriol is effective and safe for the treatment of psoriasis."

These 5 studies [12,14,19, 21-22] detail the safe and effective use of oral vitamin D_2 (1936), oral $1(OH)D_3$ (1986), oral calcitriol (1986,1988,1990,1996), and topical calcitriol (1986,1988) in treating psoriasis. There are very few reports published in the past 30 years describing the use of oral vitamin D_2 or oral vitamin D_3 (the precursors to serum $25(OH)D_3$ and calcitriol) in

treating psoriasis. Three relatively recent reports [25-26, 28] that do describe the use of oral vitamin D_3 (2012, 2013) and oral vitamin D_2 (2019) in successfully controlling plaque psoriasis will be reviewed next. These reports show similar clinical benefits and safety as the previous reports showed, even though much higher post-treatment serum 25(OH)D concentrations were observed as would be expected, as both vitamin D_2 and vitamin D_3 are metabolized into 25(OH)D prior to forming calcitriol.

2.9. Serum 25(OH)D₃ concentrations in 2 patients with plaque psoriasis after 5 months' oral vitamin D₃ in 2012 – McCullough [25]

In 2012, one of the authors (PM) presented a poster describing the results of using oral vitamin D_3 to successfully control chronic plaque psoriasis in 2 patients at the 15th Workshop on Vitamin D in Houston, Texas [25]. The patients included a 52-year-old white female and a 49-year-old white male. The study was conducted between December 2010 and May 2011. The patients were provided with over the counter 5000 IU vitamin D_3 gel caps and were instructed to take 40,000 IU/day for 2 weeks, and then reduce the dose to 10,000 IU/day.

Serum 25(OH)D₃ , calcitriol, calcium and iPTH concentrations, and PASI scores were obtained at baseline and 5 months. Baseline PASI scores were 5.7 and 14.4. Baseline 25OHD₃ levels were 23 ng/ml and 29 ng/ml. After 5 months PASI scores improved to 0 and 2.4. Serum 25(OH)D₃ concentrations increased to 51 ng/ml and 73 ng/ml. Serum calcium concentrations remained normal at 9.4 mg/dl and 9.7 mg/dl, intact PTH concentrations were 27 pg/ml and 23 pg/ml, and calcitriol concentrations were 24 pg/ml and 56 pg/ml. No adverse reactions were noted, and both patients reported marked clinical improvement in their skin and in their quality of life. Both patients later experienced recurrence of the plaques within a month after stopping oral vitamin D_3 intake, and both were able to achieve clear skin again after resuming the oral vitamin D_3. The recurrence of psoriasis with cessation of oral vitamin D intake and clearing again with resumption of oral vitamin D intake was also previously reported by Smith et al in 1988 [19].

Photos depicting the improvement in the skin over time in patient 2 after resuming oral vitamin D_3 at 40,000 IU/day are shown in Figure 1.

| Day 1 | Day 28 | Day 72 | Day 88 |

Figure 1: Improvement in psoriasis plaques after resuming 40,000 IU/day of vitamin D_3 in patient 2, whose disease recurred after stopping vitamin D_3. Nearly complete clearing of the plaques occurred by 88 days. The yearly cost of treatment with oral vitamin D_3 at a dose of 40,000 IU/day is around $104 per year, based on currently available over the counter pricing at $14/bottle for a USP verified bottle of 400 gel caps with 5000 IU/cap.

2.10. Serum 25(OH)D$_3$ concentrations after 6 months of taking 35,000 IU/day of oral vitamin D$_3$ in 25 patients with either plaque psoriasis (n=9) or vitiligo (n=16), 2013 - Finamor [26]

In 2013, results from a 6-month follow-up study using 35,000 IU/day of oral vitamin D$_3$ to treat 9 patients with psoriasis and 16 patients with vitiligo were published [26]. The goal was to assess the efficacy and safety of prolonged high-dose vitamin D$_3$ treatment in patients with psoriasis and vitiligo. Psoriasis Area and Severity Index (PASI) scores were obtained at baseline and after treatment. The PASI score significantly improved in all nine patients with psoriasis. Fourteen of 16 patients with vitiligo had 25–75% repigmentation. A significant negative correlation was observed between the PASI scores and serum 25(OH)D$_3$ concentrations.

In the psoriasis group, mean serum 25(OH)D$_3$ concentrations increased from 14.9 ± 7.4 ng/ml at baseline to 106.3 ± 31.9 ng/ml at 6 months. Mean serum PTH concentrations decreased from 57.8 ± 16.7 pg/ml at baseline to 28.9 ± 8.2 pg/ml at 6 months.

In the vitiligo group, mean serum 25(OH)D$_3$ concentrations increased from 18.4 ± 8.9 ng/ml at baseline to 132.5 ± 37.0 ng/ml at 6 months. Mean serum PTH concentrations decreased from 55.3 ± 25.0 pg/ml at baseline to 25.4 ± 10.7 pg/ml at 6 months.

The changes in mean serum 25(OH)D$_3$ concentrations and PTH concentrations were significant in both groups. Baseline serum urea, creatinine and calcium (total and ionized) concentrations did not differ significantly from those obtained at 6 months. The mean baseline serum calcium concentration was 9.7 mg/dl, and 9.4 mg/dl after 6 months. Urinary calcium excretion increased but stayed within the normal range. The authors noted that "Laboratory or clinical signs of toxicity (hypercalcemia, hypercalciuria or kidney dysfunction) were not observed in any of the 25 participants, including a patient with vitiligo who reached a serum concentration of 25OHD$_3$ of 202ng/ml." Patients were instructed to minimize calcium intake. "Reduced intestinal calcium by dietary restriction of milk, dairy products and calcium-enriched foods (like oat, rice or soya "milk") has contributed to minimize the calciotropic effects of high daily doses of vitamin D$_3$ in the current study."

The distribution of serum 25(OH)D$_3$ concentrations, mean serum 25(OH)D$_3$, PTH, calcium, urea, and creatinine concentrations, and 24-hour urinary calcium values pre-and post-treatment are shown in table 4.

Table 4: Distribution and mean serum concentrations of 25(OH)D$_3$, PTH, calcium, urea and creatinine, and 24-hour urinary calcium in 9 patients with psoriasis and 16 patients with vitiligo pre-and 6 months' post-treatment with oral vitamin D$_3$ at 35,000 IU/day.

	Treatment Group			
	Psoriasis	Psoriasis	Vitiligo	Vitiligo
Blood Test	Baseline	6 months	Baseline	6 months
25(OH)D$_3$ ng/ml	14.9 ± 7.4	106.3 ± 31.9	18.4 ± 8.9	132.5 ± 37
# > 20 ng/ml	NR	9	NR	16
# > 50 ng/ml	0	NR	0	NR
# > 100 ng/ml	0	>1	0	>1
PTH pg/ml	57.8 ± 16.7	28.9 ± 8.2	55.3 ± 25	25.4 ± 10.7
Calcium mg/dl	9.7 ± 0.7	9.4 ± 0.7	9.2 ± 0.3	9.2 ± 0.2
Urinary Calcium*	123.6 ± 60	226.8 ± 41.6*	158.3 ± 73.6	230.1 ± 81.4*
Urea mg/dl	35.8 ± 8.3	28.9 ± 9.8	35.5 ± 7.2	33.9 ± 9.9
Creatinine mg/dl	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
# patients	9	9	16	16

Note: All patients presented with serum 25(OH)D$_3$ concentrations ≤ 30 ng/ml at baseline. *Urinary calcium increased significantly but remained in the normal range. PTH=parathyroid hormone. NR = not reported. The baseline and 6 month serum 25(OH)D$_3$ concentration ranges were not reported.

The pre-treatment number of patients with baseline serum $25(OH)D_3$ concentrations > 20 ng/ml was not indicated, but there were likely several among the 25 patients based on the standard deviation of the baseline mean serum $25(OH)D_3$ concentrations. All 25 patients had serum $25(OH)D_3$ concentrations < 30 ng/ml pre-treatment.

The post-treatment number of patients achieving serum $25(OH)D_3$ concentrations > 100 ng/ml was not reported but is significant, based on the mean post treatment serum $25(OH)D_3$ concentrations of 106.3 ± 31.9 ng/ml and 132.5 ± 37 ng/ml. The highest serum $25(OH)D_3$ concentration observed post-treatment was 202 ng/ml.

"Dietary calcium limited by avoiding dairy products and calcium-enriched foods – like oat, rice or soya "milk" and minimum hydration (2.5 L daily) ensures safety." The authors' main conclusion was "In summary, the present study suggests that, at least for patients with autoimmune disorders like vitiligo and psoriasis, a daily dose of 35,000 IU of vitamin D_3 is a safe and effective therapeutic approach for reducing disease activity."

The yearly cost of treatment with oral vitamin D_3 at a dose of 35,000 IU/day is around $98 per year, based on currently available over the counter pricing at $14/bottle for a USP verified bottle of 400 gel caps with 5000 IU/cap.

2.11.   Serum $25(OH)D_2$ concentrations in a patient with plaque psoriasis after 42 months of taking 50,000 IU/day of oral vitamin D_2, 2019 - McCullough [28]

In 2019, a paper describing results from supplementing long-term hospitalized patients with 5000 IU/day to 50,000 IU/day of vitamin D_3 for over 7 years was published by one of the authors [28]. This author (PM) made it a standard of care beginning in April 2009 to offer all long-term hospitalized patients under his care at the Drake Center for Post-Acute Care supplementation with oral vitamin D_3 in doses of either 5000 IU/day or 10,000 IU/day, and this was continued after moving to Summit Behavioral Healthcare (SBH) in July 2011. This was done for several reasons:

a) patients receive very little sunshine in the hospital

b) there is very little vitamin D in the food they eat

c) serum 25-hydroxyvitamin D (25(OH)D) production in the skin from UVB phototherapy was first estimated in the 1970s to range from 10,000 to 25,000 IU/day [39, 53, 56, 110-113]

d) vitamin D, sunshine and UVB phototherapy were shown to be effective treatments for several diseases in the 1930s and 1940s, and again beginning in the 1980s as discussed earlier [12-39, 45-54]. In addition, several patients received daily doses of vitamin D_2 or vitamin D_3 ranging from 20,000 to 50,000 IU/day based on specific disease concerns.

There have been over 6000 admissions to SBH since 2011. A recent sampling of patients not on vitamin D_3 (n=777; combination of new admissions and long-term patients who declined supplementation) showed a mean serum $25(OH)D_3$ concentration of 27.1 ng/ml (range 4.9 to 74.8 ng/ml). Patients on vitamin D_3 long enough to develop serum $25(OH)D_3$ concentrations > 74.4 ng/ml (n=418) had a mean serum $25(OH)D_3$ concentration of 118.9 ng/ml (range 74.4 to 384.8 ng/ml). The highest serum $25(OH)D_3$ concentrations observed on 10,000 IU/day was 202 ng/ml.

The mean and range of serum calcium concentrations were almost identical in the two groups, despite the wide disparity in serum $25(OH)D_3$ concentrations. The average serum calcium concentrations were 9.5 mg/dl (no D_3) vs. 9.6 mg/dl (D_3), with ranges of 8.4 mg/dl to 10.7 mg/dl (no D_3) vs. 8.6 mg/dl to 10.7 mg/dl (D_3), after excluding patients with other causes of hypercalcemia. The average intact parathyroid hormone concentrations were 24.2 pg/ml (D_3) vs. 30.2 pg/ml (no D_3).

There were no adverse events observed in any patients taking 5000 to 10,000 IU/day for several years, in spite of serum $25(OH)D_3$ concentrations reaching as high as 202 ng/ml. In addition, several patients, as well one of the authors, having taken daily oral doses of vitamin D ranging from 20,000 to 60,000 IU/day for 2 to 6 years, achieved serum $25(OH)D_3$ concentrations as high as 384ng/ml without any complications [28,114].

In our 2019 report we included a case report of a patient admitted with poorly controlled plaque psoriasis whose skin improved dramatically within a few months of starting 50,000 IU/day of oral vitamin D_2 and has remained clear for many months. He is no longer using the topical steroids or medicated shampoos which he was taking at the time of admission and is no longer being

seen by specialists in the dermatology clinic at the local medical school. After his skin cleared, the patient chose to leave the dose of vitamin D_2 at 50,000 IU/day, which is provided in a single capsule, and continued on this treatment. His serum calcium and iPTH concentrations have been checked numerous times and have remained normal. No adverse events related to vitamin D supplementation have been observed. His quality of life has improved significantly.

His serum $25(OH)D_2$, iPTH and calcium blood concentrations and skin condition are shown in Table 5.

Table 5: Changes in serum $25(OH)D_2$, iPTH and calcium concentrations over time in a patient with psoriasis completely cleared on 50,000 IU/day of vitamin D_2 for > 42 months

Date	$25(OH)D_2$	iPTH	Calcium	Psoriasis status
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	skin clear
12/15/2016			9.7	skin clear
1/12/2017			9.4	skin clear
1/28/2017	262		9.5	skin clear
3/6/2017	297.6		9.6	skin clear
4/13/2017	290.8	38	9.6	Derm clinic discontinued
6/10/2017	296.4		9.8	skin clear
9/6/2017			9.4	skin clear
12/6/2017	249.6	29	9.5	skin clear
3/2/2018	308.4	32	9.6	skin clear
6/6/18			9.9	skin clear
7/17/18			9.6	skin clear
9/5/18	290	33	9.7	skin clear
3/5/19	225.2	32	9.4	skin clear
6/25/19			9.3	skin clear

Vitamin D_2 50,000 IU/day was started on 2/25/16, two days before his admission blood work was drawn. Eight serum $25(OH)D_2$ concentrations have ranged from 225 ng/ml to 308 ng/ml, 22 serum calcium levels ranged from 9.2 mg/dl to 9.9 mg/dl, and six iPTH levels ranged from 29 pg/ml to 40 pg/ml. A 24-hour urine for calcium and creatinine was collected on 6/9/17. The total 24 hr. calcium excretion was 316.8 mg (normal = 100 to 300 mg/24hr), and the urinary ca/cr ratio was 207 (normal = 0 to 260).

The yearly cost for the vitamin D_2 used was $36.50, as we are able to obtain 50,000 IU capsules of vitamin D_2, with 100 capsules/bottle for $10 a bottle.

3. Changes in serum $25(OH)D_3$ concentrations in psoriasis patients treated with UVB phototherapy and sunshine – 1996, 2009, and 2010

The use of phototherapy to treat disease dates back to the 1890s when Finsen developed a method to cure TB with refracted light rays from an electric arc lamp [28,39-44,48-50,52,54]. Several recent reviews give an excellent overview of the evolution of the use of phototherapy for treating human disease, including psoriasis [40-44]. The first documented use of UVB phototherapy in treating psoriasis dates back to Gockerman in the 1920s [41-43]. UVB phototherapy is now a well-established, relatively safe and cost-effective option for treating psoriasis [40-44, 61-64, 115-131].

In this section, we will review four UVB phototherapy psoriasis treatment studies that provided baseline and post-treatment serum 25(OH)D$_3$ concentrations [61-64]. Significant increases in 25(OH)D$_3$ from baseline were noted in the UVB phototherapy studies, with several patients obtaining serum 25(OH)D$_3$ concentrations > 100 ng/ml without any adverse effects while observing significant improvement in their skin. As noted in the oral vitamin D studies, baseline serum 25(OH)D$_3$ concentrations > 20 ng/ml were also commonly observed in these reports and increased after treatment. One study also included a group of patients treated with sunshine, in which the observed changes in serum 25(OH)D$_3$ concentrations were significantly lower than those after treatment with UVB therapy [64],

3.1. Serum 25(OH)D$_3$ concentrations in psoriasis patients (n=15) after 8 weeks of UVB phototherapy, 1996 - Prystowsky [61]

In 1996 changes in serum 25(OH)D$_3$ concentrations were assessed in 15 patients with plaque-type psoriasis treated with UVB phototherapy [61]. Seven of these patients were treated with oral calcitriol (0.5 to 2 ug/day), and eight with placebo. Nineteen patients were initially enrolled, but four did not complete the study because of protocol violations. Serum concentrations of 25(OH)D$_3$ and calcitriol were measured before, during and after treatment in 13 patients. Serum chemistry and hematology laboratory evaluations were also done.

All patients treated with phototherapy showed significant increases in their serum 25(OH)D$_3$ concentrations. No patient incurred a serious adverse event attributable to calcitriol or phototherapy that necessitated removal from the study. Significant improvement was noted in disease severity in all patients in both groups, with no significant difference between groups.

In the placebo group mean serum 25(OH)D$_3$ concentrations increased from 37.9 ng/ml at baseline to 96.1 ng/ml after UVB phototherapy. In the calcitriol group mean serum 25(OH)D$_3$ concentrations increased from 27.3 ng/ml at baseline to 67.1 ng/ml after UVB phototherapy. The authors stated there was no significant difference in the mean increments between the 2 groups.

Serum calcitriol concentrations were unchanged in the placebo treated group and increased in the calcitriol treated group. In the placebo group, the mean serum calcitriol concentration was 38.3 pg/ml (sd=9.9) at baseline and 35.2 pg/ml (sd=19.7) at the end of phototherapy. In the calcitriol group, the mean serum calcitriol concentration was 37.9 pg/ml (sd=8) at baseline and increased to 60.1 pg/ml (sd=24.9) after phototherapy.

The mean serum calcium concentration post-treatment was 9.6 mg/dl in the placebo group, and 9.7 mg/dl in the calcitriol group. Baseline serum calcium concentrations were not provided.

Hypercalcemia was observed in 2 patients in the calcitriol group, but neither had hypercalciuria. The hypercalcemia resolved with reduction in their intake of calcitriol. Three patients in each group developed hypercalciuria (values not provided). There were no adverse events related to hypercalcemia or hypercalciuria. The range and distribution of serum 25(OH)D$_3$ concentrations and mean 25(OH)D$_3$, calcium and calcitriol concentrations pre-and post UVB treatment ± oral calcitriol are shown in table 6.

Table 6: Mean, range and distribution of serum 25(OH)D$_3$ concentrations, and mean serum calcium and calcitriol concentrations before and after UVB phototherapy in 13 patients with plaque psoriasis also treated with placebo (n=7) or calcitriol (n=6).

	Placebo Group		Calcitriol Group	
Test	Pre-UVB	Post-UVB	Pre-UVB	Post-UVB

25(OH)D$_3$ ng/ml	37.9	96.1	27.3	67.1
Range ng/ml	20 to 80	45 to 159	15 to 40	45 to 123
# > 20 ng/ml	7	7	4	6
# > 50 ng/ml	2	6	0	4
# > 80 ng/ml	1	4	0	1
# > 100 ng/ml	0	2	0	1
Calcium mg/dl	NR	9.6	NR	9.7
Calcitriol pg/ml	38.8	35.2	37.9	67.1
N	7	7	6	6

Note: the distribution and range of serum 25(OH)D$_3$ concentrations are estimated from Figure 2 in reference [61]. N= number of patients in each group.

Pre-treatment 11 of 13 patients (85%) appeared to have serum 25(OH)D$_3$ concentrations > 20 ng/ml. Two of 13 patients (15%) had a baseline serum 25(OH)D$_3$ concentration > 50 ng/ml, one of whom appeared to be > 80 ng/ml. Post-treatment 13 of 13 patients (100%) were > 20 ng/ml, 10 of 13 (77%) had a serum 25(OH)D$_3$ concentrations > 50 ng/ml, and 3 patients (23%) had serum 25(OH)D$_3$ concentrations > 100 ng/ml, two in the placebo group and one in the calcitriol group. Their serum 25(OH)D$_3$ concentrations ranged from 123 ng/ml to 159 ng/ml.

The authors noted that "because phototherapy for psoriatic plaques produces changes in keratinocytes similar to those described for 1,25-(OH)2D3 (i.e. slowed proliferation and enhanced differentiation), this raises the possibility that one of the mechanisms of action of UVB may be through enhanced vitamin D metabolism."

3.2. Serum 25(OH)D$_3$ concentrations in psoriasis patients (n=29) after 1-4 months of NB-UVB phototherapy, 2010 - Ryan [62]

In a 2010 report, serum 25(OH)D$_3$, ionized calcium, intact parathyroid hormone (iPTH) and alkaline phosphatase concentrations were assessed in 30 patients with plaque psoriasis before and after treatment with narrowband (NB) UVB phototherapy [62]. Comparison was made to a matched untreated control group of 30 patients with plaque psoriasis.

Patients in the treatment group received NB-UVB phototherapy 2 to 3 times a week. Treatment continued until essentially complete clearing of the psoriasis occurred, which took between 25 to 118 days (median 51 days). Baseline PASI scores ranged from 4.2 to 16.1 (median 7.1) in the treatment group, and from 0 to 12.5 (median 3.6) in the control group.

In the NB-UVB group baseline serum 25(OH)D$_3$ concentrations ranged from 9 ng/ml to 46 ng/ml (median 23 ng/ml). Post-NB-UVB phototherapy, after complete skin clearing, the range of serum 25(OH)D$_3$ concentrations increased to 32 to 112 ng/ml (median 51 ng/ml).

In the control group, baseline serum 25(OH)D$_3$ concentrations ranged from 7 ng/ml to 42 ng/ml (median 12 ng/ml) and ranged from 7 ng/ml to 33 ng/ml (median 13 ng/ml) when reassessed at the same time as their matched NB-UVB treated partner ended the study. There was no change in the skin condition or serum 25(OH)D$_3$ concentrations in the control group. Serum ionized calcium concentrations were normal and remained unchanged in both groups throughout the study (values not provided). None of the patients developed hypercalcemia or any other adverse events. The change in serum 25(OH)D$_3$ concentrations correlated with the number of exposures to NB-UVB and cumulative UVB dose, but not with treatment response.

The distribution and median serum 25(OH)D$_3$ concentrations pre-and post UVB treatment are shown in table 7.

Table 7: Range, median and distribution of serum 25(OH)D$_3$ concentrations pre-and post NB-UVB treatment in 29 psoriasis patients and 29 untreated controls

Measurement	NB-UVB Group n=29	Control Group n=29
Pre-UVB 25(OH)D$_3$ range	9 to 46 ng/ml	7 to 42 ng/ml
Median 25(OH)D$_3$ level	23 ng/ml	12 ng/ml
# > 20 ng/ml	19	NR
# > 40 ng/ml	NR	NR
# < 20 ng/ml	10	NR
Post-UVB 25(OH)D$_3$ range	32 to 112 ng/ml	7 to 33 ng/ml
Median 25(OH)D$_3$ level	51 ng/ml	13 ng/ml
# > 20 ng/ml	29	7
# > 40 ng/ml	24	0
# > 51 ng/ml	15	0
# > 72 ng/ml	6	0
# > 100 ng/ml	1+	0
# < 20 ng/ml	0	NR

Note: N=29 patients in each group. NR = not reported. Patients were treated 2 to 3 times a week until essentially complete clearing of the psoriasis occurred, which took between 25 to 118 days. The control group did not receive NB-UVB phototherapy.

Pre-treatment 19 of 29 patients (64%) in the NB-UVB group had serum 25(OH)D$_3$ concentrations > 20 ng/ml. Post-treatment all 29 patients (100%) had serum 25(OH)D$_3$ concentrations > 20 ng/ml, 24 patients (83%) were > 40 ng/ml, 15 (50%) were > 51 ng/ml, and 6 (20%) were >72 ng/ml. The number achieving serum 25(OH)D$_3$ concentrations > 100 ng/ml post-treatment was not reported, but occurred in at least 1 patient, with a peak value of 112 ng/ml.

3.3. Serum 25(OH)D$_3$ concentrations in psoriasis patients after 8-12 weeks of NB-UVB (n=42) and BB-UVB (n=26) phototherapy, 2009 - Osmancevic [63]

In a 2009 report, serum 25(OH)D$_3$, calcitriol, iPTH, calcium and creatinine concentrations were measured in 68 patients with plaque psoriasis before and after treatment with either broadband UVB (BB-UVB, n=26) or NB-UVB (n=42) phototherapy [63]. All patients were treated with whole body exposure for 8 to 12 weeks, with the doses of UVB adjusted based on the skin phenotype and the erythemal response noted during treatment.

The purpose of the study was to determine if there was a difference in vitamin D production with NB-UVB versus BB-UVB phototherapy. The use of oral or topical vitamin D, vitamin D analogues, or any biologics was prohibited. Patients were treated either in the spring (n=39) or in the winter (n=29).

There was no significant difference in the total number of treatments needed, but the treatment time was four times longer in the NB-UVB group compared to the BB-UVB group. Psoriasis plaques improved in all patients in both groups. Mean PASI scores decreased from 8.8 to 2.3 in the NB-UVB group, and from 9.5 to 3.1 in the BB-UVB group. The improvement in psoriasis was found to correlate positively with the increase in 25OHD levels (p=0.047). It was not stated if any patients achieved complete clearing of their skin lesions.

Serum 25(OH)D$_3$ concentrations increased in both groups, with a more pronounced increase noted in the BB-UVB versus NB-UVB group. Serum concentrations of calcium, creatinine, and 1,25-dihydroxyvitamin D3 were unchanged, while iPTH concentrations decreased in the BB group. In the BB-UVB group, the baseline mean serum 25(OH)D$_3$ concentration was 37.9 ± 16.9 ng/ml and increased to 69.4 ± 19.7 ng/ml after treatment. In the NB-UVB group, the baseline mean serum 25(OH)D$_3$ concentration was 34.8 ± 11.9 ng/ml and increased to 55.3 ± 17.6 ng/ml after phototherapy.

A line plot of individual serum $25(OH)D_3$ concentrations before and after treatment for the two groups showed that at least 3 patients in the BB-UVB group had serum $25(OH)D_3$ concentrations > 100 ng/ml post-treatment, but the actual values were not indicated. The distribution and mean serum $25(OH)D_3$ concentrations pre-and post UVB treatment are shown in table 8.

Table 8: Mean, range and distribution of serum $25(OH)D_3$ concentrations before and after BB-UVB (n=26) and NB-UVB (n=42) phototherapy in 68 patients with psoriasis.

Treatment	Pre-UVB $25(OH)D_3$ ng/ml Mean ± sd	Post-UVB $25(OH)D_3$ ng/ml Mean ± sd
BB-UVB (n=26)	37.9 ± 16.9	69.4 ± 19.7
Range ng/ml	17 to 82	45 to 118
NB-UVB (n=42)	34.8 ± 11.9	55.3 ± 17.6
Range ng/ml	15 to 73	28 to 98
# > 20 ng/ml	65	68
# > 50 ng/ml	5	48
# > 80 ng/ml	1	13
# > 100 ng/ml	0	3
# < 20 ng/ml	3	0

Note: the range and distribution of serum $25(OH)D_3$ concentrations are estimated from Figure 2 in reference [63]. # > ng/ml is the sum of patients from both groups. All patients were treated with whole body exposure to UVB for 8 to 12 weeks. The difference in serum $25(OH)D_3$ concentrations after treatment was significant between the lamps (p-value=0.008).

Pre-treatment, 65 of the 68 patients (95.6%) had serum $25(OH)D_3$ concentrations > 20 ng/ml, while 5 of 68 (7.4%) were > 50 ng/ml, and one was > 80 ng/ml. Post-treatment a total of 48 of 68 patients (70.6%) had serum $25(OH)D_3$ concentrations > 50 ng/ml; 13 of 68 (19.1%) were > 80 ng/ml; and 3 of 68 (4.4%) were > 100 ng/ml (values not indicated). No adverse events related to the treatment were noted in any patient.

3.4. Serum $25(OH)D_3$ concentrations in psoriasis patients after 15 days of sunshine (n=20) or 8-12 weeks of NB-UVB or BB-UVB phototherapy (n=24), 2010 - Osmancevic [64]

In a 2010 report, serum $25(OH)D_3$, calcitriol, PTH, calcium and creatinine concentrations in psoriasis patients were measured before and after treatment with sunshine, NB-UVB and BB-UVB phototherapy [64]. This report was a discussion of data aggregated from 3 studies, including data in the previously discussed report [63]. The two additional studies included a group of 24 post-menopausal women with psoriasis who were treated with whole body BB-UVB phototherapy 2 to 3 times a week for 8 to 12 weeks, and a group 20 psoriasis patients who were treated with whole body heliotherapy (sunshine) daily for 2 weeks. The authors stated that they had 2 main aims:

a.) To increase the knowledge about the effects of phototherapy on vitamin D production during the treatment of psoriasis,

b.) To see if there were differences between the effect of BB-UVB, NB-UVB and heliotherapy on vitamin D synthesis in psoriasis patients.

A similar efficacy was reported with each treatment. An improvement in the PASI score of about 75% was observed in each group. However, the group treated with sunshine required only two weeks to achieve the same clinical improvement as seen after 2 to 3 months of UVB phototherapy.

Serum 25(OH)D$_3$ concentrations increased in each group. No changes in serum calcium concentrations were noted after any of the phototherapy regimens used. In the BB-UVB group of post-menopausal women, the mean baseline serum 25(OH)D$_3$ concentration was 36.8 ± 17 ng/ml and increased to 59.6 ± 18.7 ng/ml after phototherapy. In the sunshine group, the mean baseline serum 25(OH)D$_3$ concentration was 22.9 ± 6.0 ng/ml , which increased to 41.8 ± 6.3 ng/ml after daily sunshine exposure for 15 consecutive days. The range of serum 25(OH)D$_3$ concentrations after treatment with sunshine was much lower than in the UVB groups. This may be due to the shorter duration of treatment, as well as the fact that the patients used sunscreen on areas of their body susceptible to sunburn.

The mean, range and distribution of serum 25(OH)D$_3$ concentrations pre-and post BB-UVB and sunshine treatment in the postmenopausal and sunshine groups are shown in table 9.

Table 9: Mean, range and distribution of serum 25(OH)D$_3$ concentrations pre-and post 8-12 weeks of BB-UVB phototherapy (n=24 postmenopausal women) or 15 days of whole-body sunshine (n=20) exposure in 44 patients with plaque psoriasis.

Treatment	Pre-treatment	Post-treatment
BB-UVB		
25(OH)D$_3$ ng/ml	36.8 ± 17	59.6 ± 18.7
Range ng/ml	18 to 88	25 to 90
# > 20 ng/ml	22	24
# > 50 ng/ml	3	17
# > 80 ng/ml	0	5
# > 100 ng/ml	0	0
# < 20 ng/ml	2	0
N	24	24
Sunshine		
25(OH)D$_3$ ng/ml	22.9 ± 6	41.8 ± 6.3
Range ng/ml	18 to 42	30 to 60
# > 20 ng/ml	17	20
# > 50 ng/ml	0	4
# > 80 ng/ml	0	0
# > 100 ng/ml	0	0
# < 20 ng/ml	3	0
N	20	20

Note: the range and distribution of serum 25(OH)D$_3$ concentrations is estimated from Figure 2 in reference [64]. BB-UVB group was treated with whole body phototherapy 2 to 3 times a week for 8 to 12 weeks. Sunshine group was treated with whole body heliotherapy (sunshine) daily for 2 weeks. N= number of patients in each group.

In the BB-UVB group, pre-treatment serum 25(OH)D$_3$ concentrations were > 20 ng/ml in 22 of 24 patients (91.7%) and were > 50 ng/ml in 3 of 24 patients (12.5%). Post-treatment, a total of 17 BB-UVB patients (70.8%) had serum 25(OH)D$_3$ concentrations > 50 ng/ml, 5 (20.8%) were > 80 ng/ml, and none were above 100ng/ml. In the sunshine group, pre-treatment serum 25(OH)D$_3$ concentrations were > 20ng/ml in 17 of the 20 patients (85%), and none were > 50 ng/ml. Post-treatment, a total of four patients (20%) had serum 25(OH)D$_3$ concentrations > 50ng/ml, and none were > 100ng/ml. All patients in the sunshine treated group had serum 25(OH)D$_3$ concentrations greater than 30ng/ml after two weeks of daily sun exposure, with significant improvement in their clinical condition.

4. Summary and Discussion of Key Findings in the Reviewed Reports

The following summarizes the main points highlighted in this paper thus far:

1.) Four different oral forms of vitamin D are safe and effective treatments for plaque psoriasis

2.) Normal serum 25(OH)D concentrations (>20 ng/ml) were common pretreatment but insufficient to improve psoriatic lesions

3.) High serum 25(OH)D concentrations (>100 ng/ml) were often reported with safe control of psoriasis

4.) Changes in serum 25(OH)D concentrations after treatment vary significantly with the treatment used

5.) A therapeutic dose response of psoriasis to vitamin D appears to be present

6.) Calcitriol formation is the common endpoint after treatment with vitamin D and UVB phototherapy

7.) Psoriasis can recur with cessation of treatment with vitamin D or UVB phototherapy

8.) Psoriasis can improve again with resumption of treatment with vitamin D or UVB phototherapy

9.) Post treatment serum 25(OH)D concentrations are higher after UVB phototherapy compared to sunshine

10.) A paucity of adverse reactions was observed with vitamin D supplementation in the reviewed studies

11.) Clinical efficacy and safety of oral and topical vitamin D treatments are comparable to UVB phototherapy and sunshine treatments

12.) All authors reviewed stated unequivocal support for the safety and efficacy of vitamin D in treating psoriasis

13.) Estimates of vitamin D production in the 1970s are significantly lower than doses used clinically in treating diseases in the 1930s and 1940s— but significantly higher than the doses recommended for use today.

4.1 Four different oral forms of vitamin D are safe and effective treatments for plaque psoriasis

Since 1985 four different oral forms of vitamin D, specifically vitamin D_2, vitamin D_3, 1-hydroxyvitaminD_3 (1-OHD$_3$), and 1,25-dihydroxyvitaminD_3 (calcitriol) and several topical formulations of vitamin D including calcitriol [13-28, 81-109] have been reported safe and effective treatments for psoriasis—as has UVB phototherapy and sunshine [40-44, 61-64, 115-131]. This is consistent with findings first reported by Krafka in 1936 [12].

4.2 Normal serum 25(OH)D concentrations (>20 ng/ml) are often insufficient for disease control in psoriasis patients

The serum 25(OH)D concentrations reported in 10 of the 12 clinical trials reviewed (no data in 2 reports) consistently show a high percentage of pre-treatment serum 25(OH)D concentrations > 20 ng/ml, ranging up to 88 ng/ml, in patients with active plaque psoriasis [14,19,22,25-26,28,61-64]. These pre-treatment concentrations are within what is currently considered the normal range of serum 25(OH)D concentrations as defined by the IOM (20 to 50 ng/ml) [55] and Endocrine Society (30 to 100 ng/ml) [56] in 2011. However, the significant clinical improvement observed in many of these patients after treatment with the four different forms of oral vitamin D is evidence that the range of serum 25(OH)D concentrations currently classified as normal are not sufficient for disease control in patients suffering from active plaque psoriasis.

4.3 High serum 25(OH)D concentrations (>100 ng/ml) were often reported with safe control of psoriasis

Post-treatment serum 25(OH)D concentrations > 100 ng/ml were observed in plaque psoriasis patients treated with UVB phototherapy [61-63], oral vitamin D_2 at a dose of 50,000 IU/day for over 2 years [28], and oral vitamin D_3 at a dose of 35,000 IU/day for 6 months [26], while none were observed in patients treated with sunshine [64], oral or topical calcitriol [14,19,22], or oral 1(OH)D_3 [14]. Serum 25(OH)D concentrations > 100 ng/ml are currently considered to be above the normal range of serum 25(OH)D concentrations by the Endocrine Society[56], while serum 25(OH)D concentrations > 50 ng/ml are considered high by the IOM [55]. However, no significant clinical toxicity was observed in any plaque psoriasis patient who achieved these serum 25(OH)D concentrations, as indicated by the significant clinical improvement observed in their skin after each treatment without the observation of any adverse events.

4.4 Changes in serum 25(OH)D concentrations after treatment vary significantly with the treatment used

There were no changes in serum 25(OH)D concentrations in patients treated with either oral $1(OH)D_3$ [14], oral calcitriol [14,19,22], or topical calcitriol [14,19], as neither $1(OH)D_3$ or calcitriol is metabolized into $25(OH)D_3$. There were significant increases in serum 25(OH)D concentrations in patients treated with oral vitamin D_2, [28], oral vitamin D_3, [26], UVB phototherapy [61-64] and sunshine [64], as described in section 4.3.

The highest serum 25(OH)D concentration observed after 6 months of 35,000 IU/day of vitamin D_3 was 202 ng/ml [26]. The highest serum 25(OH)D concentration observed after more than 2 years on 50,000 IU/day of vitamin D_2 was 308 ng/ml [28]. The highest post-treatment serum 25(OH)D concentration observed after 8 weeks of UVB phototherapy was 159 ng/ml reported in 1996 [61]. Current definitions of normal serum vitamin D concentrations need to be reconsidered in light of this data.

4.5 A therapeutic dose response to vitamin D appears to be present

A dose response was noted by Huckins et al in 1990 in the treatment of psoriatic arthritis with calcitriol in doses ranging from 0.5 mcg to 2 mcg/day, as improvement reportedly never occurred at a dosage < 1.5 ug/day [21]. Similarly, when calcitriol was titrated from 0.5 to 4 mcg/day in a 3 year study of plaque psoriasis by Perez et al in 1996, mean calcitriol doses of 2.1 mcg/day at 24 months, and 2.4 mcg/day at 36 months were obtained, suggesting a dose response was also observed, although this was not stated by the authors [22]. This needs further clarification for each of the four forms of oral vitamin D shown to be effective treatments for psoriasis in this review.

4.6 Calcitirol formation is the common endpoint after treatment with vitamin D, UVB phototherapy and sunshine

Vitamin D_3, vitamin D_2, and $1(OH)D_3$ are all metabolized into calcitriol, the active hormone form of vitamin D. Sunshine and UVB phototherapy cause the formation of vitamin D_3 in the skin from the precursor molecule 7-dehydrocholesterol, which is then metabolized to 25(OH)D and subsequently into calcitriol. The formation of calcitriol appears to be the final common pathway for these six treatments. The primary function of calcitriol is regulation of gene transcription. Calcitriol regulates several thousand genes located in many different cells and tissues throughout the body [132-138], including keratinocytes [19, 83-84, 90, 103-106, 109, 131] and cells of the innate and adaptive immune system [139-207].

4.7 Psoriasis can recur with cessation of vitamin D or UVB phototherapy.

Psoriasis was observed to recur with cessation of oral calcitriol by Smith et al in 1988 [19] and with cessation oral vitamin D_3 by McCullough et al in 2012 [25]. Krafka noted in 1936 that psoriasis control improved with sunshine and worsened in the abcense of sunshine which was the motivation to use vitamin in the treatment of psoriasis [12]. The National Psoriasis Foundation has also reported that psoriasis will often recur after cessation of UVB phototherapy [8].

4.8 Psoriasis can improve again with resumption of treatment with vitamin D or UVB phototherapy.

Psoriasis was also noted to improve again after resuming oral calcitriol by Smith et al in 1988 [19] and oral vitamin D_3 by McCullough et al in 2012 [25]. Similarly, maintenance phototherapy is recommended by the National Psoriasis Foundation due to psoriasis plaques commonly reoccurring after cessation of treatment with UVB phototherapy [8].

The exact gene products regulated by calcitriol that cause the improvement in plaque psoriasis are currently unknown but may be related to the positive effect that topical vitamin D [153-158], oral vitamin D [159-207], sunshine [208-210] and UVB phototherapy [211-233] have been shown to have on the formation and functional status of regulatory T lymphocytes. Tregs have been shown to play an important role in suppression of autoimmune diseases [234-255]. Several mechanisms of action by which Tregs control psoriasis were proposed in 2013 [247].

Thus, psoriasis appears to be controlled but not cured by vitamin D and UVB phototherapy and requires maintenance therapy to maintain disease control. This is consistent with the observed dependency of regulatory T lymphocytes on vitamin D, sunshine and UVB phototherapy to maintain their functional status. Psoriasis appears to behave like an autosomal recessive disease that

becomes dominant in a state of vitamin D deficiency when Tregs are dysfunctional, and recessive in a state of vitamin D sufficiency when Treg functional status is restored.

4.9 Post treatment serum 25(OH)D concentrations are higher after UVB phototherapy compared to sunshine

Treatment with UVB phototherapy consistently resulted in several patients achieving serum 25(OH)D concentrations > 100 ng/ml in the reports reviewed [61-63]. Treatment with sunshine resulted in smaller increases in serum 25(OH)D concentrations than observed with UVB or NB phototherapy, with none > 100 ng/ml, although several were > 50 ng/ml post treatment [64]. These results are consistent with reports of serum 25(OH)D concentrations observed in healthy individuals after prolonged sun exposure, where serum 25(OH)D concentrations > 100 ng/ml were also not observed, but serum concentrations > 50 ng/ml were commonly observed [256-258]. Three reports will be discussed.

In 1971 serum 25(OH)D concentrations in eight lifeguards measured four weeks after working at an outdoor pool were included in a report by Haddad and Chyu describing the first successful assay for measuring serum 25(OH)D concentrations [256]. The mean serum 25(OH)D concentration after four weeks of sun exposure was 64.4 ± 8.7 ng/ml, and all eight were > 50 ng/ml (range 53 to 79 ng/ml).

In 2007, ninety-three individuals living in Hawaii with variable daily sun exposure ranging from total body exposure in surfers to only head, arms and hands in skateboarders, had serum 25(OH)D concentrations ranging from 11 to 71 ng/ml, of which seven (7.5%) were > 50 ng/ml [257].

In 2012, sixty traditionally living healthy dark-skinned individuals in East Africa were evaluated for serum 25(OH)D concentrations [258]. The mean serum 25(OH)D concentration was 46 ng/ml (range 23.2 to 68.4 ng/ml), with 13.3% between 20 to 32 ng/ml, 15% between 32.4 to 40 ng/ml, 28.3% between 40.4 to 48 ng/ml, 33.3% between 48.4 to 60 ng/ml, and 10% > 60.4 ng/ml, for a total of approximately 43% with serum concentrations > 50 ng/ml.

4.10 A paucity of adverse reactions was observed in the reviewed studies

Very few adverse events were reported in the patients treated with vitamin D, sunshine or UVB phototherapy reviewed in this report. No cases of hypercalcemia, nephrolithiasis, or renal dysfunction were reported in any of the vitamin D studies reviewed. Six total cases of hypercalciuria were reported in three reports, four with calcitriol [19,21] and two with UVB phototherapy [61]. No cases of hypercalciuria were reported after 6 months of treatment in 25 patients with 35,000 IU/day of vitamin D_3 [26], and a very mild elevation was noted in an individual after 2 years of treatment with 50,000 IU/day of vitamin D_2 [28].

In 1988 Smith reported two cases of hypercalciuria with oral calcitriol [19]. Both patients withdrew from the study. There were no reports of renal insufficiency, nephrolithiasis or any other adverse events.

In 1996 Prystowsky reported hypercalcemia in 2 patients in the UVB phototherapy and calcitriol group, but neither had hypercalciuria [61]. The hypercalcemia resolved with reduction in their intake of calcitriol. Three patients in both the calcitriol and placebo groups developed hypercalciuria (values not provided). There were no reports of renal insufficiency, nephrolithiasis or any other adverse events related to the hypercalcemia or hypercalciuria reported.

In 1986 Morimoto did not report any adverse events related to treatment with vitamin D [14]. The authors reported "None of the patients in the three groups suffered from any topical or systemic complications or symptoms during these observation periods. Blood and urine analysis showed values within normal limits at all times. Hepatic and renal function, …were within normal ranges and did not change significantly during the observation periods." Morimoto did report a significant difference between baseline and 3-month calcium levels was noted in the $1(OH)D_3$ and oral calcitriol groups, and for calcitriol in the $1\text{-}OHD_3$ group, but all values were within the normal range.

In 1990 Huckins reported two patients were unable to receive therapeutic doses due to hypercalciuria but did not report any other adverse events related to treatment with oral calcitriol [21].

In 1996 Perez did not report any adverse events related to treatment with oral calcitriol [22]. Perez did report that the mean 24-hour urine calcium concentrations (mg/24hr), calcium/creatinine ratios, and the serum calcium levels were significantly increased compared to baseline at 6, 12, 24 and 36 months, but remained within normal limits.

In 2009 and 2010 Osmancevic did not report any adverse events related to treatment with UVB phototherapy or sunshine [63-64]. In 2009 Osmancevic reported serum concentrations of calcium, creatinine, and 1,25-dihydroxyvitamin D3 were unchanged after UVB phototherapy, while iPTH concentrations decreased in the BB group.

In 2010 Ryan did not report any adverse events related to treatment with UVB phototherapy [62].

In 2012 and 2019 McCullough did not report any adverse events related to treatment with oral vitamin D_3 [25,28].

In 2013 Finamor did not report any adverse events related to treatment with oral vitamin D_3 [26]. The authors reported "Laboratory or clinical signs of toxicity (hypercalcemia, hypercalciuria or kidney dysfunction) were not observed in any of the 25 participants, including a patient with vitiligo who reached a serum concentration of $25OHD_3$ of 202 ng/ml.

The evidence in these studies show that the clinical efficacy and safety of oral and topical vitamin D are comparable to the clinical efficacy and safety of UVB phototherapy and sunshine in the treatment of plaque psoriasis.

4.11 Sunshine and topical vitamin D appear to work more quickly than UVB phototherapy and oral vitamin D

In comparing topical vs oral vitamin D, both Morimoto et al in 1986 [14] and Smith et al in 1988 [19] found topical calcitriol resulted in significant clearing of psoriasis plaques within a few weeks, versus a few months with oral 1(OH)D or oral calcitriol. Sunshine was also shown to clear psoriasis plaques within a few weeks compared to a few months for UVB/NB phototherapy by Osmancevic et al in 2010 [64].

4.12 Authors reported views support the safety and efficacy of vitamin D for the treatment of psoriasis

Krafka 1936 [12]: "If the treatment were at all hazardous or difficult, we would not presume to lay it before the profession. But the treatment is so simple that it should be put to a trial test in the interest of every patient suffering from this obnoxious condition. Certainly, it is worth a fair trial. We leave our results to be tested on a more elaborate scale by the larger clinics."

Morimoto 1986 [14]: "These data suggest that exogenous active forms of vitamin D_3 are effective for the treatment of psoriasis, and that the endogenous 1,25-dihydroxyvitamin D level also may be involved in the development of this disease."

Smith 1988 [19]: "Topical or oral use of 1,25-$(OH)_2D_3$ heralds a new mode of treatment that appears to be both safe and effective for the treatment of psoriasis."

Perez 1996 [22]: "Oral calcitriol is effective and safe for the treatment of psoriasis."

Prystowsky 1996 [61]: "Because phototherapy for psoriatic plaques produces changes in keratinocytes similar to those described for 1,25-(OH)2D3 (i.e. slowed proliferation and enhanced differentiation), this raises the possibility that one of the mechanisms of action of UVB may be through enhanced vitamin D metabolism."

Finamor 2013 [26]: "In summary, the present study suggests that, at least for patients with autoimmune disorders like vitiligo and psoriasis, a daily dose of 35,000 IU of vitamin D_3 is a safe and effective therapeutic approach for reducing disease activity."

McCullough previously reported on the long-term safety of daily supplementation of oral vitamin D_3 in doses ranging from 5000 IU to 60,000 IU/day and found no adverse events after treatment for up to 7 years [28,114]. Several thousand long-term hospitalized patients taking 5000 to 10,000 IU/day were included the review [28]. We recently measured 24 urine calcium and creatinine levels in 16 individuals after long-term supplementation with varying doses of vitamin D. This included measurements in 4 individuals after taking 5000 IU/day for 13 to 94 months, in 9 individuals after taking 10,000 IU/day for 7 to 105 months, in one individual after taking vitamin D_2 50,000 IU/day for 51 months reported earlier, in one individual after taking vitamin D_3 60,000 IU/day for 67 months, and in one individual after sunbathing periodically for 33 months. Normal 24 urinary calcium excretion was observed in all 16 individuals (unpublished data).

4.13 Estimates of vitamin D production in the 1970s are much lower than doses used in the 1930s and 1940s

The first estimates of the physiologic amounts of vitamin D produced in the skin after exposure to UVB radiation were not available until 1977 and were found to be greater than 10,000 IU/day [110]. This data was later confirmed by other investigators [56,111-113]. These researchers also noted that the upper limits of daily vitamin D production in the skin from UVB exposure appear to be in the range of 20,000 to 25,000 IU/day [56,111-113]. This range is much less than the 60,000 to 600,000 IU/day used successfully clinically in the 1930s and 1940s and is much higher than the upper limit of 4000 IU/day currently recommended by the IOM [55] but is within the upper limit of 10,000 IU/day recommended by the Endocrine Society [56].

These estimates of physiologic vitamin D production in the skin may explain why hypercalcemia was often observed as a side effect of treatment with vitamin D in the 1930s and 1940s but was not observed in the oral vitamin D_3 and oral vitamin D_2 studies reviewed in this report which used doses ranging from 35,000 to 50,000 IU/day for 6 months to over 2 years. The serum 25(OH)D concentrations associated with the clinical benefits reported in the 1930s and 1940s when supraphysiologic doses of vitamin D were used to cure both tuberculosis [33-39] and rickets [32,46], and to control asthma [29], psoriasis [12] and rheumatoid arthritis [30-31] are unknown as tests for measuring serum 25(OH)D concentrations were not available until 1971 [256]. The upper limit of daily vitamin D intake that that is clinically effective but does not result in adverse events in the treatment of psoriasis and other vitamin D deficiency linked diseases needs to be further investigated.

5. Implications for the treatment of other vitamin D deficiency related diseases with vitamin D or phototherapy

These observations raise important questions about the adequacy of serum 25(OH)D concentrations falling between 20 to 100ng/ml not only for patients suffering from plaque psoriasis, but for those suffering from other diseases that are also strongly linked to vitamin D deficiency. Such diseases are numerous and include asthma, atherosclerosis, autoimmune diseases, cancers, falls, fractures, infections, mortality, myopathies, muscle weakness, neurological disorders, osteomalacia, osteoporosis, and psychiatric disorders [12, 29-39, 46, 53, 65-80, 261-318]. Of particular interest currently are adverse outcomes from viral infections such as influenza [65, 275, 284,289, 300, 311] and COVID-19 [65-80], both of which have shown a strong association with vitamin D deficiency.

Many clinical trials using oral vitamin D supplementation performed and reported in the past 30 years have used daily dosing ranging from 800 IU/day to 4000 IU/day, with few exceeding 4000 IU/day [261-318]. This is well below the range of 10,000 to 25,000 IU/day reported to be produced by sun exposure to the skin, and far below the clinically effective doses of vitamin D used in the 1930s and 1940s. While several clinical trials using daily dosing ranging from 800 IU/day to 4000 IU/day were effective, others showed mixed or negative results. Three such negative trials will be briefly reviewed. Several case reports and clinical trials showing clinical benefits with supplementation with vitamin D in doses > 4000 IU/day will also be reviewed.

5.1. Inadequacy of 4000 IU/day of vitamin D_3 in the treatment of asthma and of 2000 IU/day in the prevention of cancer

Two recent clinical trials investigating the effects of daily intake of 4000 IU/day of vitamin D_3 versus placebo on asthma control in adults and children showed no significant clinical benefits [302,318]. The first clinical trial was a 28-week study published in 2014 involving 201 treated adults [302], and the second was a 48-week study published in 2020 involving 96 treated children [318]. Similarly, a 5-year clinical trial comparing the effect of daily intake of 2000 IU/day of vitamin D_3 versus placebo published in 2019 in preventing invasive cancer or cardiovascular events in 12,927 treated adults found no significant clinical benefit [317]. Mean baseline serum 25(OH)D concentrations in these three clinical trials were 18.8ng/ml, 22.5ng/ml and 30.8ng/ml respectively. On treatment mean serum 25(OH)D concentrations averaged 42ng/ml in the first study at 12, 20 and 28 weeks (range 6.3 to 97.3ng/ml at week 12), and in the second study were 57.2, 53.8 and 49.4ng/ml at weeks 16, 32 and 48 (ranges not indicated). A subgroup of 1644 participants in the third clinical trial had a baseline mean serum 25(OH)D concentration of 29.8ng/ml which increased to 41.8ng/ml at one year (range not indicated). No changes were seen in mean serum 25(OH)D concentrations in the placebo groups over the time course of the studies.

The on-treatment data reported in these clinical trials are similar to the baseline serum 25(OH)D concentrations in the psoriasis reports reviewed in this report, which were insufficient for disease control in psoriasis. This suggests the possibility that daily intakes

higher than 2000 to 4000 IU/day of vitamin D_3 may be needed for treating asthma and for preventing cancer and cardiovascular disease, which is consistent with the observations first reported in the 1930s and 1940s with asthma, psoriasis, rheumatoid arthritis, and tuberculosis, as well as with the psoriasis studies reviewed in this report. It is also consistent with several recent case reports and clinical trials of diseases showing clinical improvement with vitamin D intake > 4000 IU/day.

5.2. Case reports and clinical trials of diseases showing clinical improvement with vitamin D intake > 4000 IU/day

Several case reports and clinical trials published in the past few decades [80, 114, 267, 292-293, 301, 307-309], in addition to the 3 discussed in this report [25-26,28], have shown significant clinical benefits without toxicity with vitamin D supplementation when using doses of vitamin D above 4000 IU/day, and ranging up to 50,000 IU/day for extended periods of time, thus providing further support for this recommendation. This includes significant clinical improvement in:

1.) A 1997 case report of chronic Parkinson's disease symptoms over the course of a year using 4000 IU/day of 25(OH)D [267], roughly equivalent to 20,000 IU/day of vitamin D_3 [110],

2.) Control of chronic pain in children suffering from sickle cell disease using 50,000 IU twice weekly of vitamin D_3 for 8 weeks, followed by once weekly for 32 months in a 2011 case report [292], and subsequently in a weight-based dosing study using 40,000 IU to 100,000 IU/ week for 6 weeks in 20 children in a 6 month placebo controlled trial published in 2012 [293],

3.) Chronic fatigue in a 2014 prospective study of 171 adult patients with low serum 25(OH)D concentrations (<30 ng/ml) using 50,000 IU of vitamin D_2 three times a week for 5 weeks [301], which averages out to 21,429 IU/day,

4.) Prevention of statin intolerance secondary to myalgia, myositis, myopathy or necrosis in 171 previously statin intolerant patients with low serum 25(OH)D concentrations (<32 ng/ml) using either 50,000 or 100,000 IU/week of vitamin D_2 for 24 months published in 2015 [307],

5.) 282 patients treated with these same doses in a prospective one-year clinical safety trial from this same group using vitamin D_3 instead of vitamin D_2, and again found to be safe in 2016 [308],

6.) Prevention of progression of a case of advanced pancreatic cancer using 50,000 IU/day of vitamin D_3 for 9 months reported in 2016 [309],

7.) Asthma control in a case of long-standing asthma using 20,000 to 25,000 IU/day of vitamin D_3 for several years reported in 2019 [28,114],

8.) A non-melanoma skin cancer in an individual taking 60,000 IU/day of vitamin D_3 for several years reported in 2019 [28,114], and

9.) The need for ICU treatment in patients requiring hospitalization due to proven COVID-19 infections in 50 patients treated with 25(OH)D (532 mcg (21,280 IU) on day 1; 266 mcg (10,640 IU) on days 3 and 7, followed by 266 mcg weekly until discharge) which resulted in one ICU admission (2%), versus a group of 26 untreated patients of which thirteen (50%) required admission for care in an ICU [80].

COVID-19 deaths have now passed 2.4 million worldwide [319]. In the United States there have been over 28 million cases and over 510,000 deaths [319] with no signs of slowing down soon. A recent report analyzing over 190,000 COVID-19 infected patients in the United States showed a strong correlation with vitamin D deficiency and risk of infection, with a 53% lower SARS-CoV-2 positivity rate among patients with a serum 25(OH)D concentration > 55 ng/ml versus those < 20 ng/ml, and a 43% lower risk for contracting COVID-19 with an increase in serum 25(OH)D concentrations from 20 ng/ml to 55 ng/ml [75], providing further evidence of the urgency to conduct such clinical trials.

5.3. Need to better define the therapeutic index of vitamin D

The serum 25(OH)D concentrations in psoriasis patients before and after treatment reviewed in this report suggest revision of current definitions of vitamin D deficiency, insufficiency, sufficiency and toxicity, as well as diseases currently recognized as being responsive or unresponsive to vitamin D supplementation. There is a dearth of clinical trial data examining the clinical utility

and toxicity of oral vitamin D supplementation between the conventional dose ranges of 800 to 4000 IU/day and 60,000 to 600,000 IU/day. The supraphysiologic (by current standards) doses of vitamin D used in the 1930s and 1940s were proven clinically effective in treating asthma, rheumatoid arthritis and tuberculosis in addition to psoriasis, but were associated with reversible hypercalcemia and calcium crystal formation after prolonged daily intake [31,35,39,259-260]. Clinical trials in patients suffering from psoriasis and other diseases shown to be strongly linked to vitamin D deficiency using daily oral supplementation between these extremes, particularly dosing encompassing the range of 10,000 to 25,000 IU shown to be produced by adequate daily UVB exposure to the skin, need to be done to clarify the therapeutic index of vitamin D.

6. Conclusions and Future Directions

Psoriasis responds safely to treatment with 4 different forms of oral vitamin D: vitamin D_2, vitamin D_3, 1-alpha-hydroxyvitaminD_3, and 1,25-dihydroxyvitamin D_3 (calcitriol). Pre-treatment serum $25(OH)D_3$ concentrations above 20 ng/ml, ranging up to 67 ng/ml, were common in patients with plaque psoriasis in the oral vitamin D dosing studies reviewed. However, patients showed significant dermatological improvement in their skin without toxicity after daily treatment with four different forms of oral vitamin D. This suggests that serum $25(OH)D_3$ concentrations > 20 ng/ml are not adequate for many patients with plaque psoriasis, even though they are considered adequate for the majority of the population by the IOM [55] and the Endocrine Society [56], calling into question the definition of an adequate serum 25OHD concentration. Pre-treatment serum $25(OH)D_3$ concentrations > 20 ng/ml, ranging up to 88 ng/ml, were also commonly observed in patients with plaque psoriasis in the UVB phototherapy studies reviewed, yet these patients still showed significant improvement in their skin after treatment with UVB phototherapy. This was associated with significantly increased serum $25(OH)D_3$ concentrations post-treatment, with several patients > 100 ng/ml, and ranging up to 159 ng/ml without any adverse events.

Post-treatment serum $25(OH)D_3$ concentrations > 100 ng/ml were also observed in patients with plaque psoriasis safely treated with 35,000 IU/day of vitamin D_3 for 6 months, and in a patient treated with 50,000 IU/day of vitamin D_2 for over 3 years, without any adverse events. This was associated with peak serum $25(OH)D_3$ concentrations of 202 ng/ml and 308 ng/ml respectively. The fact that serum $25(OH)D_3$ concentrations > 100 ng/ml have been obtained safely after disease control using UVB phototherapy, 35,000 IU/day of vitamin D_3 , and 50,000 IU/day of vitamin D_2 calls into question the safe upper limit of serum $25(OH)D_3$ concentrations. Currently, a serum $25(OH)D_3$ concentration > 50 ng/ml is considered potentially dangerous for the majority of the population and is not recommended by the IOM [55] and a serum 25OHD concentration > 100 ng/ml is considered high by the Endocrine Society [56]. In contrast, several reviews [57-59] and case reports [60] on vitamin D toxicity have suggested that serum 25OHD concentrations > 100 ng/ml and ranging up to 400 ng/ml may be safe. This needs further clarification. A recent review on vitamin D safety suggests that "Vitamin D is not as toxic as was once thought" [306}.

Vitamin D toxicity was absent in the reviewed clinical reports. When it occurs, it is manifested by complications related to hypercalcemia, renal insufficiency, hypercalciuria, calcium crystal formation, and undetectable serum parathyroid hormone concentrations, which have been shown to be reversible by simply stopping the vitamin D and providing supportive care with no long-term sequelae. Several such complications induced by excessive vitamin D intake (hypercalcemia, renal insufficiency, hypercalciuria, and undetectable serum PTH) were shown to resolve when serum $25(OH)D_3$ concentrations dropped below 400 ng/ml in 2 case reports in 2011 after accidental ingestion of massive amounts of vitamin D over a period of 1 to 2 months [60]. Due to labeling and manufacturing errors of over the counter supplements, one patient took 1,864,000 units (46,000 mcg) of vitamin D_3 daily for 2 months and achieved a peak serum 25OHD concentration of 1220 ng/ml. The second took 970,000 units of vitamin D_3 a day for one month and achieved a peak serum 25OHD concentration of 645 ng/ml. Both recovered uneventfully after cessation of vitamin D intake. Our clinical experience is consistent with this, as we have not observed hypercalcemia, renal insufficiency, hypercalciuria, undetectable serum parathyroid hormone concentrations or any other toxicity in patients with serum $25(OH)D_3$ concentrations ranging from 202 ng/ml to 384 ng/ml [28].

Vitamin D has a much safer toxicity profile than methotrexate, cyclosporine and biologics such as Humira and Enbrel, which are more commonly used for the treatment of psoriasis. Biologics are among the most frequently reported drugs for adverse events

to the FDA, and many have FDA mandated black box warnings for risk of cancers such as lymphoma, serious infections such as tuberculosis and invasive fungal infections, and death [322-334]. In contrast, vitamin D was shown in the 1940s to safely cure tuberculosis infections as a single agent using daily oral intake of 100,000 to 150,000 units for 2 to 3 months [33-39], most likely by turning on genes that make antimicrobial peptides active against TB [39, 277, 285]. More recently, vitamin D has been shown to have anticancer properties [28, 279, 283, 291, 296, 299, 309], and appears to reduce the risk for developing cancer, and not increase it as biologics do. More clinical research utilizing a range of vitamin D intakes is needed to confirm these findings and to see if a dose response exists in cancer prevention, in light of the recent clinical trial reviewed earlier that showed no clinical benefit in cancer prevention after daily intake of 2000 units of vitamin D_3 over five years [317]. Vitamin D also appears to have a safer toxicity profile than sunshine, UVB phototherapy, and even acetaminophen, one of the most commonly used over the counter medications, and a leading cause of liver failure[320-321] .

The fact that both oral and topical vitamin D were able to produce the same clinical outcomes as seen with sunshine and UVB phototherapy is compelling evidence that the effects of sunshine and UVB phototherapy in treating psoriasis is mediated by vitamin D production in the skin. The mechanism of action explaining how vitamin D works to clear psoriasis skin lesions is currently unknown but appears likely to be related to the documented effects vitamin D has on stimulating the production and maintenance of regulatory T lymphocytes (Tregs), which have been characterized as master regulators of the immune system due to their ability to control autoimmune diseases [239]. This also needs further clarification. However, consistent with this notion, Tregs have been shown to be dysfunctional in a state of vitamin D deficiency, and can have their functional status restored by sunshine, phototherapy and oral or topical vitamin D [153-233]. Vitamin D causes the formation of Tregs to occur indirectly through direct effects on antigen presenting cells, which then cause naïve T cells to transform into Tregs [143].

Placebo controlled, blinded clinical trials using oral vitamin D_3 for the treatment of patients suffering from psoriasis are warranted based on the results of the studies reviewed in this paper. There is strong evidence that physiologic doses in the range of 10,000 to 25,000 IU/day, and ranging up to 50,000 IU/day, should be able to be administered safely in a clinical trial setting. Serum calcium and PTH concentrations, renal function and urine calcium concentrations can be easily monitored and readily corrected without long-term risk if they become abnormal by simply stopping vitamin D supplementation. The vitamin D could then be resumed again at a lower dose to monitor clinical efficacy and safety. There is potentially much to gain if these dose-response clinical trials are successful. Oral vitamin D is the most affordable treatment option for psoriasis by a wide margin, especially when compared to biologics. The potential cost savings to the health care system by the increased use of oral vitamin D in treating psoriasis is enormous, in the range of billions of dollars/year, with improved patient safety and satisfaction. It is not clear why the four forms of oral vitamin D discussed in this review are not currently being used to treat psoriasis, after being endorsed as safe and effective treatments by the authors of the clinical trials reviewed.

The failure of clinical trials that used sub-physiologic doses of vitamin D and achieved inadequate serum 25(OH)D concentrations has created doubt about the importance of vitamin D in the prevention and treatment of human disease. The fear of causing toxicity by using excessive amounts of vitamin D has led to the unintended consequence of causing needless suffering by perpetuating uncontrolled disease states that might otherwise be controlled by sufficient vitamin D intake or exposure to UVB radiation. Clinical trials examining the dose response of oral vitamin D_3 using 10,000 to 25,000 IU/day or higher may prove beneficial in controlling plaque psoriasis and other vitamin D related diseases without causing harm. It may have major promise in treating Covid-19 infections, where therapy with "higher than usual" doses probably need to be given only short term given the nature of the clinical course of Covid-19 infections. This was shown to be a successful treatment strategy for chronic tuberculosis infections in the 1940s. Current definitions of normal and excessive serum 25OHD concentrations need to be re-evaluated based on the clinical data reviewed in this manuscript. The therapeutic index of vitamin D in the treatment of human disease needs to be better defined.

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