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Phototherapy Enhanced Vitamin D Level in Psoriasis.

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ABSTRACT

Phototherapy: broadband UVB (BUVB), narrowband UVB (NB-UVB) and heliotherapy) is commonly used treatment modalities for widespread psoriasis. Vitamin D3, cholecalciferol, is produced in the epidermis by ultraviolet radiation (290–315 nm) of 7-dehydrocholesterol. 25-hydroxyvitamin D [25(OH) D], and 1, 25-dihydroxyvitamin D [1, 25(OH) 2D] are the major circulating metabolites. Sun exposure is the strongest factor influencing 25(OH) D. Therefore, the aim of this review was to investigate whether phototherapy was able to influence vitamin D level in psoriasis and its beneficial effect on psoriasis by increasing vitamin D level. We conducted a systematic review to assess the association between phototherapy and vitamin D status in psoriasis that was reviewed in January and April 2018. An electronic published work search was performed using PubMed, Ovid MEDLINE, Google Scholar, and Saudi Digital Library database and Medline. A total of 592 eligible articles by searching PubMed, Ovid MEDLINE, Google Scholar, and Saudi Digital Library. The titles and abstracts of 164 manuscripts were found to potentially fulfill search criteria. After the application of inclusion standards and full-text review, 23 manuscripts remained for inclusion. The sample size was 659 psoriasis patients. A total of 23 studies summarize the effect of phototherapy on vitamin D in psoriasis. Daily artificial UV therapy is an effective treatment for psoriasis patients, and vitamin D scores taking into consideration the type of UV, skin pigmentations, age of the patient and initial level of serum vitamin D.

Keywords: Vitamin D, 25(OH) D (calcifediol), 25(OH) D (calcifediol) level, 1, 25-dihydroxyvitamin D3 (calcitriol), 1, 25-dihydroxyvitamin D3 (calcitriol) level, phototherapy, BUVB, NB-UVB, PUVA, heliotherapy, psoriasis.

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INTRODUCTION

Vitamin D is an oil-soluble vitamin in the human diet that plays many important roles in maintaining calcium homeostasis and the immune system functions [1,2]. It plays its role through bone metabolism, controls calcium absorption and mediates mineralization with parathyroid hormone in the skeleton [3-5]. It has immunomodulating, antiproliferative and prodifferentiating properties so it used in dermatological diseases [6-8]. Moreover, it inhibits proliferation and stimulates differentiation of keratinocytes in vitro also [9-10]. Vitamin D is obtained in humans by photoconversion of 7-dehydrocholesterol (main source: 90-100%) or by food (about 10%). Food containing vitamin D is fish, milk, train-oil and artificial fortified butter and margarine [11].

Vitamin D deficiency is a global problem affecting overall health. Its deficiency is generally associated with poor dietary intake, insufficient sun exposure [12,13], vitamin D malabsorption problems; low vitamin D in human breast milk and a number of medications that are associated with its deficiency (such as phenobarbital, dilantin, and rifampin) [14-17].

Vitamin D deficiency is not limited to the hospitalized population and elderly; many studies worldwide have found a high prevalence of vitamin D deficiency among healthy people, immature adults, children, adult males, and women. Seasonal variations of vitamin D serum level were also reported, the highest serum level occurring after summer and the lowest serum after winter [18-33]. Its insufficiency has also been reported in patients with psoriasis independently of age, sex, body mass index and could be due to nutritional or sun exposure habits [34-36].

Psoriasis is a chronic immune-mediated inflammatory skin condition associated with vitamin D deficiency, involving epidermal hyperplasia [37]. The pathogenesis of psoriasis is not fully realized. Its management is difficult because the appearance of the disease can vary widely. The role of oral vitamin D supplements for the treatment of psoriasis was first prescribed 60 years ago based on the beneficial effects of ultraviolet radiation (UVR) along with the disease [38,39].

In psoriasis, vitamin D has a beneficial role might be due to both a surface and a systemic increase in the metabolization of vitamin D [40]. Sun ultraviolet (UV) radiation has a beneficial effect and natural treatment method for several skin diseases [41]. Sun exposure is the major and the best source of vitamin D for most humans [42]. Pre-vitamin D3 synthesis can be affected by skin pigmentation, sunscreen use, aging, time of day, season and latitude [43]. Phototherapy divided into 3 main types of UV light: broadband UVB (BUVB) (290–320 nm), narrow-band UVB (NB-UVB) (311–313 nm), and UVA (320–400 nm) [44]. The UV phototherapy is more suitable for patients with light brown to brown/black Fitzpatrick skin type II-IV [45].

Therefore, the aim of our systematic review was to summarize the phototherapy influence in vitamin D level in psoriasis patients, also phototherapy beneficial effect on psoriasis.

MATERIALS AND METHODS

Inclusion criteria

We searched in this systematic review for both retrospective and prospective study designs, both randomized and non-randomized, and were published prior to March 2018, that met the following criteria:

1. Any trials involving psoriasis vulgaris patients.
2. Undergoing phototherapy of any type of BUVB, NB-UVB, UVA, solar radiation, or climate therapy in the treatment group.
3. A measure of vitamin D serum level in summer and winter
4. Phototherapy in summer or winter.
5. Psoriasis on the body, with or without arthritis.
6. Adult patients either male or female participants.

Exclusion criteria

Any study did not describe vitamin D status in psoriasis patients without mention phototherapy, any study did not discuss the results of phototherapy, was in a non-English language. Also, we exclude conferences, case reports, abstracts, letters, editorials, review or meta-analysis.

Search strategy

MEDLINE, PubMed, Google Scholar, Ovid, and Saudi Digital Library were independently searched by two investigators using a structured search strategy with relevant key terms. Articles were identified using one, or combination of two or more, of the following search terms:

"vitamin D"; "vitamin D level"; "phototherapy"; "BUVB" "NB-UVB" "PUVA" "Climate therapy" "psoriasis vulgaris" and "psoriasis patients". The initial search was done from January 2018 to April 2018.

Study selection

All studies were screened by the two investigators for inclusion and exclusion into the review. In case of disagreement, they shall be resolved by consensus. Another investigator was assigned to checking the results and writes the research.

Data extraction

Standardized data extracted from each article that convene with inclusion criteria consisted of the study data included the country/set of participants, methods of study, sample size, duration of the study, and the results.

This manuscript is based on previous studies and does not contain any studies conducted with humans or animals by any of the authors.

RESULTS

We identified a total of 592 eligible articles by searching PubMed, Ovid MEDLINE, Google Scholar, and Saudi Digital Library. The titles and abstracts of 164 manuscripts were found to potentially fulfill search criteria. After the application of inclusion standards and full-text review, 23 manuscripts remained for inclusion (Figure 1). Patients were followed-up for 3 weeks to 4 months and the number of patients in all studies was 1074 patients, psoriasis patients (n=659), psoriasis arthritis (n=4), healthy control (n=297), and other dermatological diseases (n= 116).

Psoriasis patients expose to the different types of phototherapy in 23 studies. Psoriasis patients expose to NB-UVB (n=435), psoriasis patients expose to low dose NB-UVB (n=12), psoriasis patients expose to BUV/NB-UVB (n=68), psoriasis patients expose to home UV (n=32), psoriasis patients expose to UVB (n=26), psoriasis patients expose to PUVB (n=25), psoriasis patients expose to BUVB (n=24), psoriasis patients expose to UVB/PUVA (n=20), psoriasis patients expose to heliotherapy (n=20), and psoriasis patients expose to UVA/UVB (n=1).

A total of 23 studies summarize the effect of phototherapy on vitamin D in psoriasis (Table 1).

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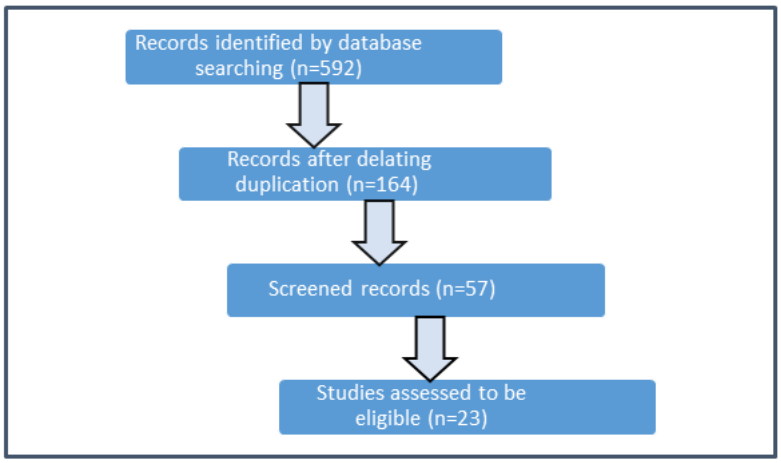

Figure 1: Flow-chart of the study selection process.

DISCUSSION

There was a strong correlation between vitamin D deficiency and psoriasis severity [37, 46]. Low serum vitamin D level was reported by many researchers in patients with psoriasis [34-36,47,48], even they usually expose themselves to the sun more than healthy persons [34]. So, the therapeutic strategy in the treatment of psoriasis is to increase vitamin D concentration and suppresses skin symptoms directly [48]. Actually, vitamin D plays its action through different mechanisms reported by many researchers. The beneficial role of vitamin D for psoriasis might be due to both a surface and a systemic increase in vitamin D metabolism [51]. Vitamin D improves the immune system functions [1,2], inhibits proliferation and stimulates differentiation of keratinocytes both *in vivo* [3-5] and *in vitro* [9-10].

As the main source, Vitamin D in humans is the photoconversion (90-100%) [11]. Exposure to the sun is the most important part of this percept [50]. Skin pigment, sunscreen use, aging, time of day, season, latitude, the level of air pollution, cloud cover, and general health conditions could affect pre-vitamin D3 synthesis through photoconversion [32,52]. Many researchers tried to investigate and hence clarified the relation of daily UV therapy and vitamin D level and hence effective treatment for psoriasis patients [48].

Artificial UVB phototherapy is a safe and effective treatment for a variety of inflammatory skin diseases such as psoriasis. The NB-UVB lamp more accepted than the standard broadband UVB because it was easier to handle and better tolerated, so it was more applicable [34]. The mechanism of action of UVB radiation may be through the cutaneous synthesis of vitamin D [53]

Improvement of vitamin D serum level and efficiency in psoriasis patients who received UV not dependent on the season or country or sex or the type of UV or even the age of the patient [54]. Improvement of vitamin D serum level was reported in cold countries like Netherlands [47], Australia [48], Switzerland [54], Finland [55], Spain [36], Poland [7], Ireland [56], Finland [57], Sweden [50], Norway [58] as well as hot countries like Kuwait [59]. The ability to synthesize vitamin D decreases with age, but no relationship between body mass index and vitamin D level [60].

Greater increase in 25(OH) D serum level in the winter patients, when compared to the summer, indicate after artificial UVB [61,63]. They reported the improvement in winter at that time a strong drop was seen in the vitamin D levels of patients not received UV. The improvement of vitamin D serum level and efficiency in psoriasis patients also not dependant on patient sex or age. UVB therapy in elderly psoriatic women improved psoriasis, increased serum 25(OH) D3 synthesis and reduced serum PTH concentrations [64]. So, the controlled use of UVB is a safe and effective method for the treatment of psoriasis [65] and the treatment of vitamin D deficiency [66].

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Table 1 summarizes the effect of phototherapy on vitamin D in psoriasis.

No	References	Country and setting	Method	Sample	Duration of exposure	Type of UV	Results
1	Saleky et al., 2017 [73]	Department of Dermatology and Venereology, Eskisehir Osmangazi University, Turkey	Prospective study	49 psoriasis patients	3/W for 6 months	NB-UVB	Serum 25(OH)D levels increased after NB-UVB treatment correlated with the number of sessions of NB-UVB.
2	Le et al., 2016 [48]	Department of Dermatology, Fremantle Hospital, Fremantle, Western Australia	Prospective study	16 psoriasis patients 4 atopic dermatitis	3/W for minimum 4 weeks	NB-UVB (n=15) UVA/UVB (n=3)	NB-UVB and UVA/UVB phototherapy significantly increased 25(OH)D serum level in patients with psoriasis and atopic dermatitis
3	Gupta et al., 2016 [74]	Department of Dermatology, Ram Manohar Lohia Hospital New Delhi, India.	Prospective study	30 psoriasis patients 30 healthy controls	3/W for 12 weeks	NB-UVB	Significant improvement in PASI and serum 25(OH) D levels after NB-UVB in psoriasis, but poorly correlated with each other.
4	Franken et al., 2015 [47]	Department of Dermatology, VU University Medical Center, Amsterdam, The Netherlands.	Comparative study	32 psoriasis patients 30 healthy controls	7/W for 6 months	Mometasone oint 0.1% + emollients + home UV	Daily low-emission UV therapy is an effective treatment for psoriasis patients and improving disease activity, quality of life, and vitamin D scores.
5	Al-Mutairi and Shaaban, 2014 [59]	Department of Dermatology, Faculty of Medicine, Kuwait University, Kuwait	Comparative study	93 psoriasis patients 50 healthy controls	3/W for 2 months	NB-UVB	Significant improvement in LL-37 and serum 25(OH)D levels after NB-UVB treatment in psoriasis patients.
6	Ala-Houhala et al., 2014 [55]	Department of Dermatology, Tampere University Hospital, Finland	Case-control study	8 psoriasis patients 4 psoriatic arthritis 15 healthy controls	3/W for 18 weeks	NB-UVB during Winter	A course of treatment with NB-UVB improves psoriasis and increases serum 25(OH)D levels.
7	Feldmeyer et al., 2013 [54]	Department of Dermatology, University Hospital Zurich Switzerland	Open observational study	25 psoriasis patients 91 other dermatological diseases	2-3/W 53 to 90 days	UVA1 (n=38) UVA/NB-UVB (n=30) NB-UVB (n=48)	Phototherapy with NB-UVB and UVA/NB-UVB increased 25(OH)D serum level significantly, UVA1 therapy alone induced a reduction in serum 25(OH)D concentrations.
8	Romaní et al., 2012 [36]	Departments of Dermatology Hospital, Parc Taulı, Barcelona, Spain	Comparative study	50 psoriasis patients 50 healthy controls	3/W for 4 months	NB-UVB	Improvement in psoriasis after NB-UVB therapy, which was not mediated by enhancement of vitamin D synthesis
9	Kolanko M and Brzezińska-Wcisło, 2012 [11]	Department of Dermatology, Medical University of Silesia, Katowice	Comparative study	36 psoriasis patients 28 healthy controls.	3/W for 7 weeks	NB-UVB	The study confirmed the impact of the initial level of serum 25(OH)D level on the increase in production of vitamin D by NB-UVB
10	Lesiak et al., 2011 [7]	Department of Dermatology, Medical University of Lodz, Poland	Comparative study	17 psoriatic winter group 13 psoriatic summer group	20 exposure	NB-UVB	Outdoor solar radiation affects the patients over a much longer period, and artificial UV light is the main factor responsible for the increase in 25(OH)D serum level
11	Lesiak et al., 2011 [8]	Department of Dermatology, Medical University of Lodz, Poland	Prospective study	47 psoriasis patients	20 exposure	NB-UVB	NB-UVB significantly increases 25(OH)D syntheses dependently on the cumulative dose.
12	Cicarma et al., 2010 [58]	Department of Radiation Biology, The Norwegian Radium Hospital, Oslo University Hospital, Norway	Comparative study	12 psoriasis patients 5 atopic dermatitis 1 vitiligo 1 itch case	9-15 exposure	Low dose NB-UVB	Low-dose NB-UVB treatment gives a significant increase in the vitamin D status in persons with low initial levels of 25(OH)D
13	Vähävihu et al., 2010 [57]	Department of Dermatology, Tampere University Hospital, Finland	Comparative study	18 psoriasis patients, 18 atopic dermatitis, 15 healthy controls	15 exposure	NB-UVB during Winter	NB-UVB treatment effectively corrects vitamin D insufficiency in patients with PS and AD and in healthy subjects.

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14	Ryan et al., 2010 [56]	Departments of Dermatology, Vincent's University Hospital, Dublin, Ireland	Prospective study	30 psoriasis patients 30 control psoriasis patients not treated	12 exposure	NB-UVB during Winter	NB-UVB effectively increases serum 25(OH)D level while clearing psoriasis.
15	Osmancevic et al., 2010 [51]	Departments of Dermatology, Sahlgrenska University Hospital, Goteborg, Sweden	Descriptive study	24 postmenopausal psoriasis patients treated with BUVB 68 psoriasis patients treated with BUVB and NB-UVB 20 psoriasis patients treated with heliotherapy	2-3/W for 8 to 12 weeks	BUVB, BUVB or NB-UVB, Heliotherapy	Vitamin D production in patients with psoriasis increased less with NB-UVB than with BUVB phototherapy.
16	Osmancevic et al., 2009 [50]	Department of Dermatology, Sahlgrenska University Hospital, Goteborg, Sweden	Prospective study	20 psoriasis patients	3 weeks	Climate therapy	Climate therapy at Gran Canaria enhanced vitamin D3 production and improved the PASI score in patients with psoriasis
17	Osmancevic et al., 2009 [68]	Departments of Dermatology, Sahlgrenska University Hospital, Goteborg, Sweden	Explorative, interventional	26 psoriasis patients treated with BUVB 42 psoriasis patients treated with BUVB	2-3/W for 8 to 12 weeks	BUVB or NB-UVB,	Serum 25(OH)D3 in psoriasis patients increased less with NB-UVB than with BUVB phototherapy
18	Osmancevic et al., 2007 [64]	Departments of Dermatology, Sahlgrenska University Hospital, Goteborg, Sweden	Explorative, interventional	24 postmenopausal psoriasis patients	2-3/W for 8 to 12 weeks	BUVB	UVB therapy in elderly psoriatic women improved psoriasis, increased serum 25(OH)D3 synthesis
19	Prystowsky et al., 1996 [10]	Departments of Dermatology, Columbia-Presbyterian Medical Center, Los Angeles, USA	A double-blind, randomized trial	8 psoriasis patients taking calcitriol 8 psoriasis patients taking a placebo	21 exposure	UVB	UVB phototherapy resulted in increments of serum 25(OH)D concentrations in both calcitriol treated and placebo-treated patients
20	Prystowsky et al., 1996 [72]	Departments of Dermatology, Columbia-Presbyterian Medical Center, Los Angeles, USA	A double-blind, randomized trial	8 psoriasis patients taking calcitriol 8 psoriasis patients taking a placebo	21 exposure	UVB	UVB phototherapy induces maximal therapeutic benefits to the skin from vitamin D; there is tittle added benefit from the use of either oral or topical forms of vitamin D.
21	Guilhou et al., 1990 [70]	Department of Dermatology and Phlebology, Hôpital Saint Charles, Montpellier, France	Descriptive study	20 psoriasis patients 15 healthy controls.	2-3/W for 3 weeks	UVB or PUVA	25 (OH) D and 24,25(OH)2D were dramatically increased by UVB (but not by PUVA) in psoriasis patients as well as in controls
22	Staberg et al., 1988 [69]	Department of Dermatology, Gentofte Hospital, Copenhagen, Denmark	Descriptive study	10 psoriasis patients	2-3/W for 3-4 weeks	UVB	After phototherapy, the mean serum level of 1, 25(OH)2D increased nearly to the level found in healthy controls.
23	Rogers et al., 1979 [71]	Royal Postgraduate Medical School, London	Comparative study	25 psoriasis patients 30 healthy controls.	3/W till the rash was clear	PUVA	Serum 25(OH)D concentration reached adequate levels and significantly higher than the summer mean for 30 normal individuals

Different types of UV could improve vitamin D serum level and efficiency in psoriasis patients by different intensities. Improvement with daily low-emission home UV for 6 months [47] as well as NB-UVB and UVA/UVB phototherapy [48,55,59] and this increase correlates with the activation of circulating regulatory T cells [67]. The effectiveness of NB-UVB in generating vitamin D has already been demonstrated in keratinocyte cultures [53]. Vitamin D production in psoriasis patients increases less with narrowband than with broadband UVB phototherapy [50].

The magnitude of the 25(OH) D response was dependent on the NB-UVB dose and on the initial level of 25(OH) D. There was an increase of 30% in serum 25(OH) D after a dose of NB-UVB as low as 2.35 J ⁄cm2. Synthesis of serum 25(OH) D seemed to reach saturation at higher doses of NB-UVB (>6.52 J ⁄cm2) [58]. Serum 25(OH) D3 in psoriasis patients increased less with NB-UVB than with broadband UVB phototherapy. Psoriasis improved on both regimens [50,51,68]. One explanation might be that the optimal wavelength for initiation of the vitamin D3 pathway was in the range of 300/5nmin vitro and *in vivo* [53] covered with broadband UVB (280–320 nm).

Importantly, NB-UVB, UVA/NB-UVB and PUVA therapies of psoriasis increased vitamin D serum levels in most insufficient and deficient individuals to the normal range [69-2]. On the other hand therapy with UVA1 slightly reduced the vitamin D serum level. Two possible explanations for this observation could be suggested. The first is that vitamin D absorbs UVA1 besides NB-UVB and becomes susceptible to degradation [73]. The second explanation is that less penetration of UV through the skin because melanin does filter more in the UVB range than in the UVA range [54,74,75]

CONCLUSION AND RECOMMENDATIONS

Daily artificial UV therapy is an effective treatment for psoriasis patients, and vitamin D scores taking in consideration the type of UV, skin pigmentations, age of the patient and initial level of serum vitamin D. Further investigations, however, are recommended and the possible side effects of the daily use of UV are necessary also.

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