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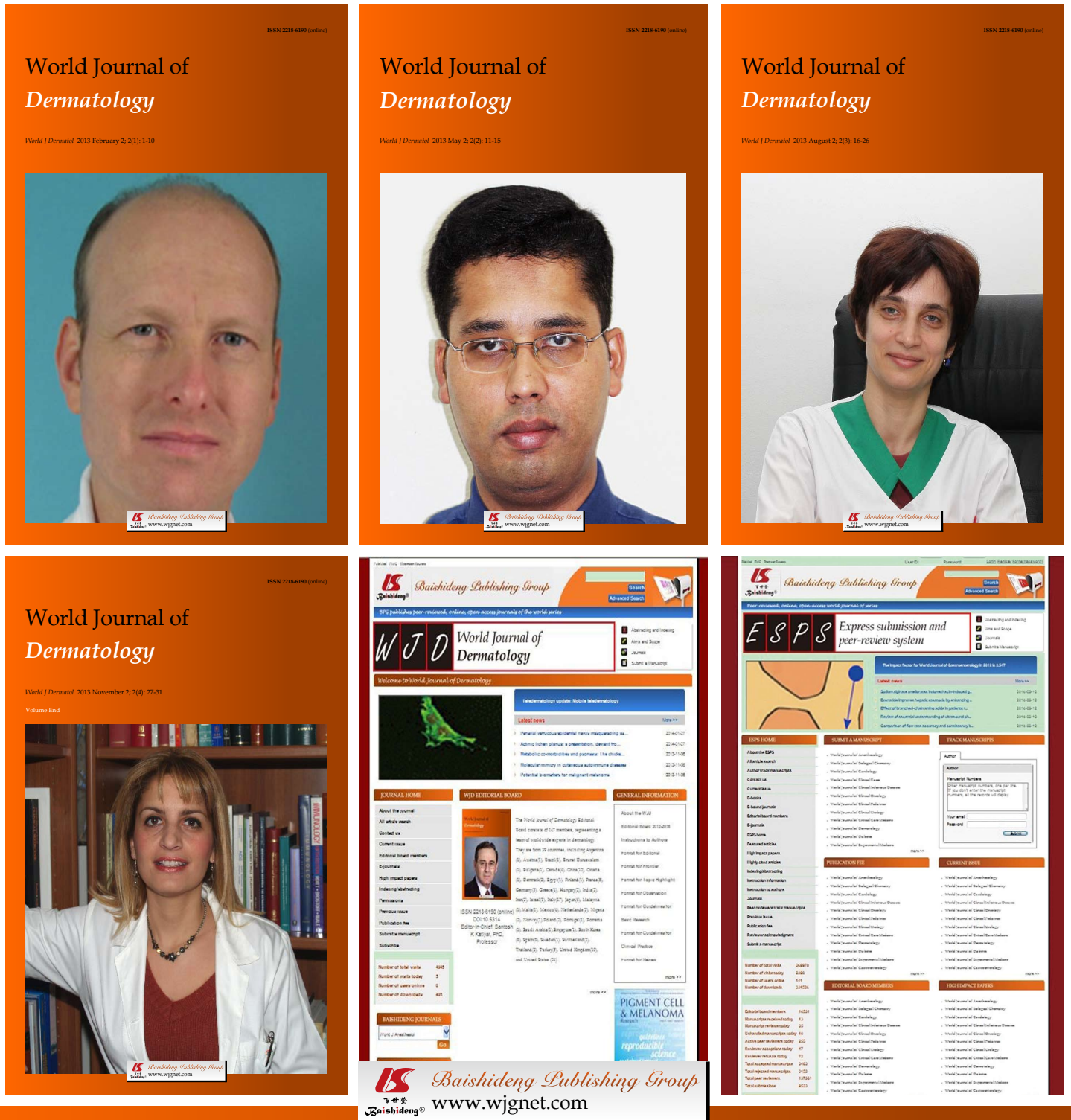

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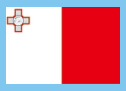

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ORIGINAL ARTICLE

Prevalence of sensitive skin and its biophysical response in a Mexican population

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Abstract

AIM: To describe the frequency and biophysical response of sensitive skin in Mexican subjects, using the lactic acid test.

METHODS: The lactic acid stinging test was applied to 250 healthy volunteers, both sexes, 18 years of age or older, without any active dermatoses on the test site. Volunteers were university students, workers of public institutions, and general population from San Luis Potosi, Mexico. Participants were not excluded based on socioeconomic status. Demographic data were obtained through a questionnaire. Skin phototype was obtained through colorimetry. Subjects were randomized to receive 10% lactic acid on one nasolabial fold and placebo on the other side. The presence and intensity of adverse sensations, such as itching, burning, or stinging, was evaluated through a 10-point Visual Analogue Scale (VAS) prior to treatment and at 3, 5, 8 and 10 min after the intervention. Subjects with a VAS of 2 or higher were considered positive for the test. A VAS lower than 2 was considered a normal response to skin manipulation. Simultaneously, biophysical changes and barrier function were assessed by colorimetry, transepidermal water loss (TEWL), and capacitance. To decrease measurement variations by skin manipulation, the nasolabial fold was segmented in four areas of 1 cm^2 for each time measurement. Descriptive analyses were made using central tendency measures. Analyses of data were performed using two-tailed χ^2 test, Fisher's test, *t*-test, logistic regression, or Mann-Whitney *U* test for non-parametric values between groups.

RESULTS: Of the included 246 subjects, 68% were women and the mean age was 32 years. The most frequent skin phototype was Ⅴ (ranges Ⅱ-Ⅴ). Thirty-six percent of the subjects identified themselves as having sensitive skin. Fifty-two percent of the subjects were positive to the lactic acid stinging test, with a mean VAS of 4.5 at 3 min. Subjects with the self-diagnosis of sensitive skin were more likely to be positive for the test (80% *vs* 36%, $P < 0.001$). Lighter skin phototypes (types Ⅱ and Ⅲ) showed a higher response to the test compared to darker skin tones (type Ⅴ; OR = 0.88, $P < 0.001$). There were no statistical differences in baseline biophysical measurements. At 3 min, TEWL was significantly higher in subjects positive to the test (27.5 *vs* 23.7, $P < 0.05$). At 5 min, TEWL and capacitance showed statistical differences (26.0 *vs* 22.4, $P < 0.05$, and 239 *vs* 179, $P < 0.05$, respectively). After 5 min, values tended to return to baseline levels in both groups.

CONCLUSION: Sensitive skin is frequent in our population. Darker skin phototypes have a lower prevalence of this syndrome, probably due to inherent differences in skin barrier function.

Key words: Sensitive skin; Lactic acid test; Transepidermal water loss; Colorimetry; Capacitance

Core tip: Self-diagnosed sensitive skin can be found in one-third of Mexican subjects, but using the lactic acid stinging test, we identified a prevalence of 50%. Baseline biophysical measures did not predict the test response, but alterations in subsequent measurements support the hypothesis of a dysfunctional skin barrier. One subgroup presented a slow response to the test, suggesting that other pathways, such as an altered neurosensitive response, are involved. This study indicates a higher prevalence of sensitive skin in subjects with lighter skin phototypes compared to darker ones. These findings suggest that pigmentation may confer a protective mechanism against sensitive skin.

Hernández-Blanco D, Castanedo-Cázares JP, Ehnis-Pérez A, Jasso-Ávila I, Conde-Salazar L, Torres-Álvarez B. Prevalence of sensitive skin and its biophysical response in a Mexican population. *World J Dermatol* 2013; 2(1): 1-7 Available from: URL: http://www.wjgnet.com/2218-6190/full/v2/i1/1.htm DOI: http://dx.doi.org/10.5314/wjd.v2.i1.1

INTRODUCTION

Sensitive skin is defined as the presence of stinging, burning, itching or other unpleasant sensations after physical (light, ultraviolet radiation, heat, cold, air), chemical (cosmetics, soap, water), hormonal, or possibly psychological stimuli[1-5]. Therefore, an exaggerated reactivity to external factors without any evidence of skin lesions or erythema is the main hallmark of this disease[2,4,6]. It is frequently a self-diagnosed condition, and there are no accurate tests to recognize or quantify it because of the individual variations in perception and intensity of the related symptoms[7,8].

Although the pathogenesis of sensitive skin syndrome is not completely understood, the most accepted theory is the presence of an altered barrier function[9-12]. Irritation results from the abnormal penetration of substances to deeper layers of the skin, where they can induce vasodilatation and stimulate c-type neuronal fibers[2,12,13]. Also, changes in the pH of the stratum corneum have been found to induce skin sensitivity through the activation of the transient potential receptor vanilloid (TRPV) neuronal receptors[14-16].

Multiple methods eliciting subclinical irritation of the skin have been explored to objectively diagnose this condition. Some methods include application of lactic acid[17,18], capsaicin[14], sodium-lauryl-sulphate[19], cross-polarized light[20], and quantification of interleukins in sebum[21]. However, the 10% lactic acid test, also known as the lactic acid stinging test (LAST), is considered the most reliable and reproducible of all[13,17]. This lactic acid irritation test creates a more acidic skin environment (pH 4-6), eliciting irritative symptoms in subjects with sensitive skin usually within the first five minutes[17,22].

Epidemiological studies based on self-assessment of sensitive skin to cosmetic or environmental factors from Europe, North America, and Japan have indicated a varied prevalence of this condition ranging between 50%-85% in women and 30%-40% in men[1,2,5,8,23,24]. The importance of sensitive skin syndrome is well-recognized in the clinical setting, especially in regards to patient intolerance to topical prescriptions that would usually be well-tolerated (*i.e.,* glycolic acid, azelaic acid, sunscreens). Some patients also reject the use of soap, moisturizers, and makeup without objective signs of cutaneous disease. Poor compliance to skin treatments due to these factors supports the presence of the syndrome. Although sensitive skin is frequent among Caucasians, its prevalence in Latin-American populations is unknown, and none of the suggested diagnostic tests have been explored so far in that population. Therefore, the aim of this study was to use the lactic acid stinging test to objectively describe the biophysical response and frequency of sensitive skin in Mexican subjects.

MATERIALS AND METHODS

Study design and test subjects

The study was a randomized, placebo-controlled, double-blind test conducted in San Luis Potosi, Mexico, from August 2011 to September 2012. We included healthy volunteers, between 18 and 70 years of age, regardless of their self-assessment of sensitive skin. Exclusion criteria were pregnancy or nursing, known allergy to lactic acid, use of any topical medication for the past 4 wk, and the presence of active dermatoses on the test site. Subjects were university students, workers of public institutions, and the general population who were asked in a random modality to participate. Demographic data included age, sex, skin phototype, previous dermatoses, and the self-diagnosis of sensitive skin. Skin phototype was assessed through the melanin angle in accordance to Chardon *et al*[25] using the following classification: phototype Ⅰ, > 55°; phototype Ⅱ, 41°-55°; phototype Ⅲ, 28°-41°; phototype Ⅳ, 10°-28°; phototype Ⅴ, 0°-10°. All subjects signed an informed consent. The study was approved by our Institution's Ethics Committee and is registered at the United States National Institutes of Health Clinical Trial Register (NCT01591993).

Sensitive skin test with lactic acid

The lactic acid stinging test was performed according to the protocol established by Frosch and Kligman[17], where 10% lactic acid is applied to the nasolabial fold with no thermal induction of sweating. The peak response in subjects with sensitive skin syndrome is consistently reported within the first three minutes, followed by a gradual decline to near baseline values at 10 min[13,17,22]. For this study, we randomly applied 10% lactic acid (Sigma Aldrich, United States) in an aqueous solution on one nasolabial fold and simultaneously applied a 0.9% saline solution as placebo on the other side by a second investigator. Solutions were absorbed in a cotton swab at a constant weight of 0.2 g and applied by a gentle

stroke on each side. Testing was blinded for subjects and investigators. Temperature and acidity of the interventions were measured and controlled for each test. The pH parameters were set at 2.1 for lactic acid and 6.9 for placebo, both at room temperature. The intervention was carried out under controlled environmental conditions of humidity (40%) and temperature (22 ℃).

Volunteers were evaluated initially and at 3, 5, 8 and 10 min after the application of lactic acid or placebo. To obtain biophysical measurements, the nasolabial fold was segmented downwards in four consecutive areas of 1 cm^2 each. This was done to decrease the possibility of inducing changes by the sequential registrations on the skin site.

The primary outcome was a verbally declared sensation of discomfort that included stinging, itching, burning, tingling, tightening, or pain on the site of application. The intensity was measured using a Visual Analogue Scale (VAS) of 10 points, where 0 meant no discomfort, 1-4 meant an increasing but tolerable discomfort, 5-9 meant an increasing and intolerable discomfort, and 10 meant the worst discomfort ever experienced[26]. Subjects declaring a VAS intensity of two or greater at any point of the study were considered positive to the test and categorized consequently with "sensitive skin". We considered that a value below 2 could be attributed to the manipulation and application of a liquid substance. Therefore, subjects with VAS of 0 or 1 were considered negative for the test and had "normal skin". Visual changes (erythema, rash, or other) were evaluated by investigators and documented by digital photography.

Biophysical measurements

Skin pigmentation and erythema were evaluated by a reflectance spectrophotometer (ChromaMeter CR-300, Minolta, Japan). It assesses color in three dimensions: *L* (luminance), which gives the relative brightness, ranging from black to white; *a*, which represents the color range from red to green; and *b*, which represents the color range from yellow to blue. The *a* axis was used to evaluate clinical or subclinical erythema. All measurements were performed without excessive pressure to the skin to avoid modifications of the blood flow.

Transepidermal water loss (TEWL) was calculated using the Evaporimeter DermaLab (Cortex Technology, Denmark), which evaluates the vapor pressure gradient of the skin. The water loss was recorded in g/m^2 per hour. Skin surface hydration was determined by capacitance using the Corneometer DermaLab Moisture Module (Cortex Technology, Denmark). This instrument measures the electrical capacitance of the stratum corneum, reflecting its water content in arbitrary units.

Statistical analysis

The sample size needed was calculated using a minimal expected sensitive skin prevalence of 20% in a large sample population (*i.e.*, ⩾ 100 000). Assuming a confidence level of 95%, at least 246 subjects were needed. Permuted block randomization was used to assign the left or right nasolabial fold to test. Descriptive analyses were made using central tendency measures. Analyses of data were performed using two-tailed χ^2 test, Fisher's test, *t*-test, Mann-Whitney *U* test for non-parametric values between groups, logistic regression, or odds ratio (OR); *P*-values < 0.05 were considered significant. All were performed using the JMP software 8.0 (Cary, NC, United States) at 95%CI.

RESULTS

The study recruited 250 subjects, of which four subjects were eliminated from analysis due to incomplete data. The remaining 246 subjects were included in all of the analyses. The mean age was 32 years (range, 18 to 66 years), 68% were women, and the most frequent skin phototype was Ⅴ (49%), followed by Ⅳ (35.4%) and Ⅲ (12.6%). Eighty-nine subjects (36%) considered themselves as having sensitive skin. The demographic characteristics of the study group are shown in Table 1.

Lactic acid test

A total of 128 subjects (52%) were positive for the LAST during the test period of 10 min. A positive response in the first three minutes was observed in 101 subjects (41%). The mean VAS of this group was 4.5 ± 2.1. Twenty-seven subjects (11%) exhibited a delayed response, demonstrating irritation five to 10 min after the start of the test. Thirty-three subjects (13%) described discomfort at 3 min on the placebo side; eleven of these subjects (63%) were also sensitive to lactic acid. In all of these subjects, discomfort on the placebo side was graded as 2 or lower in the VAS and discomfort disappeared after three minutes. The most common response was stinging (58%), followed by itching (40%), and other sensations (8%). None of the subjects presented clinical erythema during the study, even in the cases of high VAS scores.

Concerning the self-diagnosis of sensitive skin, 80% (n = 71) of individuals were positive to the LAST. On the other hand, only 36% (n = 57) of those that did not consider themselves as sensitive exhibited a positive response to the challenge (P < 0.001), as shown in Figure 1. We found a higher prevalence of responders among women compared to men (60% *vs* 34%, P < 0.001). There were also significant differences in the test outcomes among skin phototypes. We found that lighter skin tones (types Ⅱ or Ⅲ) showed a higher response to the LAST compared to the darker skin tones (type Ⅴ), as seen in Figure 2 (P < 0.001). Logistic regression analysis confirmed this relationship, suggesting that the higher pigmentation was associated with decreased prevalence of positive tests (P < 0.001, OR = 0.88). No significant differences were found among the groups by age (Table 2).

Biophysical measurements

Basal values for all the biophysical measurements did not differ between sensitive and non-sensitive subjects in response to the LAST. However, after the lactic acid challenge, significant differences were observed for all parameters in subjects who were positive relative to those subjects who were negative for the test. Colorimetric measures

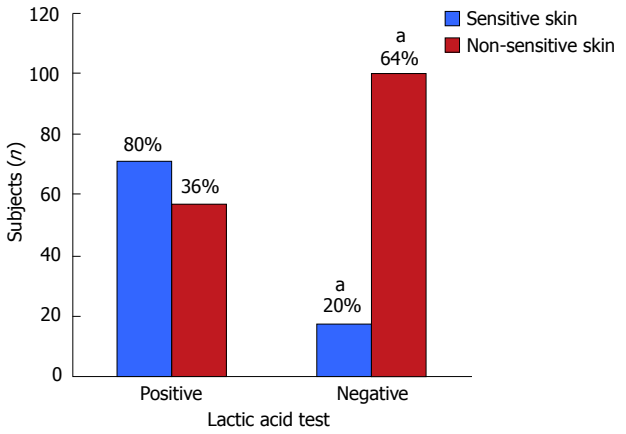

Figure 1 Relationship between the lactic acid stinging test response and self-diagnosis of sensitive skin in study subjects. Of the 246 subjects, 128 were positive and 118 were negative for the test. Bars represent the proportion of subjects with self-diagnosis of sensitive (n = 89) and non-sensitive skin (n = 157) and their results to the test. χ^2 test, $^aP < 0.05$ *vs* positive for the test.

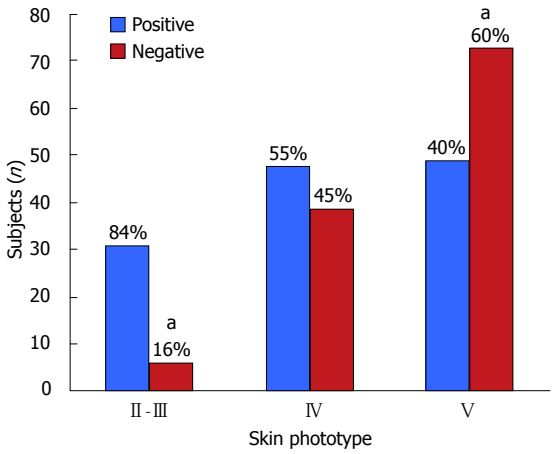

Figure 2 Relationship between skin phototype and lactic acid stinging test response. Subjects with lighter skin phototypes were more prone to display a positive response to lactic acid stinging test (84%), than subjects with the darker skin phototype in the sample population (40%). χ^2 test, $^aP < 0.05$ *vs* positive for the test.

showed statistical differences in the a^* value between onset and at 3 min and 5 min ($P = 0.006$ and $P = 0.017$, respectively), being greater in subjects negative to LAST. TEWL showed an increased water loss in subjects who were positive for the test at 3 min ($P = 0.01$), as at 5 min ($P = 0.03$). Concerning capacitance, values at three minutes were not statistically different but were significantly different at five minutes ($P = 0.002$). These data are summarized in Table 3 and Figure 3.

DISCUSSION

The term "sensitive skin" has been used by the general population and the cosmetic industry to describe an exaggerated and unpleasant reaction to common skin care products or environmental factors[2,12]. This syndrome is currently difficult to define and identify since its manifestations are notoriously subjective. Although it can be associated with other dermatoses[23,24], there is now enough evidence to consider it a true condition and not just a symptom of another disease[9,27,28]. Therefore, self-diagnosis is the preferred method to recognize sensitive skin[8]. Clinically, there are important implications such as the impact on the quality of life for these patients and their compliance to topical treatments[3,29]. In this study, we found that one third of subjects that declared themselves as having normal skin were positive to the LAST, indicating that self-diagnosis is not enough to identify the entire population affected by this condition.

In our study, we found a larger prevalence of sensitive skin than originally expected. We observed a higher prevalence of sensitive skin in women compared to men, but did not find differences in the frequency among age groups. Although some authors have reported similar rates of sensitive skin between men and women[2], most studies have shown that sensitive skin occurs more frequently in women[1,5,23,24]. On the other hand, the relationship between age and sensitive skin is still unclear; previous studies have described a lower prevalence with

Table 1 Demographic characteristics of the 246 subjects included in the study *n* (%)

Mean age in years (range)	31.8 (18-66)
Sex	
Male	78 (31.7)
Female	168 (68.3)
Skin phototype	
II	6 (2.4)
III	31 (12.6)
IV	87 (35.4)
V	122 (49.6)
Self-diagnosed sensitive skin	
Yes	89 (36.2)
No	157 (63.8)

Table 2 Prevalence of sensitive skin by self-diagnosis and response to lactic acid stinging test by age group, sex, and phototype (n = 246) (%)

	Self-diagnosis	Positive	Negative
Age groups (yr)			
< 20	16 (44.4)	18 (50.0)	18 (50.0)
21-30	32 (32.0)	49 (49.0)	51 (51.0)
31-40	17 (34.6)	31 (63.2)	18 (36.8)
41-50	15 (40.5)	21 (56.7)	16 (43.2)
> 50	9 (37.5)	9 (37.5)	15 (62.5)
Sex			
Male	18 (23.0)	27 (34.6)	51 (65.4)
Female	71 (42.2)	101 (60.1)[1]	67 (39.9)
Skin phototype			
II	6 (100)	6 (100)[1]	0 (0)
III	16 (51.6)	25 (80.7)[1]	6 (19.3)
IV	33 (37.9)	48 (55.2)	39 (44.8)
V	34 (27.8)	49 (40.2)	73 (59.8)[1]
Self-diagnosed sensitive skin			
Yes	-	71 (79.7)[1]	18 (20.3)
No	-	57 (36.3)	100 (63.7)[1]

[1] χ^2 test, $P < 0.05$ *vs* negative group.

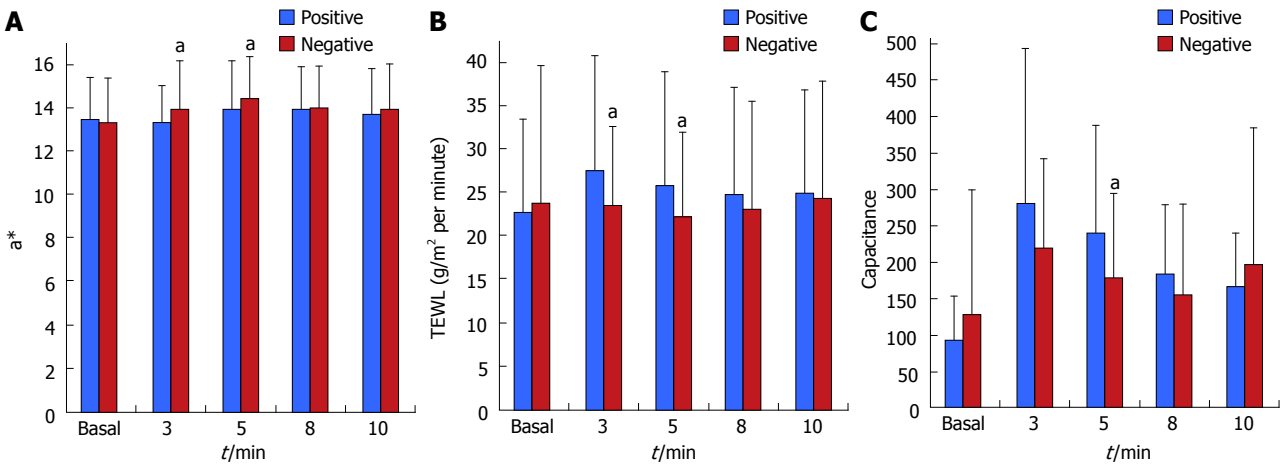

Figure 3 Differences in the skin biophysical response between those that were positive (*n* = 128) or negative (*n* = 118) to LAST. A: a* values, in arbitrary units; B: Transepidermal water loss, in g/m^2 per minute; C: Capacitance, in arbitrary units. Bars represent the mean and error bars represent the standard deviation. Mann-Whitney *U* test, $^aP < 0.05$ *vs* positive for the test.

Table 3 Biophysical measurements evaluated at onset and within 10 min after lactic acid stinging test

	a axis		TEWL		Capacitance	
	Positive	Negative	Positive	Negative	Positive	Negative
Basal	13.4 (11.6-15.2)	13.3 (11.4-15.2)	22.9 (12.5-33.3)	23.9 (8.3-39.5)	92 (30-154)	128 (42-298)
3 min	13.3 (11.7-14.6)	13.9 (11.8-16.0)[1]	27.5 (14.4-40.6)[1]	23.7 (14.9-32.5)	281 (70-492)	220 (98-342)
5 min	13.9 (11.7-16.1)	14.4 (12.6-16.2)[1]	26.0 (13.2-38.8)[1]	22.4 (13.0-31.8)	239 (92-386)[1]	179 (64-294)
8 min	14.0 (12.2-15.8)	14.0 (12.2-15.8)	24.9 (12.9-36.9)	23.1 (10.9-35.3)	182 (85-269)	156 (34-278)
10 min	13.7 (11.8-15.6)	14.0 (12.1-15.9)	25.1 (13.4-36.8)	24.4 (11.1-37.7)	168 (97-239)	196 (9-383)

Values are shown by positive and negative results to the test for the a value, transepidermal water loss (TEWL), and capacitance. TEWL was measured in g/m^2 per minute; *a* and capacitance are shown in arbitrary units. Numbers indicate mean and standard deviation in parenthesis. [1]Mann-Whitney *U* test, $P < 0.05$ *vs* negative group.

increasing age, but other studies have not delineated these differences[1,5,23]. A response was observed with the placebo application (0.9% saline solution), but it was of short duration and low score in the VAS. This placebo response could be attributed to the sensation that is felt after the skin is manipulated or put in contact with liquids.

We did not observe differences in the basal biophysical measurements between subjects with sensitive and normal skin; consequently these values could not predict skin sensitivity. However, in the first five minutes after the test, all patients with a positive response exhibited higher TEWL and capacitance levels compared to non-responders. These findings could be in accordance with the barrier function disruption theory, where the epidermal layer enhances access of a substance leading to its associated clinical response[6,10,30-32]. It is worth noting that nearly 10% of the subjects showed a delayed response to the test and responded after three minutes. This variation may support the presence of different mechanisms of irritation, such as an altered neurosensitive response, as proposed by other studies[14-16].

Although previous studies have reported an increase of the colorimetric *a** value, suggesting subclinical erythema[6,31], we did not observe this change. In contrast, we observed a higher *a** value in subjects negative to the test. These findings can be related to higher skin pigmentation of our population, in whom subtle changes in subclinical erythema can be difficult to identify through colorimetry compared to lighter skin phototypes[33]. It is also important to consider that the *a* value could have been altered by the serial measurements taken in this study; others have shown that reproducibility of erythema measured by colorimetry depends on controlling several mechanical and environmental factors[34].

An important finding was that subjects with lighter skin phototypes (II and III) had a higher prevalence of sensitive skin compared those with darker skin phototypes (V). Pigment increase has been associated with a lower surface pH and enhanced barrier function[35], which may indicate that subjects with darker pigmentation could be more resistant to lactic acid stimulation than subjects with lighter pigmentation. Regression analysis confirmed this relationship, suggesting that darker skin pigmentation may confer protection from sensitive skin. A lower prevalence of sensitivity in darker skin phototypes has also been reported in other studies[1,8,24].

Studies in Caucasians have described a higher prevalence of sensitive skin than observed in the Mexican population of this study[1,5,8,23,24]. There are no published studies that have investigated Latin-American populations,

although one study including Hispanic individuals living in the United States reported similar prevalence rates for this subgroup[1]. Differences in the self-diagnosis of our population sample may be related to inherent features of the population[35-38], as well as cultural differences, such as a low interest in using cosmetic products or reporting adverse reactions to them[23,37]. One limitation of this study is that we assessed the presence of sensitive skin by lactic acid sensitivity exclusively. As previous studies have shown, this sensitivity cannot predict the response to other irritants[7,17]. Therefore, our study may underestimate the prevalence of sensitivity to a wider number of irritants. Nevertheless, if we consider the LAST as a reference, our prevalence of sensitive skin is closer to that reported in many parts of the world[1,5,23].

In conclusion, this study shows that the prevalence of sensitive skin in a representative country of Latin-America, such as Mexico, is relatively high, but was not as high as the sensitivity reported among Caucasian populations. Darker skin phototypes may possess inherent features that confer them a certain resistance to topical irritants. These results show the importance of recognizing this condition as clinically significant in this part of the world. Patients of any ethnic background may exhibit intolerance to topical treatments, including pharmaceuticals, cosmeceuticals, and cosmetics. The proper objective identification of sensitive skin can improve poor compliance to topical treatments usually found in patients who have sensitive skin syndrome.

COMMENTS

Background

Sensitive skin is a syndrome characterized by personal experience of discomfort after the application of topical substances without any objective evidence of irritation. In Caucasians, its frequency has been described in up to 60% of females and 30% of males. There is no standard test to diagnose this syndrome, and so it is still considered a self-diagnosed entity.

Research frontiers

The prevalence of sensitive skin and its biophysical response have not been described in Latin-American populations. There are no previous studies of objective, diagnostic methods for this syndrome in this area of the world.

Innovations and breakthroughs

Self-diagnosis of sensitive skin in Mexico is less frequent than in other parts of the world. Using the lactic acid stinging test, we determined that its prevalence in Mexico is high, although not as high as that found in Europe and North America. Furthermore, individuals with darker skin showed a lower prevalence of this condition. Since this study was conducted in a relatively homogeneous population living under similar climate conditions, these differences among phototypes could be related to the inherent pigmentation of the skin.

Applications

The lactic acid stinging test is a simple, reproducible and non-expensive method for the diagnosis of sensitive skin. Subjects with lighter skin phototypes are at higher risk of having this syndrome. Identification of sensitive skin is important not only for the dermatologist, but also for the cosmetic and pharmacology industries, since these subjects can have a marked intolerance to topical treatments and poor treatment compliance within the medical context.

Terminology

The lactic acid stinging test is a diagnostic method where 10% lactic acid is applied on the nasolabial fold. Subjects with sensitive skin will indicate stinging or itching during the first three to five minutes with variable intensity. This response typically disappears 15 min after the application.

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The authors explored the prevalence and biophysical reaction of subjects with sensitive skin in a population from Mexico, through the application of the lactic acid stinging test. The results demonstrate a high prevalence of previously unknown sensitive skin and suggest that subjects with dark skin phototypes are less prone to this condition compared to subjects with lighter skin. This study is the first to explore the presence and behavior of sensitive skin in a Latin-American population. This work may also set a foundation for the investigation of pigment-associated physiological pathways that could explain the differences found among skin phototypes.

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CASE REPORT

Progressive nodular fibrosis of the skin: A pediatric case

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Abstract

The term fibromatosis describes fibrotic tumor-like lesions of the skin which are seen in all age groups. They may be congenital or acquired and occur as single or multiple lesions. Classification of fibromatosis includes several clinical and pathologic variants. Progressive nodular fibrosis of the skin is a rare condition which has been scarcely reported in the literature and never in pediatric age. The clinical presentation is not specific showing asymptomatic, reddish-brown nodules. Histology shows abundance of spindle-shaped dermal fibroblasts. Here we describe an unusual pediatric case and discuss the diagnosis, which is possible only with histopathology, and the importance of differential diagnosis.

Key words: Fibromatosis; Nodules; Childhood

Core tip: Progressive nodular fibrosis of the skin is a rare condition characterized by asymptomatic, reddish-brown nodules resembling hypertrophic scars. Histology shows abundance of spindle-shaped dermal fibroblasts. It is mandatory to achieve a correct diagnosis.

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INTRODUCTION

Fibromatosis is a term used to describe benign fibrous tissue proliferations which are apt to infiltrate the skin and recur when removed, without to metastasize. They consist of a heterogeneous group of several conditions which may be congenital or acquired and occur with singular or multiple lesions.

Progressive nodular fibrosis of the skin is considered a rare variant, although it does not appear in the classification of superficial fibromatoses. These include palmar and plantar fibromatosis, penile fibromatosis, knuckle pads and the large group of juvenile fibromatoses[1]. It is characterized by multiple skin nodules developing around the teenage years. The condition, scarcely described in the literature, is slowly progressive over several years. No organs other than the skin are involved and the prognosis is good.

Here we present a new case of progressive nodular fibrosis of the skin which, to the best of our knowledge, is the first pediatric case reported in the literature thus far.

CASE REPORT

A 5 years-old girl referred to our Dermatology Unit for the continuing eruption, during the last four months, of multiple cutaneous small nodules localized at the trunk, legs and arms.

Family history was negative for skin diseases. Personal anamnesis was negative except for varicella which occurred nine months before. For this reason the initial skin lesion had been interpreted by her paediatrician as a post-varicella keloid. Only later, after the outbreak of several

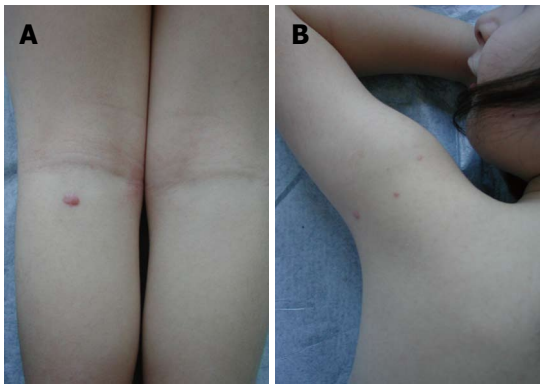

Figure 1 Clinical findings. A: The first nodular lesion was localized on the flexor surface of the left limb; B: Cluster of three reddish nodules on the left shoulder.

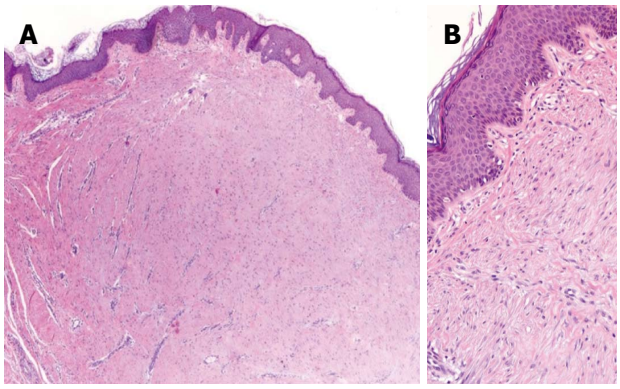

Figure 2 Pathological findings. A: Dermal fibroblastic proliferation with a variably collagenous stroma which tends to be more cellular than keloids, with less prominent hyalinised collagen fibers (HE, × 4); B: Dermal proliferation of numerous fibroblasts without cytologic atypia (HE, × 20).

small nodules throughout the following months, the child had been addressed to our unit.

At physical examination the child presented eight reddish papulonodular lesions involving the trunk, arms and legs (Figure 1). The lesions were firm, asymptomatic, with a diameter ranging from few millimetres to one centimetre. No tendency to coalescence was observed. Laboratory investigations did not disclose abnormalities. Histopathologic examination showed a normal epidermis and a dermal proliferation of numerous fibroblasts without cytologic atypia (Figure 2). At immunohistochemical examination neoplastic cells resulted negative for desmin, CD34 and S-100 protein. No excisional therapy was considered and the girl is still under follow-up.

DISCUSSION

"Progressive nodular fibrosis of the skin" or "multiple benign progressive fibromatosis of the skin" is a very rare disease. The condition was firstly described by Stevanović[2] in 1977 in a 44-year-old man who developed multiple skin nodules from the age of 10 years. We were able to discover in the literature only a further case reported by Bauer *et al*[3] in a 33-year-old man who noticed the first nodules fifteen years earlier. Thus, to the best of our knowledge, our patient is the first pediatric case of progressive nodular fibrosis of the skin reported in literature to date.

The clinical presentation of this unusual disorder is quite non specific occurring as a papulonodular eruption of reddish-brown elements without associated symptoms. In our case, at physical examination, the oldest resembled an hypertrophic scar, but the newer ones did not show any cicatricial aspect. History of varicella during the preceding months induced the suspect of a post-varicella keloid reaction in the first lesion, but the histology was not typical of a keloid scarring. In addition multiple nodules continued to occur throughout the following months.

Histological examination is mandatory to achieve a correct diagnosis showing the presence of numerous spindle-shaped fibroblasts in the dermis. Keloids are characterized by the presence of acellular hyalinized eosinophilic collagen bundles. Nodular scleroderma is a fibrosing reaction, presenting well-defined, firm, raised nodules, resembling keloids which usually occur in patients already suffering of scleroderma. Histological findings consist of inflammation at the dermal-subcutaneous junction and hyalinized collagen bundles[4]. Connective tissue nevus (collagenoma) is usually observed in the first years of life and is histopathologically characterized in the dermis by a diffuse increase of normal appearing collagen[5].

Bauer *et al*[3] in their paper reported the results of a molecular study showing an increased collagen synthesis and a reduced production of collagenase. The basic defect leading to this disorder is still unknown. However these authors postulated that the fibroblasts of those lesions may represent a clonal population of cells with an aberration in the transcription or translation during collagen synthesis. Also a posttranslational abnormality could not be excluded.

In conclusion, progressive nodular fibrosis of the skin is a rare and probably underestimated and misdiagnosed cutaneous disease. It should be added to the list of juvenile fibromatoses[1]. This condition should be suspected in the presence of multiple, spontaneous papulonodular lesions occurring in adults as well as children. Histology is required for the diagnosis. The low number of reports does not allow to carry out a reasonable, specific protocol follow-up, but regular visits are strongly suggested, in our opinion, particularly in children.

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V.

Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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AIM AND SCOPE

World Journal of Dermatology (*World J Dermatol*, *WJD*, online ISSN 2218-6190, DOI: 10.5314), is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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EDITORIAL

Teledermatology update: Mobile teledermatology

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Abstract

Mobile teledermatology is a relatively recent modification of teledermatology, which involves using mobile platforms like cellular phones to transmit images and data for the purpose of teleconsultations. With the rapidly improving quality of smart phone cameras combined with easier access to mobile internet, mobile teledermatology is emerging as a feasible and cost-effective method for teledermatology practice. Mobile teledermatology has shown good results in concordance studies comparing it to face-to-face consultations. Mobile teledermatology can be used for most types of clinical dermatology cases. Mobile teledermatology has been found to be useful in diagnosis, screening and triage of skin lesions including skin cancers. It is also useful as a tool to follow up patients with chronic dermatological problems like psoriasis and chronic wounds. The obvious advantage of mobile teledermatology is it's cost-effectiveness and the fact that access to expert dermatology care is made easier for patients especially in remote areas. Further research is however required to standardize protocols for mobile teledermatology. Collaborative research among people working in this field would be very useful in this standardization and would help in optimizing the opportunities provided by this interesting tool. This article gives a brief overview of mobile teledermatology including definitions, tools involved, indications, limitations and future applications.

Key words: Teledermatology; Mobile teledermatology; Feasibility; Concordance; Skin cancer screening

Core tip: Mobile teledermatology is emerging as a feasible and cost-effective method for teledermatology practice. Mobile teledermatology is useful in diagnosis, screening and triage of skin lesions including skin cancers. It is also useful as a tool to follow up patients with chronic dermatological problems. However more studies are required for standardization of mobile teledermatology protocols.

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INTRODUCTION

Dermatology is a visual specialty and this makes it the most apt for remote diagnosis using patient's images. Teledermatology has been shown to be an effective method for diagnosis and triage of dermatological conditions. Research in this field has grown extensively over the last decade. One particular area which has received increased interest in the last few years is "mobile teledermatology". This article focuses mainly on this newer area of teledermatology[1-3].

DEFINITIONS AND CLASSIFICATION

The WHO definition of telemedicine is: "The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the

continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities"[4]. The application of the principles of telemedicine to dermatology is generally referred to as "teledermatology"[2]. A teledermatology tool is the specific technology or modality used to deliver dermatology care and the application of teledermatology tool to actually deliver dermatology care is referred to as teledermatology practice (TP)[5].

The TP is traditionally classified into three broad groups: (1) Video based or "real time" consultations-The advantage of real-time consultations is that the expert can clarify gaps in the history directly with the referring physician or the patient. This disadvantage is that video quality is often not clear enough to make accurate diagnosis of skin lesions[2]; (2) Image based or Store and forward teledermatology (SAFT)-is the most used method of teledermatology, where the concerned images are forwarded to the expert who offers an opinion by e-mail or by a follow up real time consultation. The advantage is that clear visualization of the skin lesions can be done. The disadvantage is that gaps in history are more difficult to address. A modification of the SAFT is the online discussion groups where multiple experts can comment on cases which are difficult to diagnose or manage. Nowadays the common JPG format is used for a lot of SAFT based consultations. The Digital Imaging and Communications in Medicine format is another standard format used medical image handling and storing in the context of teledermatology, especially when the images are linked to electronic patient medical records[2]; and (3) Hybrid teledermatology, where a combination of video and image files is used. This is probably the most ideal method of teledermatology provided that both the referring side and the expert have the requisite equipment for good quality video consultations along with a effective and standardized image transfer protocol[2,6].

All the above are based on stationary platforms. In contrast with advances in mobile technology it has become feasible to use mobile phones as a medium to transmit dermatological images-clinical and dermoscopic, for diagnosis, triage and follow up purposes. Using such non-stationary platforms for data transmission, primarily in the form of mobile phones for teledermatology is generally referred to as teledermatology. Tablet computers and other hand held devices can also be used for mobile teledermatology. It should be understand that most mobile teledermatology consultations are basically a modification of SAFT[3,5,7]. The first effective used of mobile phones for teledermatology in the follow up of wound care was described by Braun *et al*[8]. A modification of the mobile teledermatology system is when the patient or the referring physician sends the images *via* the mobile phone to a fixed internet portal where the expert can log in and give his comments[9]. The images in mobile teledermatology can be sent directly through internet protocols or through the mobile phone service itself in the form of multimedia messaging services (MMS)[10].

ADVANTAGES OF MOBILE TELEDERMATOLOGY

The obvious advantage of mobile teledermatology is the mobility factor. The consulting dermatologist and the referring physician (or the patient) does not need to be at a particular location for transmitting and receiving data. Moreover, with time mobile teledermatology has become cost effective with the decreasing cost of smart phones, increased capability of mobile phone cameras and mobile broadband services. A number of feasibility studies have suggested that mobile teledermatology is a useful tool in diagnosis, triage and follow-up of dermatological cases. Ultimately an effective mobile teledermatology system could help in significant cost cutting in patient care, especially in the context of cancer screening, follow up of chronic skin conditions[11-17].

SPECIFIC CONTEXTS OF APPLICATION OF MOBILE TELEDERMATOLOGY

The application of such mobile teledermatology systems would be particularly useful in resource poor and remote areas[13,15,18]. One of these studies was conducted in human immunodeficiency virus (HIV) positive individuals in Botswana and Overall, mobile teledermatology consultations were well accepted by HIV-positive patients. Most patients in the study felt that mobile teledermatology consultations for all parts of their body would be acceptable. Facial lesions were also not a problem as long as it was ensured that personal recognition was not possible[15]. Another study from Egypt also found a good concordance between face-to-face clinical diagnosis and mobile teledermatology consults using a 5 megapixel mobile phone camera. This study also showed the feasibility of mobile teledermatology for clinical diagnosis, though this study had a limitation of a small sample size[13].

There are a number of studies which have tried to evaluate the use of teledermatology in screening for skin cancers. Mobile teledermatology has also been shown to be effective in diagnosis and triage of skin cancer. A study by Lamel *et al*[16], showed a good concordance between mobile teledermatology consultation and face-to-face consults for screening and management of skin cancers. Combining mobile teledermatology with dermoscopy (teledermoscopy) can further increase the diagnostic efficacy of mobile teledermatology in the context of screening for skin cancers. Mobile teledermoscopy can be essentially implemented as a triage screening tool for malignant tumors to facilitate early detection and diagnosis, which in turn would lead to improved patient outcomes. At the same time this would lead to a reduction in the cost burden for skin cancer screening programs[14,19-21].

The other major indication of mobile teledermatology is in the follow up of chronic patients. Studies have shown that mobile teledermatology is feasible in following up patients with chronic skin conditions like psoriasis[17,22] and for wound follow up[8].

The suitability of cases for teledermatology consultations has been addressed by various studies including our own studies[6,23]. Logically most cases suitable for teledermatology in general would be suitable for mobile teledermatology also. In our previous study[6], we found that certainty of diagnosis was more in cases like viral warts, herpes zoster, acne vulgaris, irritant dermatitis, vitiligo, and superficial bacterial and fungal infections. In some cases like papulosquamous diseases, chronic granulomatous conditions, autoimmune vesiculobullous conditions and vasculitis the certainty of diagnosis was relatively lower. However in our study the utility of teledermatology as a screening and triage tool was evident.

We have also been using mobile teledermatology over the last two years (using mobile phones at both ends of the consultation) and have found a high level of satisfaction among the patients for this model of teledermatology. This probably reflects the high levels of satisfaction in general with teledermatology that has been reported by various studies in the past[24-26].

PROBLEMS AND DISADVANTAGES

Most of the problems inherent to SAFT exist in the case of mobile teledermatology also-these include legal, ethical and cultural issues-especially in the case of genital and facial lesions. Like in SAFT the referring physician should have a general idea of which lesions to focus on and should have a basic understanding of dermatological nomenclature to really effectively convey the patient history. Standardization of the images is another issue. The referring physician should be familiar with the basic of dermatological photography and ideally both ends of the teledermatology consult should have the same type of mobile equipment. Mobile internet connectivity is another issue especially in resource poor regions. Mobile dermoscopy is another valuable addition to mobile teledermatology, but equipment for the same is limited and costly at present. Another issue that should be understood that for a given value of megapixels, the resolution for a mobile phones tends to be less than that of a proper digital camera, essentially because the size of the sensor tends to be smaller in a mobile phone. Also the macro mode for taking close-up images of skin lesions does not work as well in mobile phones as in a dedicated camera. Previous studies have mentioned a lack of support among administration and clinicians in general for implementation of teledermatology services. This could be a hindrance in the development of mobile teledermatology programs also[27]. The lack of proper rapport with the patients is an inherent problem with SAFT and the same applies to mobile teledermatology also[28,29].

THE FUTURE AND CHALLENGES IN MOBILE TELEDERMATOLOGY

With the advent of various tools which can convert smart phones into dermoscopes, mobile teledermoscopy combined with the normal clinical images could definitely lead to more effective diagnosis and triage for dermatological diseases especially malignancies. Self monitoring mobile based protocols to assess melanomas and further refinement of mobile dermoscopy for melanoma screening are being given increasing importance. However it is suggested to exercise some amount of caution in diagnosis of melanoma risk analysis while using mobile teledermatology considering the lack of proper standardization at present[30-32].

Options for transferring histopathology images to mobile phone and transmit it along with clinical and dermoscopic images would be another exciting possibility in the future. Teledermoscopy has already proven to be an effective triage tool for melanomas. Often clinical images are insufficient for accurate diagnosis of melanoma. Combining the clinical images with dermoscopy has shown to significantly improve diagnostic accuracy for melanomas. The development of a standardized and cost effective method for teledermoscopy would enhance the effectiveness of teledermatology in screening for skin cancers[33-35].

Electronic medical records are gradually becoming the norm the world over including dermatology[36]. Designing electronic medical records which are adapted for the mobile phone will also help in better documentation of mobile teledermatology consultations.

Mobile teledermatology could be a very useful tool in dermatological and aesthetic surgery, in the future. This could be especially useful in patient follow up for wound care thus avoiding unnecessary direct visits for follow up after minor procedures. Nurses and other allied health professionals may also be trained for follow of cases of dermatological surgery. The future might also see more of patient initiated mobile teledermatology[37-48].

Standardization of dermatological imaging for teledermatology and the legal aspects associated with transmission of medical images will require a lot of streamlining and clarity in the context of mobile teledermatology. The person at the referring end should be able to take good quality images for proper training for this will be an essential pre-requisite for effective mobile teledermatology[49-52].

Finally we can expect to see more of hybrid mobile based consultations where initially clinical or dermoscopic images are sent to the expert and later followed up by a real time/video consult where any gaps in history can be addressed.

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REVIEW

Stress involvement as trigger factor in different skin conditions

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Abstract

Dermatological conditions are intimately related to stress. There was a great interest in this field in the last years. Stress could be involved as a trigger factor for a lot of cutaneous diseases: alopecia areata, psoriasis, vitiligo, lichen planus, acne, atopic dermatitis, urticaria. For other conditions: seborrheic dermatitis, hyperhydrosis, herpes, pemphigus, a.s.o, there are anecdotal notices. On the other hand, the skin disease itself could induce a secondary stress for the patient, influencing his quality of life. The stress *per se* is less important than the "perceived stress", the patient's perception of the stressful situation. This perception could be influenced by the psychological state of the patient. Anxiety, depression could change the perception of the event. It is important to take care of these aspects during the consultation. A good cooperation with psychiatrist or/and psychologist could improve the results, besides the specific therapy.

Key words: Stress; Alopecia areata; Vitiligo; Psoriasis; Lichen planus; Acne; Urticarial; Atopic dermatitis

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INTRODUCTION

The state of health represents the balance between the mental, emotional, physical and relational areas. The stress means an abnormal or extreme physiological adjustment to the adverse effects of the environment. Selye defined stress and described the physiologic changes induced by stress, under the designation "general adaptation syndrome". About 80% of affections could be induced or aggravated by stress. The reaction to stress could be influenced by the genetics and also by someone's perception. The stressors could be environmental, behavioral or psychological[1]. The state of stress could be influenced by external factors (life events, social, work or natural environment) and individual factors (attitudes, traits, temperament, past experiences and needs) that are interconnected. The reaction depends on "how the person interprets or appraises (consciously or unconsciously) the significance of harmful, threatening or challenging event".

Stressful events could induce a psychosomatic disease, especially in some patients with high reactivity to stress. We can expect similar reactions of patients to major life events listed by Holmes and Rahe (death, serious illness-personal or of a family member, separations and divorces *etc*). But, there are other situations that can depend on the psychological traits of the patient, previous experiences, family models (reactions to exams, to different changes in life, to arguments). Alongside the effect of life stressful event, another factor that could influence the appearance and evolution of psychosomatic diseases is the psychological vulnerability of the patient experiencing the stress. Higher trait of anxiety could suggest this vulnerability.

Perceived stress could be more important and with a greater effect than the stressful event itself. The reaction of the individual is an attempt to restore the balance and depends on the coping abilities. Persons with high stress resistance are characterized by a control on the events and life situations, acceptance of the responsibility of the facts that are happening. They are involved in everything they are doing and they accept the changes as natural. The ability of patients to cope with stress could be reduced by alexythimia (incapacity to verbally express the emotions), insecure attachment and poor social support[2-4]. Social programs including stress management and psychological support are important in the achievement of coping abilities[5].

Even there are previous observations of stress relation with different dermatoses, first mentions of psychosomatic dermatology are from the early 80's, when Cermak and Panconesi described the connection between "psyche and skin diseases"[6,7].

Skin responds to different types of stressful stimuli and psychologic states. Stress intervenes through the hypothalamic-pituitary-adrenal (HPA) axis with the release of neuromediators from the nerve endings and dermal cells (neuropeptides, neurotrophins, lymphokines). There are connections among endocrine-nervous and immune systems. Stress has been reported to cause decreased natural killer cell cytotoxicity, depressed mitogenic responses in lymphocytes, increased IgA levels, enhanced neutrophil phagocytosis and activation of interferon synthesis in lymphocytes[8].

Corticotropin-releasing hormone (CRH) coordinates the systemic stress response *via* hypothalamic-pituitary-adrenal axis activation with subsequent modulation of the inflammatory response. Stress can affect expression of immune-mediated inflammatory diseases, associated with HPA axis abnormalities. HPA axis components including CRH and its receptors (CRH-R) exist in the skin and exhibit differential expression according to cell type, physiological fluctuations and disease states. This confirms a local functioning cutaneous HPA-like system. Peripheral CRH may exhibit proinflammatory effects. CRH may influence mast cell activation, modulation of immune cells and angiogenesis[9].

Mast cells play an important role closely linked to the sensory nerves in the skin. During psychological stress there is a release of neuromediators, CRH and alfa-MSH (melanocyte-stimulating hormone) that are activating mast cells. Mast cells' mediators (histamine, tryptase and NGF-nerve growth factor) can stimulate the neuropeptide-containing C fibers, increasing the inflammation. Mast cells are releasing pro-inflammatory cytokines and chemokines[10].

Psychological stress has a negative impact on cutaneous permeability barrier function, mediated by increased endogenous glucocorticoids[11,12]. There is an inhibition of epidermal lipid synthesis[12]. Psychological stress could also compromise the antimicrobial defense, also by glucocorticoid-dependent mechanisms[13].

The role of stressful events in psoriasis, alopecia areata, atopic dermatitis, pruritus and urticaria seems to be apparently clearer. The role of stressful events in vitiligo, lichen planus, acne, rosacea, pemphigus and seborrhoeic dermatitis is either controversial or insufficiently explored[1,14-16].

ALOPECIA AREATA

Hair is very important in our lives, even since childhood, so hair loss could affect both self-image and social relations. The aetiopathogenesis of alopecia areata is complex, and includes genetic factors, autoimmune processes, infectious factors and psychological factors (stress and personality characteristics of patients).

First observations are dating from early "60's when alopecia areata was related to mental stress[17,18]. It took about 15 years to come again to the idea of "alopecia areata and stressful events"[19] or correlating hair loss in children to underlying emotional disturbance[20]. Patients with alopecia areata are considered by some authors to lack symbolic or language schemes of representation for experiences of separation and loss, which affects personality and creates a devoid-of-affect impression. Alopecia areata patients have high rates of alexithymia and avoidant behavior that could reduce the ability to cope with stress[1,21,22]. In 1991, there is a case-control study on 92 Saudi patients associating atopy and psychological stress to alopecia areata[23].

There are different opinions regarding the involvement of stress in alopecia areata. Some believe that general events could appear in up to 80% of cases with alopecia areata, with 62% stating this as a serious event[24]. Other studies found stress involvement as precipitating or aggravating factor in 55% to 75% of cases (compared to 20% in controls)[25]. On the other hand, Tan *et al*[26] found that stressful events preceded hair loss in only 9.8% of 132 alopecia areata patients. Van der Steen *et al*[27]. did not correlate the pathogenesis of alopecia areata with emotional stress. It seems that stress in alopecia areata is not recent (*i.e.*, during the past year), the "aetiology" being much more insidious. Old stressful situations are reported more often, revealing a chronic stress[28]. A case-control study on 90 patients reported total lifetime and early childhood traumatic disease, alopecia areata patients having a higher score of the global impact to their traumatic experiences than controls[29].

Some studies mention the importance of perceived stress, which is sometimes even more important than the stressful situation itself for both the first episode and recurrence[30,31]. Gupta cited a study by Andersen, in which only 23% of subjects had recent stresses that occurred less than 3 mo before disease onset[32]. Gupta *et al*[33] described alopecia areata patients in their study as having high reactivity to stress; these patients also had higher scores for depression. Picardi *et al*[3] did not find significant differences between the same two groups when comparing the total number of stressful events

and the number of undesirable or major events (21 cases studied). Moreover, the control group had a greater number of uncontrollable events. The authors support the idea of the influence of personality characteristics (alexithymia, avoidance of attachment relationships) or poor social support on individual susceptibility to stressful situations. As for children and adolescents are even fewer reports regarding stress, starting from no correlation with stress (to involvement of stressful events in up to 80% of children)[34].

There are reports that alopecia areata pediatric patients experienced more stressful events[35,36]. In studies regarding alopecia areata in children and teenagers stress seemed to be a precipitating factor in 9.5% of cases (up to 3 mo prior to onset of disease)[37], or even in 58% of cases[38]. Liakopoulou *et al*[39] correlate the alopecia areata in children with the lack of positive events during the time before the onset (33 cases). There are other studies[40] that had found no significant difference between the mean number of positive or negative life events in children with alopecia areata (12 cases compared to a normative sample). The types of events noticed by children with alopecia areata were mostly related to school (beginning school or kindergarten, exams at the end of gymnasium, change of class or school, problems with school-mates or teachers, too many classes or homework, children feeling over-solicited)[38]. Other data[37] had found similar types of events involved before the onset of alopecia areata in children: family disputes, starting school, parent's divorce, operation, but also different kinds (birth of a sibling, commencement of speech therapy). The study of Andreoli[35] on 180 children and teenagers has proposed as potential stressful events: separations (from people, pets, habits, things or familiar environment) in 37% of cases, relational problems (in family, school, with friends) in 32% of cases, but also the difficulties for the child to fulfill the parents' expectations (especially in school activity) in 24% of cases.

PSORIASIS

Psoriasis is a chronic inflammatory with a prevalence of 2% in general European population and even higher in children (4% in children under 16 years old)[41]. Even the impact on the patient's and family's life is important, only a few studies are searching for the presence of stress as potential triggering factor.

The aetiopathogenesis is complex, including genetic and environmental factors. Among risk factors, stressful life events[42-45] seem to play important roles. In 1980, Fava[46] noticed that patients with psoriasis were exposed to stressful life situations before onset significantly more than those with fungal infections. In Burkhart *et al*[14] review, the role of stressful events in psoriasis seems to be clear for both onset (42%-72%) and relapses (80%). But, there are other studies that found no difference comparing psoriatic patients to controls regarding the mean number of recently experienced life events, the number of undesirable, uncontrollable or major events[4,47]. In a prospective cohort study[48] no association between psoriasis and antecedents of stress was revealed. Despite the constant interest for stress involvement in psoriasis, case-control studies were made only during last years and only a few were using a type of questionnaire to investigate the presence of life events[4,47,49]. Most of papers are presenting self-reported situations.

There are different data in the literature. Results regarding stress involvement are starting from values of 6.9% (precipitating)[50], 35% (for onset)[51], 45%-50% (for onset/recurrence)[52-54], up to 60%-72% (for onset[55,56] or exacerbation[51,56-58]). "Incubation" period differs from 15 d (honeymoon)[56], to one month before the onset/exacerbation[52], three months[55], or six months[52]. Compared to controls, patients with psoriasis reported more stressful events during the last 12 mo[49]. There is a comparative study presenting stress induced exacerbations in children (50.4%) and adults (42.7%)[59].

There are studies that found no significant differences between patients and controls regarding the total number of stressful events, the number of undesirable, uncontrollable and major adverse events, or no correlation between the severity of stress and the moment of onset or exacerbation of psoriasis[4,60]. A prospective study, but on a small sample (9 women) does not support the idea of psoriasis worsening by stress[61]. Stress was associated with psoriasis only for patients experiencing four or more stressful events in the preceding year[14]. Patients with psoriasis had a very high level of perceived stress and a deeply altered quality of life[62]. Patients' beliefs of stress involvement range from 37% to 78%[63]. Daily stressors influence disease outcome in patients with psoriasis by affecting cortisol levels at moments of high stress. Furthermore, patients with persistently high levels of stressors seem to have a specific psychophysiological profile of lowered cortisol levels and may be particularly vulnerable to the influence of stressors on their psoriasis[64].

Family stress influences the psychological well being more than other types of daily stress events in patients with psoriasis[65]. Family matters were mentioned by 42.7% of psoriatic patients, statistically significant compared with controls ($P < 0.0001$). In 35% of psoriatic cases, "the stressful event" was represented by the illness/death of someone dear[54].

An interesting study[66] compared the differences in stressful situations described by psoriatic patients during peace and war time. During peace periods there were evoked, as in our study, death of a family member, own disease or serious disease of a family member, but also problems with children education, divorce or marriage. War time stressful situations were different: killing/wounding some member of family or close to person, wounding inquiring person, separation from wife/children, loosing of property or soldiering in the army[67].

There are studies mentioning that up to one third of patients could have the very first lesions even since childhood[41,67], which can increase the psychological distress

during the formative years. Negative traumatic experiences could influence the onset of psoriasis both in early childhood and adulthood[68].

There is a lack of studies in pediatric dermatology regarding the subject of stress involvement. There are reports of stress[67,69] as trigger in psoriasis among other factors such infections[67,69,70], summertime[69] or trauma[69]. Most of the data mention inflammatory focus as the most frequently trigger in childhood psoriasis[70,71]. Negative traumatic experiences during childhood seem to be present in psoriatic patients, but there is no correlation between the severity of the disease and traumatic experiences[68]. Seyhan *et al*[71] found the presence of emotional stress in more than half of a group of 61 cases. A study[59] on 223 cases reports that psoriatic lesions could be exacerbated by stress (50%), but also by upper respiratory tract infection (28%) and trauma (49.6%). In a very recent case-control study, children with psoriasis mentioned more often than controls the presence of stressful life events in the year preceding the disease and also environmental tobacco smoke exposure at home[72]. But, there are also reports of patients not aware of any role of infections, injury or stress as precipitating factors of psoriasis[73].

VITILIGO

With a 3000 year history, vitiligo is one of the important stigmatizing skin conditions. The importance of stressful events, including the number of these, before the onset has been described in several case-control studies[74,75]. Stress is reported before onset in more than half, up to 65% of patients[74,76,77]. Patients with vitiligo had a significant number of stressful events in the year preceding the onset of the lesions, compared to controls[78]. But, there are other studies with no differences between vitiligo patients and controls, comparing the number of stressful events[2,74]. Women seem to be more sensitive to stress, mentioning more stressful events than controls[74]. Vitiligo patients reported more than controls the exposure to three or more uncontrollable events, suggesting that alexithymia, insecure attachments and poor social support could reduce the ability to cope with stress, increasing the susceptibility to vitiligo[2].

Potential stressful situations reported in other vitiligo studies were marital or financial problems[75], loss of loved ones (*e.g.*, death, separation), illnesses and changes in eating or sleeping habits[75]. In a study by Silvan, 40% of vitiligo patients experienced the death of a close friend or family member. In comparison, 25% of vitiligo patients experienced loss in a study by Papadopoulos *et al*[75]; loss in this case meaning relocation, or the loss of friends, family, or familiar surroundings[75,79]. Patients with vitiligo often have different perceptions of the etiology of their disease. They thought that both stress (30%-60% of cases) and genetic background (2432%) are involved[77,80]. There are few reports of the psychosocial impact of vitiligo on children and adolescents although vitiligo can have a serious impact on their lives. This ranges from vitiligo having no correlation with stress to involvement of stressful events in about 50% of cases[70,81]. Psychological vulnerability can also influence the onset and evolution of psychosomatic dermatoses, alongside the presence of stressful events. A recent study[82] on the temperament of children with vitiligo revealed that these children score high on the "harm avoidance" scale, meaning that compared to their healthy siblings, children with vitiligo seem to have a greater fear of strangers and have a heightened response to any changes in a close relative. Age, change of location, and situational or environmental alterations can also be predictors of stress. About half of vitiligo vulgaris patients have onset of their illness during childhood, which can increase psychological distress during the formative years[83]. On the other hand, in the prepubertal period, children are not focused yet on their physical appearance, so an early onset could also act as a "protective factor", enabling the child to develop compensatory mechanisms of coping with disease and ways to strengthen self-esteem[84]. Periods of adjustment to new conditions, such as the beginning of education (school or kindergarten), being an only child, or having separated parents (particularly in boys) could be considered special situations in which children with vitiligo need more support and require the intervention of families, teachers and doctors[81].

LICHEN PLANUS

Lichen planus is a dermatological condition that could appear in 0.38% to 6%[85,86] of outpatients, mostly over 45 years old[87]. There are different opinions regarding the etio-pathogenesis of lichen planus, some of them correlating stress involvement with the onset/extension of the disease. There are not so many papers studying the presumed role of stress in lichen planus patients, and most of them are referring to oral lesions only. Stress, alongside spicy food, poor oral hygiene could precipitate or aggravate oral lichen planus[88,89]. Burkhart *et al*[14] made a correlation between stress and oral lichen planus, a stressful situation before the onset being reported in 51% of cases, but there was no control group included[90], but with no control match. There is another study on 46 patients with lichen planus that revealed with stress involvement in 67% of cases, compared to 21% in controls[91]. In a study of 55 cases, Mansur[92] described stressful events in almost 90% of patients with cutaneous lichen planus. As for oral lichen planus, there is a mention of stress presence in up to 90% of 30 cases (case-control study)[93]. On the other hand, there are studies that did not observe more stressful life events in oral lichen planus patients compared with controls[94,95]. Patients with lichen planus could have higher levels of salivary cortisol than controls, revealing a correlation with the level of stress[93,96,97]. A study on oral lichen planus has not found any difference between patients (30) and controls regarding the salivary cortisol level[94]. Family problems seem to be

more important as stressful events in patients' lives[91,92]. Lundqvist *et al*[98] found moderately increased perceived stress in 17% of lichen planus cases (erosive lesions: oral and genital) compared with 8% in controls. Thirteen per cent of cases reported high stress level compared to 3% in controls. Symptoms from both genital and oral area interfered with daily life, work and social life/spare, higher scores of perceived stress influencing this interference.

ACNE

During the last years it was a debate regarding the importance of stress involvement in acne evolution. Some studies reveal the presence of perceived stress. Patients' beliefs should be taken in consideration, they consider stress as aggravating factor.

The skin, especially the pilo-sebaceous unit, could be seen as an endocrine organ, being a target for hormones, synthesizing hormonal substances and expressing diverse hormone receptors. Recently, neurogenic factors were considered involved in the acne pathogenesis. The effects of neuropeptides on the morphology of sebaceous gland were studied. The substance P that could be increased in stressful situations induces the proliferation and differentiation at the sebaceous gland[99,100]. At the level of acne-involved skin there is an over-expression of CRH system, activating inflammatory and immunological processes with an exacerbation of acne lesion during stressful situations[101].

There are studies suggesting stress as an important factor in the pathogenesis of acne, up to 90% of cases[102-105]. Both girls and boys are mentioning mental stress, the score of stress increasing with the severity of acne[106]. Teenagers from Singapore were evaluated in periods of intense stress (before examinations) and low stress (summer holiday). There were no differences in the secretion of sebum. There was a correlation between the level of stress and the severity of lesions, suggesting other mechanisms besides the seborrhea[107]. More important was the perception of stress and patient's belief related to the possible cause. Stress is seen as a precipitating and aggravating factor for acne lesions, besides hot weather, excessive sweat, poor hygiene, smoking, alcohol intake or chocolate[108-113]. Patients with high levels of stress and with the tendency to develop dysmorphophobia have to be approached in a complex manner together with psychiatrists and psychologists[114]. Stress involvement in the precipitation and exacerbation of acne is still a dilemma, some studies denying this hypothesis[115]. The debate is open, future studies will certify or deny the observations and patients' beliefs.

ATOPIC DERMATITIS

Atopic dermatitis is a complex disease traditionally involving interaction of genetic, environmental, and immunologic factors. First observations of the correlation of life situations, emotions and atopic dermatitis are coming from 1949[116]. In 1976, emotional stress had to be considered in the evaluation of children with atopic dermatitis[117]. Then, in 1986, data from 19 countries from Europe and North America include psychic stress among decisive factors[118].

Stress is considered as a triggering factor, besides exercise, climatologic factors, sweating, irritants, aeroallergens, food, microbial organisms[119-121]. Patients with atopic dermatitis have a hyporesponsive hypothalamo-pituitary-adrenal axis, with a concurrent over reactivity of sympathetic adrenomedullary system[121-124]. Psychological stress has different immunologic effects in patients with atopic dermatitis including a shift in immunity toward a T helper type 2 cell/allergic response[125,126]. Neuropeptides released in the skin may also mediate neurogenic inflammation, including mast cell degranulation[127,128]. Suckling reduces the plasma levels of SP, VIP and NGF[129]. There is a correlation between self-reported stress during pregnancy and maternal NGF levels, important in predicting children with a risk of atopic dermatitis[130]. Patients with atopic dermatitis showed increased IgE levels 24 h after Trier Social Stress Test (free speech and mental arithmetic tasks in front of an audience)[131]. High technology causes stress that could aggravate the atopic dermatitis symptoms. Playing video games and computer-induced stress increase the plasma levels of substance P and VIP, specifically in patients with atopic dermatitis[132]. Writing mail on a mobile phone enhance the plasma NGF and allergic symptoms[131,133]. Laughter caused by viewing a comic video reduces the plasma NGF, neurotrophin-3 and allergic responses[134]. Humorous films could be useful in the treatment of night-time wakening that is often in patients with atopic dermatitis. These patients have elevated salivary ghrelin levels at 2 am, ghrelin being involved in growth hormone secretion, regulation of appetite, anxiety, night-time wakening and stress[135]. Stress impairs skin barrier function, both the barrier homeostatis and stratum corneum integrity[1,127,128]. Teenagers with atopic dermatitis had reported mental distress correlated with their symptoms[136]. Divorce/separation of the parents, severe disease or death of a family member could influence the risk of developing atopic eczema in children[137]. Family environment is important predictor of symptom severity[138]. Stressful social interactions with more negative communication patterns could add to the patients' level of stress aggravating the course of atopic dermatitis[139]. Stress caused by a natural disaster is also influencing the symptoms[140]. Stress-induced exacerbations make psychosomatic counseling recommended. "Eczema schools" educational programs are helpful[141].

URTICARIA

Stressful life events seem to be important as precipitating and aggravating factor in chronic urticaria[142,143]. 16% of the patients in the chronic urticaria group reported stressful events within 1 year preceding onset or exacerbation of skin disease[144]. In the 6 mo preceding disease

onset, patients with chronic idiopathic urticaria had significantly more life events with a higher subjective impact of them[145,146]. More than 37% of chronic urticaria patients reported stress as aggravating factor[147,148]. In the chronic urticaria group, the most common stressful life event seen was death of a close family member. Family disputes, financial problems, sexual problems, illness of a family member, getting married or engaged, trouble at work could be also be involved[147]. Posttraumatic stress was associated with chronic idiopathic urticaria through alexithymia and defensive attitude[149,150]. Perceived stress is also important in the evolution of chronic urticaria[151,152]. There are other reports that do not correlate stress with the course of the disorder (*e.g.*, psychosocial stress test does not alter the dermographic reaction)[152,153]. Insomnia could be an important predisposing factor for urticaria[145]. Good ego-function, coping strategies and family support were associated with decreased frequency of urticaria[147]. Relaxation therapies, stress management could be useful in the complex approach of chronic urticaria patients[145,154,155]. Skin tests in allergic patients could be significantly improved with autogenic training and relaxation[156].

SEBORRHEIC DERMATITIS AND OTHER DISEASES

The role of stressful events in seborrheic dermatitis is controversial or insufficiently studied[14]. Mental stress can influence the disease, causing flare-ups and being the main triggering factor[157-159]. Stress suggests a poor prognosis[159]. Studies on musicians reveal an important incidence of hyperhydrosis, lichen planus, psoriasis, seborrheic dermatitis and urticaria, because of the emotional factor involved[160]. Overtiredness and mental stress could induce more frequent relapse for both oral and genital herpes[161,162]. Stressful life events can worsen or trigger pemphigus[163].

CONCLUSION

Stress is a very important factor to be taken in consideration as precipitating or aggravating factor in different skin conditions. We should consider both stressful life event itself and the impact on patients' life (perceived stress). Psychosomatic approach is recommended, involving stress management, relaxation sessions, educational programs and psychiatric consultations.

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EDITORIAL

Adipocytokines and psoriasis: Insights into mechanisms linking obesity and inflammation to psoriasis

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Abstract

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease and metabolic diseases, including obesity. Adipose tissue is considered a genuine endocrine organ producing a variety of bioactive adipocytokines, like leptin, adiponectin, resistin and visfatin, participating in physiological and pathological processes, such as energy balance, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity, weight control and pharmacologic approaches such as metformin. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

Key words: Psoriasis; Adipocytokine; Obesity; Leptin; Adiponectin; Omentin; Resistin; Visfatin

Core tip: Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions may incorporate increased physical activity, weight control and pharmacologic approaches such as metformin.

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PSORIASIS AND ADIPOSE TISSUE

Psoriasis represents a complex, chronic, systemic, T-cell immune-mediated inflammatory dermatopathy characterized by skin and joint manifestations, and presenting commonly with erythematous, scaly plaques on various surfaces of the body[1,2]. Its prevalence varies approximately from 0.1% to 3% worldwide, with a mean prevalence rate of 1.90% in Western countries and a lower one in Asia[3].

The etiology of psoriasis remains unknown but the disease is believed to result from an interaction between genetic susceptibility and exogenous environmental factors, such as infection, in particular with β-hemolytic streptococci, stress and trauma[1-2,4]. Several human leukocyte antigen (HLA) alleles including HLA-Cw*0602 are associated with psoriasis, with *PSORS1* being the major susceptibility gene mapped next to the HLA-Cw6 antigen[2,5]. Moreover, non-HLA related genes and loci have been identified and associated with psoriasis risk such as interleukin (IL)-12B and IL-23R[2].

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease, metabolic diseases, autoimmune disease, malignancy, chronic obstructive pulmonary disease, sleep apnea and psychiatric disorders[1,2,6,7]. Overweight/obesity, metabolic syndrome (Mets), diabetes mellitus type 2 (t2DM) and dyslipidemia occur at a higher frequency in psoriasis patients than in general population[8]. Mets constitutes a constellation of cardiometabolic risk factors comprising central obesity, impaired glucose tolerance, elevated blood pressure and dyslipidemia[9]. Both psoriasis and Mets share common genetic predisposition; though their exact interplay remains enigmatic. Also, psoriasis and metabolic disorders share common risk factors such as smoking, obesity, physical inactivity and psychological stress[8]. Hence, all these cardio-metabolic risk factors, lifestyle parameters and the underlying chronic systemic psoriatic inflammation may all contribute to an increased risk for cardiovascular disease.

Apart from its fat storage function, adipose tissue constitutes an active endocrine organ secreting several bioactive adipocytokines regulating physiological and pathological processes, such as appetite, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis[10]. Increased adiposity following weight gain is associated with elevated levels of adipocytokines, comprising leptin, resistin and visfatin, and decreased levels of adiponectin and omentin, that may promote stimulation of monocytes and T cells, leading to both T-helper (Th)1 and Th17 immune responses and impairing the function of T regulatory cells[10-12]. Besides, the etiopathogenesis of Mets is attributed to hyperinsulinemia and insulin resistance mediated by adipocytokines, such as tumor necrosis factor-alpha (TNF-α), leptin, adiponectin and resistin[11]. It seems that obesity may potentiate the inflammation of psoriasis while, at the same time, it may help the development of Mets. Therefore, adipocytokines may represent a missing link in the association between psoriasis and metabolic co-morbidities, and could be used as potential biomarkers for assessing psoriasis severity, progression, treatment outcome, and risk of co-morbidities.

ADIPOCYTOKINES AND PSORIASIS

Leptin

Leptin is a 16-kDa, 167-amino acid adipocytokine that is primarily produced in adipose tissue. It is a pleiotropic molecule regulating food intake, appetite, energy expenditure, immunity, inflammation, hematopoiesis, cell differentiation and proliferation[12,13]. Leptin levels are directly proportional to the amount of body fat and fluctuate with acute changes in caloric intake, signaling the amount of energy stored in adipose tissue[12,13]. Although patients with hypoleptinemia and leptin deficiency are obese, common forms of obesity, insulin resistance and metabolic syndrome are accompanied by hyperleptinemia due to leptin resistance[12]. Leptin may be involved in the pathogenesis of psoriasis. It stimulates monocytes and macrophages, enhances the secretion of proinflammatory cytokines TNF-α, IL-6, IL-1, and IL-12, and shifts T-cell differentiation to Th1 phenotype[12,14]. Leptin stimulates also keratinocyte proliferation, angiogenesis and expression of adhesion molecules[14]. Despite the small size of epidemiologic studies and the lack of adjustment for body mass index (BMI) in analyses, the majority of studies examining the association between leptin and psoriasis has documented that psoriasis is associated with hyperleptinemia[14-17]. Also, elevated leptin levels characterize psoriatic arthritis and correlate with Psoriatic Arthritis Joint Activity Index[18]. In most studies, leptin correlated with Psoriasis Area Severity Index (PASI) score, representing, therefore, a biomarker of psoriasis severity and chronicity[19]. Indeed, severely affected psoriatic patients exhibit a significant increase in leptin levels compared to moderately affected patients[14]. Furthermore, leptin receptor and leptin expression in skin biopsies were found increased in severe psoriasis[19]. However, a possible association of psoriasis with leptin needs to be analyzed further with larger prospective, longitudinal and mechanistic studies in order to provide further insights into the paracrine and endocrine mechanisms underlying leptin's role in psoriasis.

Adiponectin and omentin

Adiponectin is a 30 kDa, 244-amino-acid protein produced predominantly by white adipose tissue, sharing a homology with TNF-α, collagen Ⅷ, X and complement factor C1q[10,11]. Adiponectin exhibits insulin-sensitizing, anti-inflammatory, anti-atherogenic, cardioprotective and anti-neoplastic effects as well as distinct actions in lipid metabolism[10,11]. The high molecular weight isoform is the biologically active configuration of adiponectin, being related with Mets, insulin resistance and cardiovascular

disease[11]. Hypoadiponectinemia is the common pathodenominator of the constellation of risk factors that compose Mets, such as hypertension, dyslipidemia, obesity, hyperglycemia and insulin resistance[11]. In contrast, hyperadiponectinemia is present in chronic inflammatory and autoimmune diseases not related to obesity such as rheumatoid arthritis and inflammatory bowel disease[10]. Adiponectin exhibits powerful anti-inflammatory properties by inhibiting the inflammatory cytokine network and down-regulating TNF-α-induced expression of endothelial adhesion molecules, TNF-α-expression in macrophages and adipose tissue, TNF-α-induced secretion of IL-6 in monocyte cells and keratinocytes *in vitro* as well as TNF-α, IL-6, IL-17, IL-22 and interferon-γ from T-lymphocytes[3,10,14]. Despite the fact that psoriasis is often associated with disease states characterized by hypoadiponectinemia such as Mets and obesity, controversial data exist in the literature regarding the association of adiponectinemia with psoriasis. A decrease, no change and even an increase in adiponectin levels have been reported in psoriasis patients[14,20-22]. Although not all results were adjusted for BMI, some studies have indicated a BMI independent change in adiponectin levels especially after treatment[21] as well as a negative correlation with PASI and pro-inflammatory cytokines such as TNF-α and IL-6[20,22].

Omentin, a newer 40-kDa adipocytokine, secreted mainly by stromal cells in the visceral fat, with similar properties to adiponectin, was found decreased in psoriatic patients in comparison to controls[23].

Resistin

Resistin is a 12 kDa cysteine-rich polypeptide which is produced in humans predominantly by stromal macrophages and monocytes of the visceral adipose tissue[24]. Elevated resistin levels are found in obesity and inflammation, and may play a significant role in the pathogenesis of insulin resistance, Mets and t2DM[24-27]. More importantly, resistin acts as a pro-inflammatory factor leading to an increased mRNA expression of twenty chemokines and cytokines including TNF-α, IL-1, IL-6, IL-12, chemokine ligand CXCL8, monocyte chemoattractant protein-1 and resistin itself *via* the nuclear factor-kappa B (NF-κB)[25]. In the majority of studies exploring the association of resistin with psoriasis, hyperrestinemia characterized untreated psoriatic patients and correlated with disease severity and nail psoriasis severity index[14,25-29].

Visfatin and other adipocytokines

Visfatin is a 52-kDa pleiotropic adipocytokine secreted by the macrophages of the visceral fat, acting as a cytokine, a growth factor and an enzyme, and playing a significant role in the cellular energy metabolism and in a variety of metabolic and stress responses[30-32]. Despite the conflicting association of visfatin with metabolic and anthropometric parameters, its concentrations are usually elevated in obese individuals, obese children and adolescents, in patients with coronary heart disease, t2DM, Mets and non-alcoholic fatty liver disease as well as in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease[31-34]. Visfatin enhances the production of IL-1α, IL-6, TNF-α, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 through the pro-inflammatory transcription factor NF-κB, and may contribute to the pathogenesis of vascular inflammation of obesity[31,32]. Visfatin may play a significant role in psoriasis pathophysiology. In a small size study, serum visfatin was significantly elevated in psoriasis patients than in healthy controls, correlating positively with disease chronicity and severity[23]. *In vivo*, the visfatin gene expression profile was increased in psoriasis while *in vitro* visfatin upregulated TNF-α-induced chemokine ligands: CXCL 8, 10 and CCl20 production and mRNA expression in human keratinocytes[35,36].

Data regarding newer and promising adipocytokines, such as vaspin, retinol-binding protein 4 and chemerin with respect to psoriasis are sparse and controversial[14,37].

The controversy of results in epidemiologic studies examining the association of adipocytokines with psoriasis may be attributed to the (1) retrospective study design; (2) small sample size; (3) non-adjustment of the results for BMI, waist circumference and metabolic parameters as well as for important confounders such as coronary disease; (4) different ethnic groups examined; (5) importance of measuring fasting samples *vs* non-fasting; and (6) different laboratory assays used.

In conclusion, adipocytokines such as leptin, adiponectin, resistin and visfatin represent key players in many physiologic processes including energy balance, immunity and inflammation. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, treatment success and risk of any co-morbidities. We also speculate that interventions to decrease pro-inflammatory adipocytokine levels could represent a preventive and therapeutic option for improving disease severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity[38], weight control and pharmacologic approaches such as metformin[10,11]. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

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