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ARTICLE

Oral vitamin D_3 supplementation for chronic plaque psoriasis: a randomized, double-blind, placebo-controlled trial

Michelle A. Ingram[a], M. Beatrix Jones[b], Welma Stonehouse[c], Paul Jarrett[d,e], Robert Scragg[f], Owen Mugridge[a] and Pamela R. von Hurst[a]

[a]School of Sport, Exercise and Nutrition, Massey University, Albany Campus, North Shore City, Auckland, New Zealand; [b]Institute of Natural and Mathematical Sciences, Massey University, Albany Campus, North Shore City, Auckland, New Zealand; [c]Food and Nutrition Flagship, Commonwealth Scientific and Industrial Research Organisation, Adelaide, South Australia, Australia; [d]Department of Dermatology, Middlemore Hospital, Otahuhu, Auckland, New Zealand; [e]Department of Medicine, The University of Auckland, Auckland, New Zealand; [f]School of Population Health, The University of Auckland, Auckland, New Zealand

ABSTRACT

Purpose: The management of psoriasis remains a challenge for dermatologist and patient. This study aimed to determine whether vitamin D_3 supplementation improves psoriasis compared to placebo.

Materials and methods: In a randomized, doubled-blind, placebo-controlled trial, 101 participants ≥18 years with psoriasis were grouped by severity and allocated to 100,000 International Units (IU) vitamin D_3/month for 12 months (200,000 IU at baseline; $n = 67$) or an identical placebo ($n = 34$). Psoriasis Area and Severity Index (PASI) and serum 25(OH)D concentrations were assessed at 3-monthly intervals. The primary outcome was the difference in PASI between groups over time. The relationship between 25(OH)D and PASI across the sample was also considered in a *post hoc* analysis.

Results: PASI did not differ between groups at any time (group $F(1, 104) = 0.48$, $p = .49$; group*time $F(4, 384) = 0.26$, $p = .90$). However, 25(OH)D increased in both groups, rendering these findings inconclusive. A significant inverse relationship existed between PASI and 25(OH)D, with elevation of 25(OH)D by up to 125 nmol/L associated with mild decreases in PASI (estimated range of decrease 0–2.6; $p = .002$).

Conclusions: A direct benefit of vitamin D_3 supplementation for psoriasis could not be determined. However, these findings suggest a relationship between 25(OH)D and psoriasis severity, at least in some subgroups.

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Vitamin D; psoriasis; supplementation; randomized

Introduction

Vitamin D can regulate keratinocyte proliferation and differentiation, and modulate the immune response (1), and analogs of topical vitamin D are a well-established treatment for mild-to-moderate psoriasis. However, the management of psoriasis remains a challenge for both the physician and the patient, and no available treatments are universally beneficial, convenient, or without associated risks (2).

In past decades, there has been interest in whether supra-physiologic doses of oral 1,25-(OH_2)D, the hormonally active form of vitamin D, or its analogs, can treat psoriasis (3–7). While some findings showed promise, results were inconsistent, and most studies were limited by small numbers of participants, short time frames, lack of control groups, and open-label dosing. Furthermore, the calciotropic actions of 1,25-(OH_2)D and its analogs meant managing the risk of hypercalcemia was a challenge. More recently, findings from several studies have shown a significant inverse relationship between serum 25(OH)D concentration, the best indicator of vitamin D status (8,9), and severity of psoriasis (10–14). This suggests that raising 25(OH)D through supplementation of vitamin D_3 (cholecalciferol), which is safe (15), inexpensive and widely available, might be beneficial for psoriasis. In a recent open-label pilot study, oral vitamin D_3 led to significant improvements for all 9 psoriasis patients (12).

The objective of this trial was therefore to determine if oral vitamin D_3 supplementation is an effective treatment for psoriasis. It was hypothesized that supplementation with 200,000 IU vitamin D_3 at baseline followed by 100,000 IU/month would lead to a significant improvement in psoriasis over a 12-month period compared to placebo.

Materials and methods

Study design and participants

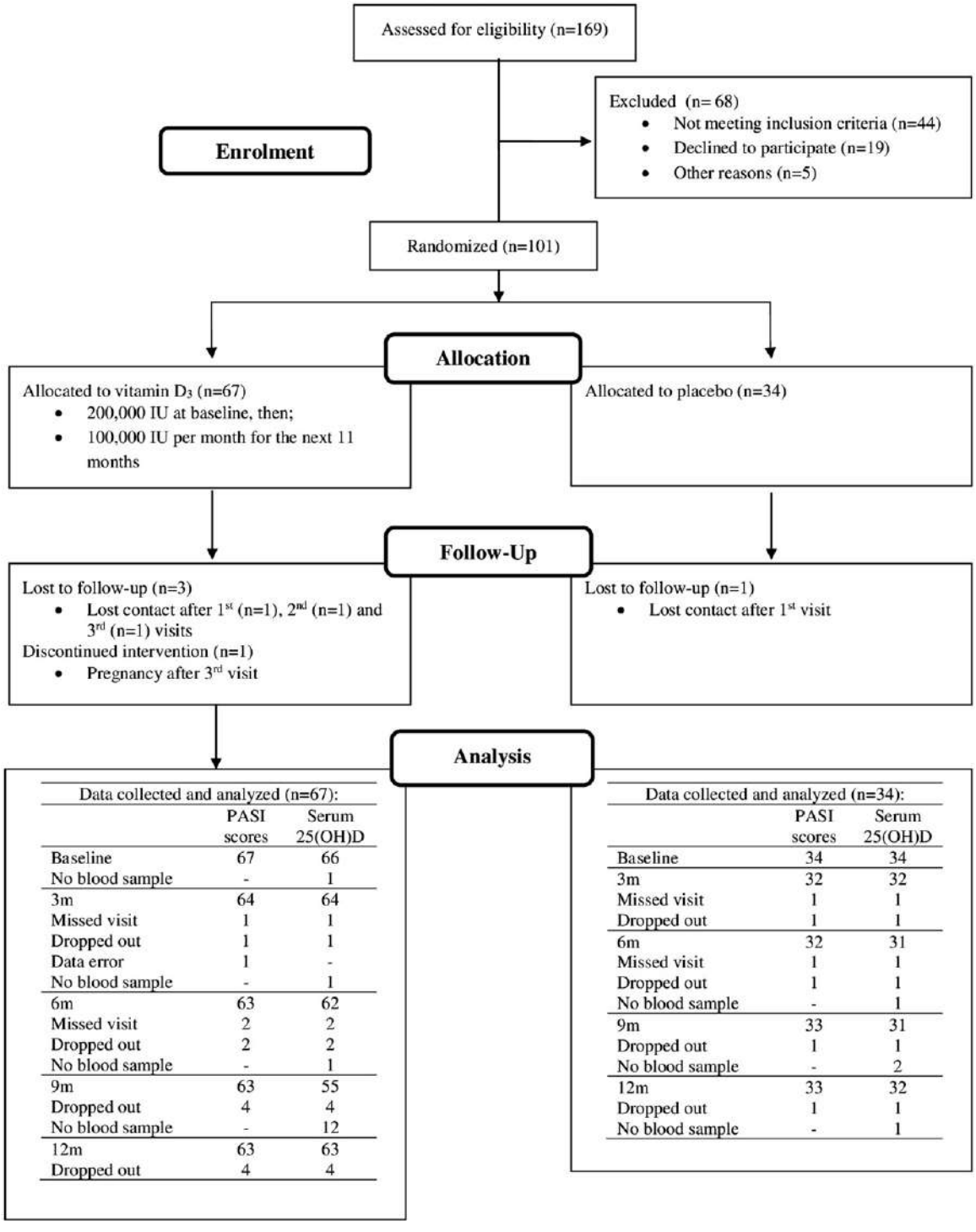
This was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at Massey University's Human Nutrition Research Unit (HNRU) in Auckland, New Zealand (latitude 37°S). A 2:1 ratio of treatment:placebo was chosen with the aim of enhancing recruitment (16).

Recruitment was conducted between April 2012 and March 2013 through local medical centers and dermatologists, newspaper articles, a database of people interested in nutrition

CONTACT Michelle A. Ingram michelle.a.ingram@gmail.com School of Sport, Exercise and Nutrition, Massey University, Albany Campus, Private Bag 102904, North Shore City, Auckland 0745, New Zealand

research at the university, and online advertisements (social media, the university website, and a research website). Respondents completed an online screening questionnaire. Eligible participants were ≥18 years with chronic plaque psoriasis. Exclusion criteria were chronic kidney or liver disease; smoking; vitamin D supplements ≥1000 IU/day currently or within the last 2 months; pregnancy, lactation, or planned pregnancy in the next year; and UVB phototherapy. Psoriasis treatments used for longer than 3 months immediately prior to the trial were permitted. For ethical reasons, participants were not prohibited from starting new treatments during the trial period but were asked to do so only if necessary, and to document the start date, the dose and the frequency so these could be accounted for in analysis.

Respondents meeting these criteria visited the HNRU for a skin assessment and other baseline measurements (see below), and presence of psoriasis was confirmed by the study's dermatologist (PJ). One hundred and one participants were eligible and were grouped according to psoriasis severity then randomized onto treatment ($n = 67$) or placebo ($n = 34$). Over the trial period, four participants in the treatment group and one in the placebo group discontinued the intervention or were lost to follow-up (Figure 1).



Data collected and analyzed (n=67):	PASI scores	Serum 25(OH)D
Baseline	67	66
No blood sample	-	1
3m	64	64
Missed visit	1	1
Dropped out	1	1
Data error	1	-
No blood sample	-	1
6m	63	62
Missed visit	2	2
Dropped out	2	2
No blood sample	-	1
9m	63	55
Dropped out	4	4
No blood sample	-	12
12m	63	63
Dropped out	4	4

Data collected and analyzed (n=34):	PASI scores	Serum 25(OH)D
Baseline	34	34
3m	32	32
Missed visit	1	1
Dropped out	1	1
6m	32	31
Missed visit	1	1
Dropped out	1	1
No blood sample	-	1
9m	33	31
Dropped out	1	1
No blood sample	-	2
12m	33	32
Dropped out	1	1
No blood sample	-	1

Figure 1. CONSORT flow diagram of participants through different phases of the study.

Ethics and trial registration

This study was conducted according to the Declaration of Helsinki guidelines and all procedures involving human participants were approved by the New Zealand Health and Disability Ethics Committee (NTX/11/07/063/AM01). It was registered with the Australian New Zealand Clinical Trials Registry (http://www.ANZCTR.org.au), #12611000648921 prior to its commencement. All participants provided informed, signed consent before undergoing any assessments.

Study procedures

Participants attended appointments every three months for a total of five visits over a one-year period. At each visit, psoriasis was assessed by a trained researcher using the Psoriasis Area and Severity Index score (PASI) (17), then classified as mild (<7), moderate (7–12) or severe (>12) (18).

Serum 25(OH)D concentration was measured at all visits, and serum calcium and albumin were assessed at baseline, 3, and 12 months to monitor for hypercalcemia. High-sensitivity C-reactive protein (hsCRP) was measured at baseline, 6, and 12 months, due to the potential of systemic inflammation to confound vitamin D status (19).

Other baseline characteristics included demographics, Fitzpatrick skin type (20), and anthropometrics: height was measured twice using a standardized method, and body weight and fat percentage were assessed using bioelectrical impedance analysis (InBody 230, Biospace Co. Ltd., Seoul) by a trained researcher following a standardized procedure, with follow up measurements at 12 months. Psoriasis characteristics were age of onset, known family history, typical seasonal changes, details of current treatments and presence of psoriatic arthritis. Any other health conditions, or medications thought to exacerbate psoriasis (beta blockers, lithium, systemic steroids, interferon, antimalarials, tetracyclines, or non-steroid anti-inflammatory drugs [NSAIDs]) (21) were noted.

At visits 2–5, any changes to psoriasis treatment or non-psoriasis medication, or any major changes in sun exposure, were recorded.

Randomization and blinding

To group participants with a 2:1 ratio according to psoriasis severity, 38 blocks of three randomly ordered treatment allocations (1, 2, and 3) were computer-generated. A third party, a pharmacist not otherwise involved in this research, designated two numbers as vitamin D and one as placebo, and allocated the capsules into identical bottles. Bottled capsules were stored in boxes labeled 1, 2, or 3 until allocated to participants. All study personnel remained blinded until the trial concluded and 25(OH)D concentrations were analyzed. Following baseline appointments, participants were assigned to the next available slot in a block of three, grouped according to psoriasis severity, which corresponded to group 1, 2, or 3.

Vitamin D and placebo interventions

Vitamin D_3 (cholecalciferol) was given as a monthly mega-dose (200,000 IU at baseline, followed by 100,000 IU per month, equivalent to 3340 IU per day) taken as gelatin capsules. The placebo capsule was identical in appearance and composition, but contained no vitamin D_3. All capsules were supplied by Tishcon Corporation (Westbury, NY). The first three months' capsules were couriered to participants, and they received subsequent capsules at each appointment.

Compliance

Participants were reminded by text message, email or phone to take their capsule on the same day each month, then confirmed they had done so, with researchers following up when required. Taking the capsule within one week on either side of their designated day was considered compliant.

Biochemical analyses

Serum was collected, and all samples were frozen in separate aliquots in small non-reactive Eppendorf tubes and stored at −80 °C until analysis. Serum 25(OH)D was measured using an automated immunoassay (ADVIA Centaur Vitamin D Total Assay, Siemens Healthcare Diagnostics Inc. [Tarrytown, NY]), which has an assay range of 9.2 nmol/L to 374 nmol/L and a CV of 4.8%–11.1% (22). For the purpose of baseline vitamin D status classification in this study, deficiency was defined as serum 25(OH)D <50 nmol/L, insufficiency as 50–74 nmol/L and sufficiency as ≥75 nmol/L (23).

Serum calcium was measured with the Dimension Vista System using the CA method (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) and was adjusted for albumin. Normal serum calcium was within the range 2.1–2.6 mmol/L. Serum hsCRP was measured with the Dimension Vista System CardioPhase method (Siemens Healthcare Diagnostics Inc. [Tarrytown, NY]). Average hsCRP concentration was defined as 1.0–3.0 mg/L. Biomarker analysis was carried out by an accredited laboratory (North Shore Hospital Laboratory, Auckland, New Zealand).

Statistical analysis

All statistical analyses were conducted using SPSS Statistics version 20.0. Power calculations were conducted using Glimmpse (version 2.0.0), based on detecting a 50% reduction in PASI over 5 visits. Taking the 2:1 randomization into account and assuming a gradual improvement in PASI over 12 months in the vitamin D group, a sample size of 99 was required to detect an effect of treatment, at 80% statistical power and an α-level of .05.

Baseline characteristics are given as mean (SD) for normally distributed variables, median [25th, 75th percentiles] for non-normally distributed variables, and geometric mean [95% CI] where a natural log transformation was used. The Independent *T*-test or Mann Whitney test was used to determine baseline differences in continuous data. The Kruskal–Wallis test was used to compare baseline PASI scores according to season of trial commencement.

All differences between and within groups over time were assessed using linear mixed models with a random intercept per person, which controlled for baseline variability between participants and correlated scores within participants.

To assess difference in PASI between groups at each time point (group*time), hsCRP and body fat percentage were included as covariates due to baseline differences between groups. To account for the effect of changes in treatment use over time, variables capturing changes to systemic/biologic treatments (−1 = decreased/stopped, 0 = no change or none, and 1 = increased/started), use of new topical treatments and frequency of topical treatments per week were also included in the model. As residuals versus predicted values plots showed non-homogeneity of variance, the natural log of PASI was used (following addition of a constant so that the minimum value was one (24)).

When assessing differences in serum 25(OH)D concentration between groups over time, body fat percentage was also included as a covariate due to its impact on change in 25(OH)D following vitamin D supplementation (25).

A non-predetermined, exploratory analysis was also conducted to identify whether an independent relationship existed between serum 25(OH)D concentration and PASI score over time across the whole sample. Ln PASI was the dependent variable, and initially entered as fixed factors/covariates were body fat percentage, hsCRP level, frequency of topical treatments per week, age of diagnosis, Fitzpatrick skin type, season, gender, known family history of psoriasis, 'summer responder', diagnosed psoriatic arthritis, started new topical treatment in past 3 months, on systemic or biologic psoriasis treatment, started/stopped/changed systemic or biologic treatment in past 3 months, on beta-blockers, on systemic steroids, on antimalarials, on NSAIDs and on tetracyclines. Multicollinearity was assessed by inspection of a correlation matrix. Variables with the largest p values $>.05$ were individually removed from the model until all remaining variables were considered significant contributors to the variance in PASI score.

As the beta-coefficients derived from the model could not be directly interpreted due to the log-transformation of PASI, they were used to calculate the estimated average improvement (EAI) in PASI score for each participant at different increases in serum 25(OH)D. The EAIs show the hypothetical improvement in PASI following increases in 25(OH)D based on the fitted model. EAIs in PASI for each person were calculated up to the highest 25(OH)D concentration achieved by a participant in the same body fat percentage category.

The direction of the relationship between PASI and serum 25(OH)D concentration for individual participants was also assessed using Pearson's correlations.

All reported p values were based on 2-tailed tests, and $p < .05$ was considered statistically significant.

Results

Participant characteristics

Participant characteristics at baseline are in Table 1. The groups were similar in PASI score, serum 25(OH)D concentration, age, number of years with psoriasis, family history of psoriasis, weight, BMI, and education level. A higher percentage of the placebo group was deficient or insufficient in vitamin D at baseline compared to the treatment group. The placebo group had a significantly higher mean serum hsCRP level ($t(98) = 2.231$, $p = .028$), and trended towards higher body fat percentage ($t(99) = 1.91$, $p = .058$). There was no difference in baseline PASI between participants who began the trial in different seasons ($H(3) = 0.608$, $p = .90$).

PASI scores

PASI scores are reported in Table 2. PASI did not differ between groups over the five time points (treatment group $F(1, 104) = 0.48$, $p = .49$; treatment group*time $F(4, 384) = 0.26$, $p = .90$) when adjusting for differences in hsCRP, body fat percentage, changes in treatment use, and individual variation. A comparable proportion of people in the vitamin D group (11.9%) and placebo group (11.8%) achieved at least a 50% reduction in PASI by 12 months. Both groups showed statistically significant improvements in mean PASI score: in the vitamin D group, there was a trend towards a significant difference from baseline at 6 months ($p = .06$), and PASI score was significantly lower than baseline at 9 months and 12 months (both $p = .02$). In the placebo group, PASI had significantly improved from baseline at 6 months ($p = .03$), 9 months ($p = .02$), and 12 months ($p < .01$) (Table 2). In the model, changes to systemic/biologic treatments and starting a new topical treatment in the past 3 months were both significant contributors to the variation in PASI score over time ($p = .05$ and $p = .03$, respectively), suggesting some of this improvement was due to changes in treatment regimens.

Serum 25(OH)D concentrations

The treatment group had a significantly higher 25(OH)D concentration than the placebo group from 3 to 12 months ($p < .001$ for comparison at 3 and 6 months, and $p = .002$ for comparison at 9 months) (Figure 2). In the treatment group, mean 25(OH)D increased from 62 nmol/L to 96 nmol/L by 3 months (mean difference 33 [95% CI 27–38] nmol/L; $F(4, 245) = 81.70$, $p < .001$), reaching a plateau around 103 nmol/L from 6 months onwards. Seventy-nine percent of the vitamin D group had achieved vitamin D sufficiency by 3 months, and this reached 87% by 9 months (Table 3). The remainder of participants in that group achieved 25(OH)D concentrations >50 nmol/L, except for 3 people who became deficient again at 12 months. The maximum serum 25(OH)D reached in the treatment group was 194 nmol/L.

In the placebo group, mean 25(OH)D also increased significantly between 3 and 6 months to 78 nmol/L ($p < .001$) (Figure 2), which was an increase of 24 [95% CI 17–30] nmol/L from baseline ($p < .001$). Sixty-two percent of the placebo group was vitamin D sufficient by 6 months, and mean serum 25(OH)D concentrations in the placebo group remained similarly elevated at 9 and 12 months.

Relationship between serum 25(OH)D and PASI

A significant inverse association was observed between serum 25(OH)D and PASI ($F(1, 409) = 9.52$, $p = .002$) after adjusting for gender, body fat percentage, starting a new topical treatment, or change in systemic/biologic treatment, in the past 3 months, and individual variability in PASI at baseline (Table 4; Figure 3). There was significant variance in intercepts (baseline PASI scores) across participants (SD of intercepts [range of transformed PASI scores] $= 0.5$ [0.4–3.1], $\chi^2(1) = 485.76$, $p < .01$), but no variance in slopes (the relationship between serum 25(OH)D and PASI over time between participants; $\chi^2(1) = 0.08$, $p > .05$). The strongest correlation between variables entered in the model was $r = 0.58$ (psoriatic arthritis and use of systemic/biologic treatment), with all others <0.4, indicating multicollinearity was not a concern.

Elevation of serum 25(OH)D by amounts from 25 nmol/L to 125 nmol/L (the greatest increase observed in this study) was associated with small decreases in PASI (range of decrease 0–2.6). Table 5 gives the estimated average improvements from baseline PASI at different increments between these concentrations. The variability in baseline PASI across the sample is reflected in the range of improvement at each increment of serum 25(OH)D. Due to the apparent non-linear relationship between PASI and 25(OH)D, the degree of estimated improvement was greater in those with higher initial PASI scores.

As visual inspection of the data suggested that not every participant who increased their serum 25(OH)D concentration improved their PASI score, individual correlations between serum 25(OH)D and PASI were explored and showed that an inverse relationship was present in 61 of 97 people (63%). The range of correlations was -0.98 to 1, and the distribution of correlations was similar between groups.

Table 1. Participant characteristics at baseline by group.

	Vitamin D[a] ($n = 67$)	%, (SD) or [25th, 75th]	Placebo[a] ($n = 34$)	%, (SD) or [25th, 75th]
Gender (male)	39	58%	17	50%
Age (years)	50.7	(13.4)	46.7	(13.7)
Age of diagnosis (years)	28.0	[16.0, 40.0]	24.5	[15.8, 40.0]
Years with psoriasis	18.0	[10.0, 31.0]	14.0	[6.0, 30.3]
Ethnicity[b]	($n = 66$)			
NZ European	55	82%	26	77%
Maori or Pacific	4	6%	4	12%
Asian	1	1.5%	3	8.8%
European	4	6.0%	3	8.8%
Other	4	6.0%	0	0%
Weight (kg)	81.3	[77.7–85.1]	83.0	[76.2–90.3]
BMI (kg/m^2)	27.3	[26.2–28.5]	28.7	[26.9–30.6]
Body fat (%)	31.7[c]	(8.8)	35.2	(8.2)
PASI score	5.2	[3.3, 6.5]	4.2	[3.1, 7.0]
Serum 25(OH)D (nmol/L)	($n = 66$) 62	(26)	55	(19)
Vitamin D status:	($n = 66$)			
Very deficient (< 25 nmol/L)	3	5%	2	6%
Deficient (25–49 nmol/L)	18	27%	12	35%
Insufficient (50–74 nmol/L)	25	38%	16	47%
Sufficient (75–250 nmol/L)	20	30%	4	12%
hsCRP (mg/L)	($n = 66$) 1.21[d]	[0.94–1.57]	2.01	[1.37–2.93]
Fitzpatrick skin type:				
I	1	2%	1	3%
II	12	18%	4	12%
III	27	40%	17	50%
IV	22	33%	10	29%
V	5	7.5%	2	6%
Known family history psoriasis (y)	29	43%	15	44%
Residential area:	($n = 66$)			
Urban	8	12%	3	9%
Suburban	47	70%	28	82%
Rural	11	16%	3	9%
Highest qualification:	($n = 66$)			
None	5	8%	1	3%
Secondary school	15	22%	10	29%
Trade/technical	10	15%	5	15%
Diploma/Bachelors	24	36%	11	33%
Postgraduate	7	11%	5	15%
Professional	5	8%	2	6%
Work status:				
Employed	51	76%	29	85%
Unemployed (not retired)	2	3.0%	0	0%
At-home parent/student	5	7.5%	2	5.9%
Retired	9	13.4%	3	8.8%

25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; hsCRP: high sensitivity C-reactive protein; NZ: New Zealand; PASI: Psoriasis Area and Severity Index.
[a]Data are number (%), mean (SD), median [25th, 75th percentile], except weight, BMI and hsCRP, which are geometric mean [95% CI].
[b]7 participants identified as two ethnicities; 'Other' includes American, Australian, British, and South African.
[c]$p = .058$ for trend towards difference between groups.
[d]Significantly different to placebo, $p = .028$.

Table 2. PASI scores over 12 months by group.

	Vitamin D					Placebo				
	n	Unadjusted PASI score[f]	25th, 75th percentile	Min, Max	Adjusted PASI score[a,g]	n	Unadjusted PASI score[f]	25th, 75th percentile	Min, Max	Adjusted PASI score[a,g]
0m	67	5.2	3.3, 6.5	0.4, 21.8	4.8	34	4.2	3.1, 7.0	0.8, 13.2	4.5
3m	64	4.7	2.9, 6.8	0.1, 22.0	4.5	32	3.6	2.7, 7.0	0.6, 15.8	4.1
6m	63	4.6	2.6, 7.0	0.2, 23.2	4.4[b]	32	3.4	1.9, 7.9	0.5, 18.6	3.9[c]
9m	63	4.0	2.2, 5.9	0.4, 22.0	4.0[d]	33	3.6	1.9, 6.5	0.4, 16.4	3.8[c]
12m	63	3.7	2.0, 6.4	0.1, 19.4	3.9[d]	33	3.4	2.4, 4.9	0.3, 14.6	3.5[e]

PASI: Psoriasis Area and Severity Index.
[a]No difference in PASI scores between groups over time (treatment group $F(1, 104) = 0.48$, $p = .49$; treatment group*time $F(4, 384) = 0.26$, $p = .90$).
[b]Trend towards significant difference to baseline, $p = .06$.
[c]Significantly different to baseline, $p < .05$.
[d]Significantly different to baseline, $p < .001$.
[e]Significantly different to baseline, $p = .001$.
[f]Values are median.
[g]Values are average predicted PASI scores for an individual with mean high-sensitivity C-reactive protein level and body fat percentage as calculated using a linear mixed model with a random intercept per person; values are back-transformed from ln(PASI +0.9).

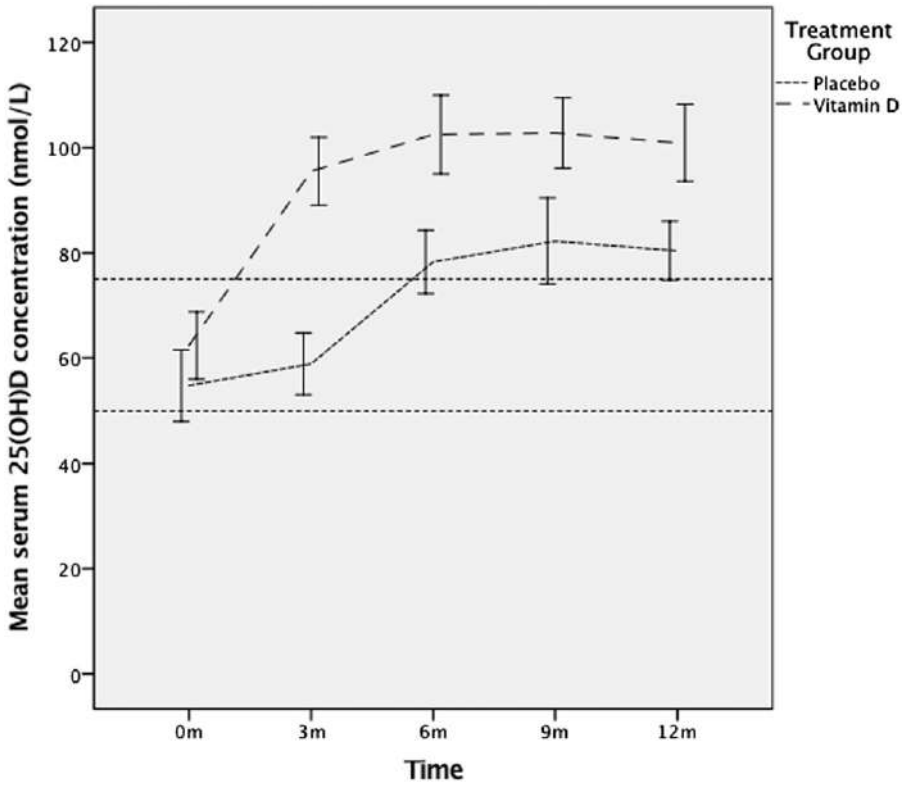


Figure 2. Mean serum 25(OH)D concentrations over 12 months in each group. Error bars represent 95% confidence intervals. Reference lines are at 75 nmol/L (vitamin D sufficiency) and 50 nmol/L (below which is vitamin D deficiency) (7).

Table 3. Percentage of participants in each group according to vitamin D status[a].

	Treatment ($n = 67$) %			Placebo ($n = 34$) %		
	<50 nmol/L	50–74 nmol/L	≥75 nmol/L	<50 nmol/L	50–74 nmol/L	≥75 nmol/L
0m	31	37	30	41	47	12
3m	0	21	79	26	47	26
6m	0	16	84	3	35	62
9m	0	13	87	3	38	59
12m	4	9	87	0	32	68

[a]<50 nmol/L, deficiency; 50–74 nmol/L, insufficiency; ≥75 nmol/L, sufficiency (7).

Table 4. Linear mixed model beta-coefficients and 95% confidence intervals for variables associated with log-transformed PASI score[a].

	β	SE β	95% CI	p value
Intercept	.518	.269	−.011 to 1.047	.055
Serum 25(OH)D	−.002	.001	−.003 to −.001	.002
Body fat %	.016	.006	.005 to .027	.006
New topical in past 3m	.122	.053	.071 to .266	.022
Systemic/biologic in past 3m				
Decreased or stopped	.498	.184	.136 to .861	.007
No change or none	.265	.132	.006 to .525	.045
Increased or started	(reference)			
Gender (male)	.640	.109	.425 to 1.23	<.001

25(OH)D: 25-hydroxyvitamin D; PASI: Psoriasis Area and Severity Index.
[a]$n = 101$; dependent variable is ln PASI +0.9.

Compliance

Compliance was high, with 96% of capsules taken within two weeks of their designated day. An effect of missed or delayed capsules on serum 25(OH)D concentration, if any, was not apparent from the data. All participants who missed or delayed capsules were included in data analysis based on the intention-to-treat principle.

Safety

There was no evidence of vitamin D toxicity in participants. All but one participant had serum calcium levels <2.6 mmol/L at baseline, 3 and 12 months. That participant had an adjusted calcium level of 2.65 mmol/L (unadjusted level 2.35 mmol/L) at baseline, but levels at 3 and 12 months were normal. No adverse effects of taking the capsules were reported.

Discussion

The findings of this research did not demonstrate a benefit of oral vitamin D_3 for psoriasis, as there were no differences in PASI scores between those taking 100,000 IU of vitamin D_3 a month and those taking an identical placebo when assessed at 3-monthly intervals over a 12-month period. However, these results are inconclusive when also considering serum 25(OH)D concentrations, as these significantly increased in the placebo group as well as the treatment group. A *post hoc* analysis of the relationship between PASI score and serum 25(OH)D concentration across the whole sample suggests that at a population level, higher vitamin D levels are associated with less severe psoriasis.

Both the vitamin D and placebo groups demonstrated similarly improved PASI scores compared to baseline from around 6 and 9 months, albeit to a mild degree, alongside elevated serum 25(OH)D concentrations. The increase in serum 25(OH)D in both groups meant we could not place confidence in our null findings, as the difference in 25(OH)D between groups from 6 months onwards was only ~25 nmol/L, and a discrepancy of this size is possibly too small to have allowed for detection of any beneficial effect of vitamin D. For instance, this difference was much smaller than the increase of 228 nmol/L in Finamor et al. (12), in which marked improvement in psoriasis was seen, and even the

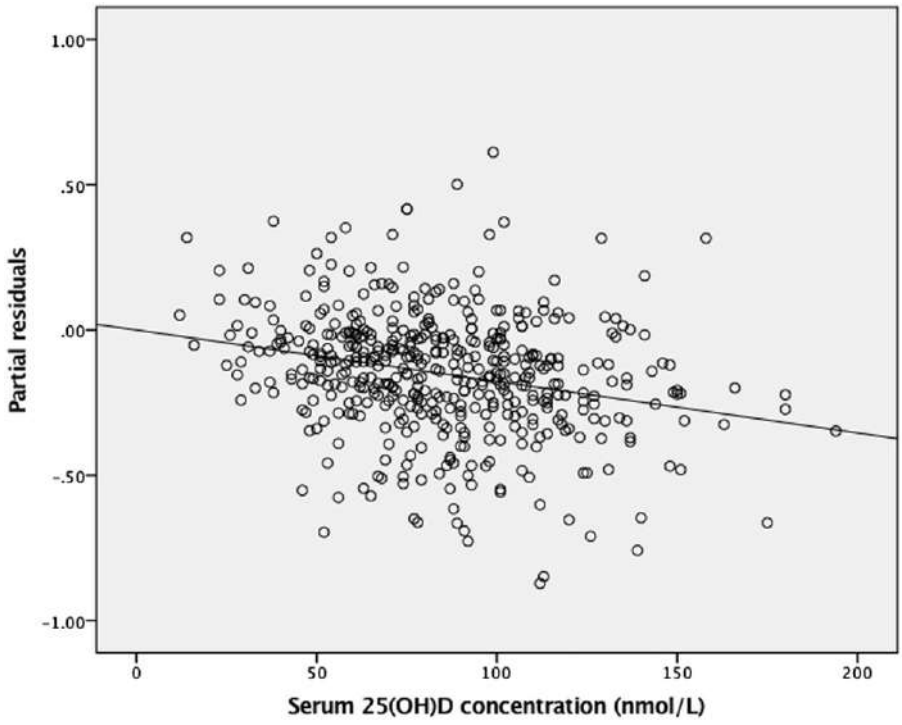


Figure 3. Partial residual plot showing the association of serum 25(OH)D concentration with PASI score while controlling for gender, body fat, use of new topical treatments and change of systemic/biologic treatments in the previous 3 months and individual effects (469 time-points from 101 participants during the 12 month follow-up period). 25(OH)D: 25-hydroxyvitamin D; PASI: Psoriasis Area and Severity Index. A partial residual plot shows the relationship between one predictor variable (in this case, serum 25(OH)D concentration) and the dependent variable (PASI) while controlling for the effects of other predictor variables.

Table 5. Estimated average decreases in PASI scores at increments of change in serum 25(OH)D concentration[a].

	Increase in serum 25(OH)D concentration (nmol/L)				
Initial PASI score[b]	25	50	75	100	125
0.6–3.4 ($n = 34$)	0–0.1	0.1–0.3	0.1–0.4 ($n = 24$)	0.2–0.5 ($n = 12$)	0.3–0.6 ($n = 5$)
3.6–6.9 ($n = 39$)	0.1–0.2	0.3–0.5 ($n = 35$)	0.4–0.7 ($n = 30$)	0.5–0.9 ($n = 17$)	0.6–0.9 ($n = 8$)
7.1–11.5 ($n = 17$)	0.2–0.4	0.5–0.7 ($n = 15$)	0.7–1.0 ($n = 11$)	0.9–1.3 ($n = 5$)	1.1–1.6 ($n = 2$)
12.0–22.3 ($n = 9$)	0.4–0.7 ($n = 8$)	0.8–1.4 ($n = 8$)	1.2–2.0 ($n = 6$)	1.6–2.1 ($n = 4$)	2.6 ($n = 1$)

25(OH)D: 25-hydroxyvitamin D; PASI: Psoriasis Area and Severity Index.
[a]As serum 25(OH)D was inversely correlated with body fat percentage, the highest change in 25(OH)D used to estimate PASI for each person was the maximum observed increase in 25(OH)D achieved by a participant in the same body fat category as that person. *N* for each increment of 25(OH)D refers to the number of participants in the same body fat category as the participant who achieved the largest increase in serum 25(OH)D.
[b]Initial PASI scores are those predicted by the linear mixed model at baseline; ranges are based on psoriasis severity: 0.1–6.9 = mild; 7–12 = moderate; <12 = severe (15). 'Mild' was split to further differentiate between low and high mild scores.

~65 nmol/L increase in trials where UVB phototherapy led to a significant difference in psoriasis between groups (14,26).

Our findings highlight a challenge of conducting controlled studies of vitamin D supplementation, as unlike for other nutrients or pharmacological interventions, vitamin D levels are not primarily determined by intake, but rather through sun exposure, and thus it is difficult to ensure a true control group. To our knowledge, only one other randomized controlled trial of vitamin D supplementation has been published, and also found no significant difference in PASI between the treatment and placebo groups (27). That trial ran concurrently to ours, and gave the same dose of vitamin D_3 to older participants (>50 years) with mild psoriasis over 12 months (27). Unlike in the current study, the authors could not assess serum 25(OH)D concentrations in the placebo group, and were therefore unable to confirm these remained relatively stable and that supplementation had led to the expected difference in 25(OH)D between groups; this would have been of interest as small improvements in PASI also appeared to occur in each group.

Because both groups in our trial showed an overall improvement in psoriasis as well as an increase in serum 25(OH)D, we felt it was important to determine if there was a relationship between these variables. The significant inverse association we observed between PASI and 25(OH)D concentration supports a benefit of higher vitamin D levels for psoriasis, at least at a population level. Propositions about a connection between serum 25(OH)D and psoriasis have thus far been tentative, with inverse relationships noted in some studies (10–14) but not others (28,29). However, in those studies where no relationship was found, analysis was limited to one measurement of 25(OH)D and PASI from each person (28,29), whereas the relationship observed in our study was based on five regular observations over a 12-month period. Furthermore, our analysis accounted for the repeated-measure nature of these observations, the natural individual variation in psoriasis that

occurs between people, and the influence of several other confounders. Our data also suggest the relationship between PASI and 25(OH)D may be non-linear, which could explain the lack of correlation found in some studies. Therefore, although our finding of a relationship between serum 25(OH)D and PASI was based on a *post hoc* analysis, it does suggest that, despite the null findings of Jarrett et al. (27), it may still be worth exploring the potential of elevating vitamin D through supplementation for psoriasis.

The estimated average improvements in PASI scores based on increasing 25(OH)D were very small from a clinical perspective, with the largest estimated improvement being 2.6, from an initial PASI of 17.7, following an increase of 125 nmol/L. Yet, it is important to note that the model from which these estimated average improvements were derived was based on a sample of individuals who were considerably heterogeneous in terms of the relationship between serum 25(OH)D and PASI. Correlation analysis at an individual level showed that higher serum 25(OH)D was associated with lower PASI score in just two-thirds of our participants, suggesting some might respond to elevated vitamin D levels, while others might not. Amongst those who did show an inverse relationship between 25(OH)D and PASI, there was also considerable variability in the degree of change, with 3.8–87% being the average range of observed improvement in PASI across all visits. Also, of the participants whose psoriasis had improved by 3 months, only half ($n = 18$) still had some improvement from baseline at all subsequent visits, perhaps reflecting aggravation of psoriasis by other unknown factors that overrode any benefit of vitamin D. Based on this apparent variability in the relationship between serum 25(OH)D and PASI amongst individuals, the estimated improvements should therefore be considered as the average reduction in PASI that may be associated with elevating serum 25(OH)D across a population, with any individual improvements varying considerably around that average. It is therefore also possible that more clinically significant improvements may be seen in some individuals following elevation of serum 25(OH)D compared to others.

The variability we observed in the relationship between 25(OH)D and PASI amongst participants is in line with previous research into psoriasis, which has noted a widely variable response to both topical vitamin D analogs and oral calcitriol between individuals (3–6,30,31), as well as a differentiation between 'responders' and 'non-responders' in terms of clinical improvement (32). Some studies have shown associations between VDR polymorphisms and degree of response to topical vitamin D (33–35), but so far, findings between studies have been inconsistent (36). It has also been proposed that people with psoriasis might require higher 25(OH)D concentrations than the general population, allowing them to compensate for a relative resistance to vitamin D due to genetic polymorphisms related to vitamin D metabolism (12). We were unable to consider genetic variability in this study to identify if this was a factor in relation to response to supplementation. With regards to the 37% of people in the current study who did not demonstrate a relationship between 25(OH)D and PASI, it is therefore also unclear whether they are unresponsive to vitamin D, whether other unknown factors are overriding any potential effect of vitamin D, or whether they may require a higher serum 25(OH)D concentration to see any effect.

Although the findings of the present study cannot demonstrate response or non-response to vitamin D at a cellular level, the presence of an inverse relationship between serum 25(OH)D and PASI at both higher and lower concentrations of 25(OH)D supports the conclusion that increased levels of vitamin D may have contributed to the improvements in psoriasis in both groups. Had the relationship only been observed at higher concentrations, it might have suggested that serum 25(OH)D was instead acting as a proxy for other benefits of sunlight. The presence of this inverse relationship across the range of 25(OH)D concentrations also makes it unlikely that elevating 25(OH)D was only of benefit to psoriasis in those who were initially deficient in vitamin D (<50 nmol/L).

The major limitation of this study was the unexpected increase in 25(OH)D in the placebo group, and the reason for this increase is not clear. It was not a seasonal effect, as most 6 month visits took place in winter or summer (41% or 32% of placebo group, respectively), and mean 6 month 25(OH)D in winter (85 ± 15 nmol/L) was higher than in summer (78 ± 18 nmol/L). Several participants for whom 25(OH)D increased at this time reported more recent sun exposure compared to normal; conversely, some reported no change or less sun than normal. However, sun exposure was not formally measured, and it is possible for serum 25(OH)D to increase quickly and dramatically following exposure of skin to the sun under the right conditions (37). It is possible some participants may have increased sun exposure subconsciously, particularly after having learned of the links between vitamin D and psoriasis, or assumed they were on the placebo after the initial few months and decided to self-supplement with vitamin D_3.

The sample size for this study was calculated based on improving PASI by at least 50%, at which quality of life tends to improve (38). In hindsight, the degree to which this form of oral vitamin D_3, and potentially also the dose used, might have an independent effect on psoriasis was possibly overestimated, particularly in light of the fact that use of other treatments (if already established) was permitted. If this were the case, a larger sample size would have been required to allow detection of differences in PASI between groups.

In conclusion, these findings are unable to confirm whether supplemental vitamin D_3 is beneficial for psoriasis, but do provide further support for the notion that higher serum 25(OH)D concentrations are associated with less severe psoriasis, at least in some of the psoriatic population. Additionally, this study has highlighted the challenge of controlling placebo group 25(OH)D concentrations in trials of vitamin D_3 supplementation. Further research into the factors differentiating response to vitamin D in those with psoriasis would be most useful. Until then, it seems reasonable to ensure that vitamin D levels in psoriasis patients are at least at a level of sufficiency (≥75 nmol/L), and for awareness amongst medical professionals that a relationship between higher 25(OH)D concentrations and PASI score may be present in some (as yet undefined) patient subgroups.

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ORCID

Michelle A. Ingram http://orcid.org/0000-0003-1698-3593
M. Beatrix Jones http://orcid.org/0000-0001-9685-020X
Welma Stonehouse http://orcid.org/0000-0002-2856-4962
Paul Jarrett http://orcid.org/0000-0001-5030-8896
Robert Scragg http://orcid.org/0000-0003-0013-2620
Pamela R. von Hurst http://orcid.org/0000-0001-6326-7501

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