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Narrow band ultraviolet B therapy deactivates Th1/Th17 pathway and activates Th2 cytokines secretion in Egyptian psoriatic arthritis patients

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ABSTRACT

Psoriasis is a chronic autoimmune disorder that affects 3-4% of the world population. Keratinocytes and immune cells in patient's skin secrets excess pro-inflammatory cytokines that in turn activates the differentiation of T helper cells (Th) into Th1 and Th17 and deactivates Th2 pathway. Several phototherapies have been used in treatment of moderate and severe psoriatic patients; among them narrowband ultraviolet B (NB-UVB, 311 nm) is the most effective. We aims to evaluate the therapeutic effect of NB-UVB exposure in 80 Egyptian plaque psoriatic patients with and without psoriasis arthritis development. This will be accomplished by measuring serum cytokines levels (IL-10, -12, -17, -23 and -34) and high sensitive C reactive protein before and after treatment. A significant elevation in Th2 pathway cytokine, IL-10, and significant decrease in Th1/Th17 pathway cytokines were observed after treatment. This indicates the success of NB-UVB therapy in down modulating IL-12 and IL-23/Th17 axis. The pathological conditions in psoriatic arthritis patients were improved by NB-UVB targeted to the skin. As serum cytokines levels in these patients indicated that the reduction in Th1/Th17 inflammatory cytokines and elevation of Th2 anti-inflammatory cytokines was not restricted to skin lesions only, but also, spread in patients' body and improve their pathologic.

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KEYWORDS
Plaque psoriasis; NB-UVB; IL-10; Il-17; IL-23; HS-CRP

1. Introduction

Psoriasis is a long-lasting autoimmune cutaneous disorder that is characterized by patches of abnormal skin due to epidermal hyperproliferation and inflammation with a marked infiltration of T cells, neutrophils, and macrophages (Menter et al., 2008). Five main types of psoriasis are known: plaque, guttate, inverse, pustular, and erythrodermic psoriasis; however, 90% of patients have plaque psoriasis (Boehncke & Schön, 2015). Psoriasis begins at adulthood, but it may start at any age, and may be associated with development of psoriatic arthritis, lymphomas, cardiovascular disease, Crohn disease, and depression. Psoriatic arthritis affects up to 30% of individuals with psoriasis (Palfreeman, McNamee, & McCann, 2013).

It is a chronic inflammatory disease that affects 2–3% of the world's population. It is linked to genetic predisposition, autoimmune disorders, psychiatry and psychological health, or environmental factors such as infection, stress, and trauma (Grine et al., 2020). The pathogenesis is closely associated with abnormal stimulations between innate immunity, T-cells, keratinocytes, etc. Immune cells in patients release excess pro-inflammatory factors that lead to uncontrollable activation of the adaptive immune system, such as the signaling pathway of the nuclear factor-kappa B (NF-kB) and the differentiation of T-helper (Th) cells into Th1 and/or Th17 cells (Zhang & Wu, 2018).

The classical Th1/Th2 model, previously explaining psoriasis development, has recently been confronted by the discovery of Th17 (Ibrahim, Labib, Nofal, & Boghdadi, 2015). Several researches reported the elevated levels of Th17 related cytokines, IL-17, IL-6, and TNF-α, as well as IL-23 in cutaneous and serum samples of psoriatic patients (Lowes et al., 2008). Also, IL-23 receptor gene with psoriasis raises the interest in IL-23/Th17 axis in disease development (Shibata et al., 2010).

Furthermore, IL-12 has a heterodimer structure formed from p40 and p35 subunits and secreted form activated antigen presenting cells as dendritic cells and macrophages (Trinchieri, 2003). Yawalkar, Karlen, Hunger, Brand, and Braathen (1998) reported the elevated levels of IL-12p40 mRNA and IL-12p70 heterodimer in psoriatic skin lesions. IL-23, a member of IL-12 family, has a heterodimer structure that share the same p40 subunit with IL-12. In spite of their similarities, both cytokines activates divergent immunological pathways. IL-12 plays a crucial role in differentiation of naïve T lymphocytes into IFN-γ producing Th1 cells whereas IL-23 plays a role in maintenance of Th17 responses (Toichi et al., 2006). Several studies reported elevated levels of both cytokines in skin biopsies from psoriasis patients (Shaker, Moustafa, Essmat, Abdel-Halim, & El-Komy, 2006).

IL-34 is a novel cytokine that was identified in 2008 in a comprehensive proteomic analysis as a tissue-specific

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ligand of CSF-1 receptor (Baghdadi et al., 2018). It has a homeostatic function in the skin where it is secreted from keratinocytes (Greter et al., 2012). Pro-inflammatory cytokines, IL-1β and TNF-α, stimulates IL-34 secretion (Chemel et al., 2012); which in turn elevates IL-17 production (McGinley et al., 2020; Moon et al., 2013; Tian, Shen, Xia, & Lu, 2013). Both TNF-α and IL-17 participate in pathogenesis of psoriasis with and without arthritis (Al Saadany, Hussein, Gaber, & Zaytoun, 2016; Işık et al., 2016). Moreover, the induced secretion of IL-6 by TNF-α stimulates liver to produce C-reactive protein (CRP) that is considered as an inflammatory biomarker (Vandevoorde, Haegeman, & Fiers, 1992). CRP can be identified within 24–48 hours after tissue damage.

Treatment choices for psoriasis can be divided into two types: systemic and topical treatments. The first includes immune inhibitors, as methotrexate, and immune modulators as glycyrrhizin (Goldenberg, Lanoue, & Dong, 2016). In addition, newly discovered biological agents as tumor necrosis factor α antagonists have been used to treat moderate to severe psoriasis with psoriasis area and severity index (PASI) more than 10 (Zhang & Wu, 2018). Topical treatment, for mild to moderate psoriasis, includes ointments as calcipotriol and phototherapy. Phototherapy is a safe and effective therapy without any systemic side effects, unlike biological agents or other medicines, especially for stable plaque psoriasis. Moreover, it can be paired with biologic agents to treat severe psoriasis (Calzavara-Pinton et al., 2013).

Phototherapy in the form of sunlight has long been used for treatment of psoriasis (Menter & Griffiths, 2007). Narrow-band ultraviolet B (NB-UVB) therapy reverses pathologic alterations in psoriasis by reducing epidermal T lymphocytes and dendritic cells numbers (Erkin et al., 2007), suppressing IFN-γ production and targeting IL-17 pathway (Johnson-Huang et al., 2010). NB-UVB induces DNA damage in the form of pyrimidine dimers that interferes with the cell cycle and stops it. This interruption of the cell cycle, induced by NB-UVB, reduces the rapid skin cell division seen in psoriasis and decreases the activity of many types of immune cells found in the skin (Dogra & De, 2010).

The present work aims to evaluate the relation between IL-12 and IL-23/th17 axis in Egyptian patients with psoriasis and psoriasis arthritis; and to find the influence of NB-UVB therapy on serum cytokines levels. This will be accomplished by measuring serum levels of different cytokines, IL-10, −12, −17, −23, and −34, involved in pathogenesis of psoriasis. Cytokines can be defined as a variety of low molecular weight proteins that have a stimulating or inhibiting effect on immune system cells' proliferation, differentiation and function (Farid et al., 2020a, 2020b). Because of the abnormal nature of the diseases, cytokines are a significant subject of research for understanding autoimmune disorders (El Amir et al., 2019; Farid, Eissa, Nada, El Amir, & El Amir, 2019) and parasitic infections (El Amir, Farid, Mohamed, Ramadan, & Diab, 2020; Farid, Amadou, & Safwat, 2020). Furthermore, the potential for the use of NB-UVB in the improvement of symptoms in patients with psoriasis arthritis will be measured.

2. Materials and methods

2.1. Patients

Eighty plaque psoriatic patients, 30 of them developed psoriasis arthritis, were included in the study. Patients were randomly selected from Dermatology Outpatient Clinics of Cairo University Hospitals. Eighty healthy volunteers, age and sex matched, with no family history of psoriasis participated in the study. Exclusion criteria for both patients and controls were: 1 – history of diabetes, cancer or other inflammatory disease; 2 – patients on steroids or biological therapy for 6 months before the study were excluded. The study was conducted in accordance with the World Medical Association Declaration of Helsinki for human subjects and approved by the ethics committee of Cairo University and all participants gave an informed written consent. Patients were subjected to full history taking and thorough clinical examination including skin, hair, mucous membrane, and joint examination. The diagnosis of psoriasis was clinically based on characteristic lesions. The PASI score was used to evaluate the severity of psoriasis in relation to three parameters: E, erythema; I, infiltration; and D, desquamation (Fredriksson & Pettersson, 1978). Psoriatic arthritis patients fulfilled the diagnostic criteria defined according to the Classification Criteria for Psoriatic Arthritis (CASPAR).

2.2. Treatment Protocol by NB-UVB

Patients with and without arthritis, group I and II, were treated with NB-UVB. UV-100 L Waldman lighting, provided with UVB lamp of 7–10 mW/cm^2 physical irradiance and 0.4–0.6 mW/cm^2 biological effective (erythematous) irradiance, was used in the study. Patients were subjected to three sessions/week for six weeks with initial radiation dose according to patient's skin condition; and the dose increment was determined according to the erythema degree as follows: 20% and 10% for no and minimum erythema, respectively, and no dose increment was done for intense erythema (Zanolli, Felmam, Clark, & Fleicher, 2000).

2.3. Measurement of Serum Levels of IL-10, −12, −17, −23, −34, and HS- CRP

Cytokines and hs-CRP were measured before and after treatment for all patients and healthy control groups. Blood sample, 5 ml, were collected from patients and healthy controls and centrifuged for sera separation.

Sera aliquots were frozen at −20°C until analysis. Human IL-10 (ab46034), IL-12 (ab46035), IL-17 (RAB0262-1KT), IL-23 (ab64708), IL-34 (ab213797), and hs-CRP (MBS2506093) ELISA kits were used for measuring different immunological parameters.

2.4. Statistical analysis

Results were analyzed using SPSS 15.0.1 for windows; SPSS Inc., Chicago, IL, 2001. Mean and standard deviation (m± SD) were used to describe continuous data; number and percentage for categorical data. Paired samples *t*-test was used to assess the statistical significance of the difference. *P* values <0.05 were considered statistically significant.

3. Results

3.1. Demographic data and clinical characteristics

The study involved 80 psoriasis patients, 50 of them have psoriasis (group I) and 30 of them have psoriasis arthritis (group II), with a mean age of 45 ± 11.2 and 49 ± 8.2, respectively. The disease durations were 8 ± 6.1 and 15 ± 2.6 for group I and II, respectively. Group II patients consisted of 18 male and 12 females with mean PASI score of 20.2 ± 2.3, which was higher than that of group I (14.3 ± 7.1). Nail involvement was found among patients of both groups, but its percent was higher in psoriatic arthritis patients (53.3%) than psoriasis patients without arthritis (6%). Demographic data, occupation and residence, are presented in Table 1.

3.2. Lipid profile

Triglycerides levels in both patients groups (144.12 and 149.57 mg/dl for group I and II, respectively) were significantly higher than that of healthy control group (91.47 mg/dl). A significant elevation in both cholesterol and LDL-C was, also, observed in patients groups I and II (Table 2). On the contrary, level of HDL-C was significantly decreased in psoriasis patients (43.82 and 41.19 mg/dl for group I and II, respectively) when compared to healthy controls (55.94 mg/dl).

3.3. Immunological results

Serum levels of different cytokines and hs-CRP in both groups I and II, before treatment, were higher than those of healthy controls (Table 3). Before NB-UVB exposure, levels of IL-12, −17, −23, and −34 were higher in psoriatic arthritis patients (group II) than in psoriasis patients without arthritis (group I). On the other hand, after NB-UVB treatment, a significant reduction in their levels was observed in both groups. IL-12, IL-17, and IL-23 serum levels, after treatment, in groups I and II were highly reduced to reach similar levels of healthy controls (IL-12, group I: 93.44 ± 4.3 and group II: 101 ± 8.6 vs. controls: 90.41 ± 9.1; IL-17, group I: 14.17 ± 0.4 and group II: 16.23 ± 4.3 vs. controls: 11.05 ± 0.9; IL-23, group I: 34.26 ± 1.6 and group II: 31.21 ± 6.1 vs. controls: 28.78 ± 3.7). On the other hand, IL-34 serum levels in both groups, after treatment, were greatly reduced but remain higher than that of control group (group I: 201.46 ± 12.6 and group II: 223.09 ± 0.6 vs. controls: 192.47 ± 9.4). This reduction in cytokines levels, after NB-UVB treatment, was coincides with a reduction in hs-CRP level and PASI in psoriasis patients with and without arthritis. On the contrary, IL-10 serum levels in both groups after treatment (110.69 ± 10.4 and 96.06 ± 2.4 for group I and II, respectively) were higher than those before treatment (65.79 ± 8.2 and 59.24 ± 7.8 for group I and II, respectively).

4. Discussion

Phototherapy, NB-UVB and psoralen ultraviolet A (PUVA), is an effective common treatment for psoriasis (Duarte, Cunha, Bedrikow, & Lazzarini, 2009). It induces apoptosis of immune cells and keratinocytes, affects cytokine production, suppresses IL-23/Th17 axis, and stimulates regulatory T cells. It is responsible for resolution of psoriasis lesions (Yu & Wolf, 2020). NB-UVB, with

Table 1. Demographic data, clinical characteristics, and disease activity in psoriatic patients with and without arthritis in comparison to healthy controls.

Data	Controls (80)	Ps (*n* = 50) Group I	PsA (*n* = 30) Group II
Age (years)	42 ± 9.5	45 ± 11.2	49 ± 8.2
Sex (male/female)	39/41	35/15	18/12
Ps duration (years)	-	8 ± 6.1	15 ± 2.6
PASI	-	14.3 ± 7.1	20.2 ± 2.3
Nail involvement	-	3 (6%)	16 (53.3%)
Occupation			
Farmers	25 (31.25%)	13 (26%)	5 (16.66%)
Workers	26 (32.5%)	29 (58%)	27 (90%)
Unemployed	29 (36.25%)	8 (16%)	8 (26.66%)
Residence			
Urban	53 (66.25%)	39 (78%)	21 (70%)
Rural	27 (33.75%)	11 (22%)	9 (30%)

Results are presented as mean ± SD or *n* (%); * represents significance compared with the corresponding healthy controls. PASI: psoriasis skin area severity index.

Table 2. Lipid profile in psoriatic patients with and without arthritis in comparison to healthy controls.

Data	Controls (80)	Ps (n = 50) Group I	PsA (n = 30) Group II
Lipid profile			
Triglycerides (mg/dl)	91.47 ± 22.2	144.12 ± 5.6*	149.57 ± 19.3*
Cholesterol (mg/dl)	153.13 ± 13.9	232.43 ± 7.1*	254.49 ± 5.6*
LDL-C (mg/dl)	89.03 ± 9.6	132.77 ± 11.9*	141.47 ± 4.3*
HDL-C (mg/dl)	55.94 ± 14.3	43.82 ± 10.7	41.19 ± 17.1

Results are presented as mean ± SD or n (%); * represents significance compared with the corresponding healthy controls. LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol, Ps: psoriasis patients and PsA: psoriatic arthritis patients.

Table 3. Serum levels of IL-17, IL-23, IL-34, and hs-CRP before and after NB-UVB among groups I and II patients.

		Group I			Group II		
Cytokine	Controls	Before	After	P value	Before	After	P value
PASI	-	14.03 ± 7.1	9.41 ± 8.3	0.2	20.2 ± 2.3	11.36 ± 3.0	0.02
IL-10 (pg/ml)	33.45 ± 1.1	65.79 ± 8.2	110.69 ± 10.4	<0.01*	59.24 ± 7.8	96.06 ± 2.4	<0.01*
IL-12 (pg/ml)	90.41 ± 9.1	160.07 ± 8.6	93.44 ± 4.3	<0.001*	175.02 ± 4.6	101.04 ± 8.6	<0.001*
IL-17 (pg/ml)	11.05 ± 0.9	24.48 ± 5.1	14.17 ± 0.4	<0.03	35.53 ± 0.9	16.23 ± 4.3	<0.01*
IL-23 (pg/ml)	28.78 ± 3.7	190.18 ± 6.4	34.26 ± 1.6	<0.001*	240.01 ± 7.5	31.21 ± 6.1	<0.001*
IL-34 (pg/ml)	192.47 ± 9.4	346.43 ± 5.5	201.46 ± 12.6	<0.001*	514.99 ± 3.1	223.09 ± 0.6	<0.001*
hs-CRP (mg/L)	3.85 ± 5.6	6.19 ± 9.9	4.11 ± 0.2	<0.02	9.74 ± 10.1	5.38 ± 2.4	<0.001*

In each raw, results are presented as mean ± SD; * represents a significant difference by paired samples t-test. IL: interleukin and hs-CRP: high sensitivity C reactive protein. Group I: psoriasis patients without arthritis and group II: psoriatic arthritis patients.

a wavelength of 311–313 nanometer, is the most common treatment in skin diseases and disorders. It is, also, known as the biological spectrum due to the sensitivity of human body to its wavelength (Lee, Koo, & Berger, 2014). Several studies have demonstrated its effectiveness in treating psoriasis patients who have moderate to severe conditions (Lapolla, Yentzer, Bagel, Halvorson, & Feldman, 2011; Zhang & Wu, 2018). NB-UVB is an effective first-line treatment for generalized plaque psoriasis (Yanovsky, Huang, & Buzney, 2020). However, the biological process by which NB-UVB improves psoriasis is still under investigations. Our study aims to evaluate the possible mechanisms responsible for treatment in 80 Egyptian psoriasis patients, with and without arthritis, treated by NB-UVB for six weeks.

Our results showed a reduction in PASI score, in both groups, upon treatment. And that reduction coincided with a significant elevation in serum level of IL-10 and a significant reduction in serum levels of IL-12, −17, −23, −34, and hs-CRP. Our results were in agreement with Rácz et al. (2011) who reported the suppression in Th17 pathway after NB-UVB treatment. And Coimbra et al. (2010) reported the reduction in pro-inflammatory cytokines, TNF-α, IL-22, −23, −17, and −8, after PUVA and NB-UVB therapy. Furthermore, Johnson-Huang et al. (2010) found that NB-UVB down regulated IL-23/Th17 pathway in psoriatic skin lesions.

Psoriasis is characterized with an elevation in Th1 and Th17 cytokines and a reduction in Th2 cytokines (Schlaak et al., 1994). Several researches demonstrated that NB-UVB reverses cytokines secretion toward Th2 pathway. IL-10, an anti-inflammatory cytokine secreted from Th2, was secreted from keratinocyte cultures irradiated with UVB (Enk, Sredni, Blauvelt, & Katz, 1995). Levels of IL-10 in skin of psoriatic patient were significantly increased after irradiation by UVB (Barr et al., 1999). Asadullah et al. (1998) found that administration of recombinant IL-10 in psoriatic plaques elevated Th2 cytokines, IL-4 and −10, and reduced Th1 cytokines as IL-12 and TNF-α. Moreover, Søyland et al. (2011) found that sun exposure down-regulate the Th1/Th17 pro-inflammatory pathways, specifically IL-17 and IL-23, in the psoriatic lesions. Also, Yu and Wolf (2020) reported the immunomodulatory effect of UV light on epidermal Langerhans cells that inhibits their antigen-presenting capability to the T lymphocytes. Moreover, NB-UVB induces the apoptosis of T lymphocytes in the epidermis and dermis of psoriatic lesions, both *in vivo* and *in vitro* (Ozawa et al., 1999). PUVA therapy, for six weeks, enhanced keratinocyte apoptosis in 30 psoriasis patients (Ceović et al., 2007). This UVB-mediated apoptosis can be explained by DNA damage, formation of pyrimidine dimers, and injury in cell membrane that results in death receptor activation (Kulms et al., 1999). NB-UVB induces clustering of TNF, IL-1, and EGF receptors on cell surfaces (Rosette & Karin, 1996), and activation of CD95, both of which trigger programmed cell death (Aragane et al., 1998). In addition, NB-UVB immunosuppressed Langerhans cells (DeSilva, McKenzie, Hunter, & Norval, 2008), decreased mast cell degranulation and histamine (Toda, Danno, Tachibana, & Horio, 1986) and increased recruitment of FOXP3+ regulatory T cells that suppress immune system activation in dermis of human psoriatic skin irradiated with natural sunlight (Søyland et al., 2011). Also, NB-UVB has an important role in synthesis of vitamin D3 that in turn abolishes Th1 cytokines and favors Th2 cytokines (Boonstra et al., 2001).

In conclusion, according to our results, in both patients groups, NB-UVB therapy caused a significant elevation in Th2 pathway cytokine, IL-10, and significant decrease in Th1/Th17 pathway cytokines. The parallel increase in serum levels of IL-12, −17, and −23 in patients before treatment and their parallel decrease after treatment indicates the role of IL-12 and IL-23/

Th17 axis in psoriasis disease development and the success of NB-UVB therapy in down modulating this axis. Also, IL-34 has an important role in stimulating IL-17 secretion that in turn increases the level of hs-CRP in psoriatic patients. To our knowledge, there are no researches in the literature that evaluated the therapeutic effect of NB-UVB in psoriatic arthritis patients as this type of treatment was commonly used on psoriasis patients without arthritis development. We found that psoriatic arthritis patients were improved by NB-UVB targeted to the skin, which was evident in the reduction of PASI score. Moreover, serum cytokines levels in these patients indicated that the reduction in Th1/Th17 inflammatory cytokines and the elevation of Th2 anti-inflammatory cytokines were not restricted to psoriatic skin lesions only, but also, spread in patients' body and improve their pathologic condition in skin and joints.

Disclosure statement

The authors declare that: there is no conflict of interest.

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