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Iranian Society of Dermatology
Unit 1, No 14, Sharifi St, North Gandi Ave, Tehran, Iran
Post Box: 14155-6157
Tel: +98 - 21 - 88202914-15
Fax: +98 - 21- 88784721
Website: www.iranjd.org; www.iranjd.ir; www.iransocderm.com
Email: iranjdermatol@gmail.com

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Contents

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Farhad Handjani, MD
Editor-in-Chief
Iranian Journal of Dermatology
Unit 1, No 14, Sharifi St, North Gandi Ave, Tehran, Iran
Post Box: 14155-6157
Tel: +98 - 21 - 88202914-15
Fax: +98 - 21 - 88784721
Website: www.iranjd.ir
E-mail: iranjdermatol@gmail.com

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Comparison of COX_2 expression in radiation induced basal cell carcinoma and non-radiation induced basal cell carcinoma

Yalda Nahidi, MD [1]
Naser Tayyebi Meibodi, MD [1*]
Amir Hossein Jafarian, MD [2]
Habibollah Esmaily, MD [3]
Elham Pishnamaz, MD [4]

1. *Cutaneous Leishmaniasis Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
2. *Pathology Department, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
3. *Health Sciences Research Center, Department of Biostatistics and Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran*
4. *Radiology Department, Birjand University of Medical Sciences, Birjand, Iran*

** Corresponding Author:*
Naser Tayyebi Meibodi, Cutaneous Leishmaniasis Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +985138022210
E-mail: tayebin@mums.ac.ir

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Background: Radiation-induced basal cell carcinoma (BCC) can be multiple, large, and recurring, which complicates its treatment in some cases. According to reports on the role of cyclooxygenase 2 (COX_2) inhibitors in the treatment or prevention of non-melanoma skin cancers and considering the fact that COX_2 expression has not been evaluated in radiation-induced basal cell carcinoma, we set out to assess the expression of COX_2 in these lesions.

Methods: In this study, COX_2 expression was assessed by immunohistochemistry using anti-COX_2 antibody on paraffin-embedded blocks of 86 patients referred to Emam Reza Hospital in Mashhad with BCC diagnosis by pathological examination (43 patients with and 43 without a history of radiotherapy) followed by semi-quantitative evaluation of COX_2.

Results: In our study, COX_2 expression score was significantly higher in patients with a history of radiotherapy than those without radiotherapy ($P<0.001$). No correlation was found between the intensity and percentage of staining with sex, age, site of lesion, recurrence, and pathology of the tumor.

Conclusion: Given the higher expression level of COX_2 in the radiation-induced BCC patients, the use of COX_2 inhibitors in these individuals may be effective in the incidence, recurrence, or treatment of BCC.

Keywords: basal cell carcinoma, cyclooxygenase 2, immunohistochemistry, radiotherapy

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INTRODUCTION

Basal cell carcinoma (BCC) has attracted considerable attention as the most common skin malignancy in human [1]. The natural course of the majority of BCC varieties is slow and does not cause mortality, but it is remarkable due to chronicity and incapacitation of the patient. A history of radiotherapy in childhood is one of the known risk factors for the occurrence of BCC [2]. Radiation-induced BCC is often multiple, large, and recurrent that often requires extensive excision and graft, leaving deformity or chronic ulcer in some cases [3]. On the other hand, radiodermatitis due to a previous radiotherapy reduces the successful regeneration rate of the surgery site with graft and flap; therefore, the search for non-surgical treatments to prevent relapse or occurrence of BCC in those with a history of radiotherapy seems to be logical. COX_2 is considered as a factor in the

recurrence of BCC. El-Khalawany *et al.* concluded that COX_2 overexpression is a risk factor for BCC relapse [4]. Tjiu *et al.* showed that in human BCC samples, high levels of COX_2 were not only associated with neovascularization but also with the depth of tumor invasion and they stated that the tumor-associated macrophages might activate COX_2 in BCC cells and thus enhance the invasion and angiogenesis [5,6]. It was shown that the inhibition of PGE2 production by COX_2 inhibitors and NSAIDs somewhat inhibits UV-associated carcinogenesis [7,8]. Vogel stated that COX_2 expression affects the risk of BCC development [9]. Karahan showed that COX_2 expression might be associated with local invasion and recurrence of BCC [10]. The reduced induction of skin carcinoma or papilloma by UVB has been demonstrated following feeding the mice with Celexib or Indomethacin [11]. Tang *et al.* have shown that oral Celexib reduces carcinogenesis in PTCH-/+ mice and it has also a considerable impact against BCC in human subjects with nevoid basal cell carcinoma syndrome [12]. Considering the fact that COX_2 expression in radiation-induced basal cell carcinoma has not been investigated so far, we tried to evaluate and compare the expression of COX_2 by immunohistochemistry in radiation-induced basal cell carcinoma with BCC due to other factors.

MATERIAL AND METHODS

In this cross-sectional study, 86 paraffin-embedded basal cell carcinoma samples (43 blocks from patients with a history of radiation therapy and 43 blocks from those without radiotherapy history) were extracted from the archives of Department of Pathology, Imam Reza Hospital, Mashhad University of Medical Sciences, and their histopathology was re-examined by a dermatopathologist. Then, demographic characteristics of patients, including age, sex, clinical type, relapse, and radiotherapy history were registered in the questionnaires and all the patients were contacted by the phone call to ensure their history of radiotherapy. Inclusion criterion was a definite diagnosis of basal cell carcinoma in pathological examination and exclusion criteria were incomplete patient records, lack of or insufficient tissue in paraffin-embedded blocks. Finally, COX-2 expression was evaluated by immunohistochemistry using anti-COX_2 antibodies on paraffin blocks and COX_2 was semi-quantitatively analyzed. In terms of staining percentage of cells (P), the samples were divided to five groups (including less than 1%, 1-25%, 25-50%, 51-75%, 76-100%) and were divided into four groups (negative, weak, moderate, severe) according to the staining intensity (I). The score ranges of 0-4 and 0-3 were attributed to percentage of staining and staining intensity groups, respectively. Then, for each sample, the scores of percentage and intensity of staining were summed up and the resulting figure represented the COX_2 expression score. The samples with a score above 2 are considered positive and those with a score above 4 are considered strongly positive. Accordingly, based on COX_2 score, the samples were divided into three groups: group 1 with a score of (0-2), group 2 with a score of (3-4), and group 3 with a score of (5-7). Evaluation of the stained slides was conducted by two pathologists and in cases of disagreement between them, the slides were simultaneously assessed by them using a binocular microscope to resolve the problem. COX_2 immunohistochemical staining kit (Novocastra, England) was used to detect COX_2 marker. The stained slides were assessed under a light microscope (Nickon, Japan) with 100× and 400× magnification. The accuracy of staining was ensured via comparison with positive and negative control samples, COX_2 intensity and percentage was assessed in 10 fields with 100× and 400×magnification, respectively, and the average staining level was assessed and expressed as percentage of staining. To describe the data, diagrams, and statistical tables, SPSS statistical software version 16 was used and chi-square test, t-test or its non-parametric equivalent, as well as Mann-Whitney and Kruskal-Wallis tests were used for statistical analysis.

RESULTS

Eighty-six patients with basal cell carcinoma were enrolled in this study that were divided into two groups of 43 patients with and without a history of radiotherapy.

Fourteen patients (32.6%) with a history of radiotherapy and 19 patients (44.2%) without a history of radiotherapy were women and 29 patients (67.4%) with a history of radiotherapy

and 24 patients (8.55%) without a history of radiotherapy were men. Chi-square test showed no statistically significant difference between the history of radiotherapy and gender (P=0.3).

Majority of the patients under study were within the age group of 60-69 years, including 32 patients (37.2%) and the age group of 40-49 years had the lowest frequency with 11 patients (12.8%). Majority of the patients with a history of radiotherapy were within the age group of 60-69 years and the lowest number of these patients was within the age group of 40-49 years. Mean age of patients was 61.5 years with SD of 1.006 and median of 60. Maximum and minimum age of the patients was 40 and 91 years, respectively. Statistical analysis by t-test showed no significant correlation between age and history of radiotherapy (P=0.3). There were six cases of relapse among which five patients (11.6%) had a history of radiotherapy and 88.4% of patients with a history of radiotherapy did not mention their history of recurrent lesions. Chi-square test indicated no relationship between relapse and history of radiotherapy (P=0.2).

In patients without a history of radiotherapy, most of lesions were on face (52.3%) and the least on the neck (4.7%). In total, 37 lesions (43%) were on the head, 45 (52.3%) on face, and 4 (4.7%) on the neck. In cases with a history of radiotherapy, 30 patients (69.8%) had lesions on head, 10 (23.3%) on face, and 3 (7%) on the neck. Statistical analysis by chi-square test indicated a significant relationship between location of lesion with a history of radiotherapy (P<0.001) and scalp was a common site for radiation-induced BCC.

Out of 86 samples under study, 38 cases (44.2%) were solid, 16 (18.6%) infiltrative, 24 (27.9%) mix (solid+ pigmented/solid+ adenoid/infiltrative+ adenoid) pathology subtypes and 8 (9.3%) were related to other subtypes (superficial /micronodular /morphemic /adenoids). In total, there was a higher frequency of solid pathology subtype.

In 43 samples of patients with a history of radiotherapy, 20 cases (46.5%) were of solid type, 6 cases (14%) of the infiltrative type, 10 cases (23.3%) of mix type and 7 cases (16.3%) of other types.

The frequency of solid pathology subtype was higher among the samples of patients with and without a history of radiotherapy. Statistical analysis by chi-square test showed no significant relationship between pathology subtype and a history of radiotherapy (P=0.09).

In assessment of COX_2 expression score in the two groups with and without a history of radiotherapy, based on the results of Table 1 and using Mann-Whitney test, score intensity of COX_2 expression in radiation-induced BCC was considerably higher than the group without such history (P<0.001).

There was no correlation between COX_2 expression intensity in basal cell carcinoma samples and gender of patients in Mann-Whitney test (P=0.68). In addition, Kruskal-Wallis test showed no correlation between the intensity of COX_2 expression score in BCC samples, age of patients (P=0.22), pathology subtypes (P=0.7), and tumor location (P=0.18).

DISCUSSION

BCC is the most common skin cancer in human and the chronicity and incapacitation of patients with BCC causes significant morbidity, but the normal course of the majority of its forms is slow with no mortality. History of childhood radiotherapy is among the most well known risk factors for BCC. The first reports on a possible role of ionizing radiation in the development of non-melanoma skin cancers (NMSC) were related to the incidence of these cancers on the hands of radiology technicians working without protection. Increased NMSC has been observed among the

Table 1. Distribution of subjects based on the staining score of tumor cells (considering the score intensity) and a history of radiotherapy.

COX_2 expression score	History of radiotherapy				Total	
	Positive		Negative			
	Number	Percent	Number	Percent	Number	Percent
(0-2) $^{-}$	8	18.6	21	48.8	29	33.7
(3-4) $^{+}$	12	27.9	16	37.2	28	32.6
(5-7) $^{++}$	23	53.5	6	14.0	29	33.7
Total	43	100.0	43	100.0	86	100.0

Mann-Whitney test result: z score= 3.91 P-value<0.001

workers in uranium mines, radiologists, and those with a history of radiotherapy in childhood for treatment of Tinea capitis. There was also a significant increase in this type of cancer after atomic bombing of Hiroshima and Nagasaki [2]. The number of BCC lesions in patients with a history of radiotherapy was higher compared to the group without a radiotherapy history in the study of Meibodi *et al.* [3]. In the prospective study by Karagas *et al.* for comparison of two groups with and without a history of radiotherapy (not necessarily because of Tinea capitis), BCC incidence was significantly higher in the group with a history of radiotherapy [2]. In the study of Maalej and colleagues on 98 patients with a history of radiotherapy in childhood who had tumors in the irradiated area, it was concluded that BCC was the most common tumor that occurred in radiodermatitis sites [13]. Radiation-induced BCC is often multiple and recurrent and due to its large size 3 often requires extensive excision and graft, leaving deformity or chronic ulcer for patient in some cases. On the other hand, radiodermatitis induced by a previous radiotherapy reduces the successful repairing of surgery site with graft and flap; therefore, it appears logical to find non-surgical treatments to prevent relapse or BCC occurrence in those with a history of radiotherapy. COX_2 is a factor considered involved in the recurrence of BCC.

Cyclooxygenase (COX) is an enzyme responsible for biosynthesis of prostaglandins (including prostaglandins, prostacyclin and thromboxane) that are among the most important chemical mediators in the body. At present, three isoenzymes of COX, including COX_1, COX_2, COX_3, have been identified [14]. COX_1 is expressed in many tissues and plays different physiological roles whereas the overexpression of COX_2 occurs in several types of epithelial tumors [15]. COX_2 is a rate-limiting enzyme in the biosynthesis of prostaglandins from arachidonic acid and the expression of its gene is increased by various stimuli like mitogens, cytokines, growth factors, and tumor promoters. It has been implicated in the development of several types of tumors [16].

Recent studies have indicated the relationship between COX_2 with invasion induction [17], apoptosis suppression [18], cellular immune response suppression, and tumor angiogenesis [19]. COX_2 production after UV exposure contributes to epidermal hyperplasia, edema, and inflammation and inhibits UV-induced apoptosis. Inhibition of COX_2 activity or reduced expression of it in mice with deleted genes leads to a significant reduction in UV-dependent carcinogenicity; while leading to COX_2 overexpression in transgenic mice increases the UV-dependent tumor growth [20]. COX_2 expression level in some tumors corresponds with tumor aggressiveness and prognosis, suggesting an important role of COX_2 in tumor development and progression [16]. COX_2 can be found in normal skin, benign proliferations, and malignant cutaneous neoplasms. UVB radiation affects keratinocytes and increases prostaglandin E production and COX_2 expression in them [21]. Studies showed that BCC is positive in a small percentage of biopsies studied for COX_2, the expression of which was consistent with angiogenesis in BCC [22,23].

In our study, COX_2 expression score was significantly higher in tumor cells of patients with a history of radiotherapy than those without a history of radiotherapy ($P<0.001$). There was no correlation between COX_2 expression score with gender and age of patients, site of lesion, relapse history, and tumor pathology subtype. In the study of El-Khalawany *et al.* in 2013, to evaluate the predictive markers for recurrence of BCC, COX_2 expression was significantly different in 20 out of 22 samples of recurrent BCC (90.9%<) compared to 14 cases (59.1%) out of 22 BCC cases without relapse ($P=0.04$). Moderate to high intensity was observed in 13 cases of recurrence and 2 cases without tumor recurrence and it was concluded that the overexpression of COX_2 can be used as a risk factor of relapse in addition to other clinical and histological factors of BCC [4].

According to the study of El-Khalawany, this biomarker has a promising role in prognosis assessment of BCC and early detection of recurrence, as well as a high expression level of COX_2 is a risk factor for BCC relapse [4]. In the study of Karahan, COX_2 expression in primary BCC group of infiltrative type was significantly higher than superficial and nodular types and in the recurrent BCC type, COX_2 expression was significantly higher than primary BCCs ($P=0.013$). It was stated that COX_2 expression may be associated with local invasion and recurrence in BCC and COX_2 inhibition can be an adjunctive therapy, especially in recurrent tumors with a high COX_2 expression [10].

However, in our study, no relationship was found between COX_2 expressions with recurrence of lesions, which may be due to low number of relapse samples in this experiment. There was no correlation between COX_2 expressions with pathology subtypes of tumors.

Reduction in UVB-induced skin papilloma or carcinoma has been observed following feeding of mice with Celexib or indomethacin. Topical use of Celexib also inhibits chronic inflammation and UVB-induced carcinoma in mice [11]. More importantly, interrupting the COX_2 signaling is an effective strategy for preventive treatment of non-melanocytic skin cancers, especially in people with a high risk of developing these cancers. However, any potential benefit of these drugs should be contrasted with their known adverse events (e.g. cardiovascular and gastrointestinal complications) for each patient. Topical NSAIDs are effective to prevent sunburn reactions such as redness of the skin. In five out of six studies on the use of topical Diclofenac, as a non-specific inhibitor of COX having a more prominent effect on COX_2 relative to COX_1, there has been significant impact with respect to the improvement of precancerous lesions (actinic keratosis) due to apoptosis. Currently, Diclofenac gel has been approved for topical treatment of actinic keratosis in USA and Europe. In contrast, the use of oral Celexib (a specific inhibitor of COX_2) is effective to prevent SCC and BCC but it has no effect on actinic keratosis [24].

Preventive topical treatment by green tea extract ($1mg/cm^2$) widely inhibits acute COX_2 response to UVB in mice and humans [15]. Tang *et al.* showed the effects of oral Celexib in PTCH1+/- mice, as well as its effect against BCC in patients with nevoid basal cell carcinoma syndrome [12].

CONCLUSION

Radiation-induced BCC is often multiple and recurrent and given the overexpression of COX_2 in BCC lesions caused by radiotherapy, COX_2 inhibitor drugs such as Celexib may play a role in the prevention of BCC or its recurrence in patients with a history of radiotherapy, which requires a clinical trial. We also proposed another study on role of COX_2 in the pathogenesis of radiation induced basal cell carcinoma.

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Conflict of Interest: None declared.

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The association of androgenetic alopecia with metabolic syndrome: a case control study on Iranian population

Ahmad Reza Taheri, MD [1]
Mozhgan Afkhamizadeh, MD [2]
Sara Sabourirad, MD [1]
Omid Hassani, MD [3]
Somaye Ghanizadeh, MD [4*]

1. *Cutaneous Leishmaniasis Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
2. *Metabolic Syndrome Research Center, Department of Endocrinology, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.*
3. *Birjand University of Medical Sciences, Birjand, Iran.*
4. *Dermatology Department, Mashhad University of Medical Sciences, Mashhad, Iran*

**Corresponding author:*
Somaye Ghanizadeh, MD
Mashhad university of Medical Sciences, Mashhad, Iran
Tel: 00985138583845
Email: somayeghanizadeh@gmail.com

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Background: Androgenetic alopecia (AGA) is the most prevailing type of progressive hair loss**.** Thus far, some previous studies have investigated the correlation between AGA and metabolic syndrome (MetS). However, due to the inconsistency of their results, our study aims at evaluating the association between AGA and MetS.

Methods: Fifty two male patients with grade III-V AGA, based on Ebling's scale, and 50 control subjects were enrolled in the present study. All participants were evaluated for the presence of Mets based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).

Results: The prevalence of MetS was 51.3% in AGA group and 17.8% in control group (P=0.003). Among MetS parameters, Systolic blood pressure (P=0.003) and waist circumference (P<0.001) were statistically significant in AGA patients compared to the control group.

Conclusion: Our study demonstrated that the association between AGA and MetS is of great importance. Therefore, early detection can be beneficial for early intervention to lower the incidence of MetS and further complications.

Keywords: Alopecia, metabolic syndrome, androgens

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INTRODUCTION

Androgenetic alopecia (AGA), the most common type of progressive hair loss, is an inheritable thinning of hair caused by androgens in a genetically predisposed individual [1]. Androgens, particularly dihydrotestosterone which is a testosterone metabolite, have an important role in the development of AGA in males [2]. AGA involves the vertex and frontotemporal regions of the scalp in males and the crown in females because these regions are more sensitive to the effects of androgen [3].

Metabolic syndrome (MetS) is defined as a group of metabolic disorders such as glucose intolerance, insulin resistance (IR), dyslipidemia, central obesity, and hypertension. It is also associated with increased risk of cardiovascular disease (CVD) [4].

In 1972, Cotton *et al.* were the first who proposed that AGA might be a risk factor for CVD. Their study indicated a relevance between hair loss and the occurrence of CVD [5]. Many subsequent studies have revealed the correlation of AGA with several disorders such as insulin resistance (IR) [6], abnormal serum lipid profiles [6,7], hypertension [8], and obesity [9].

Until now, only a few studies [10-17] have reported the association between AGA and MetS. However,

it should be noted that four studies reported a non-significant relationship between these two conditions [18-21]. These controversies necessitate a more cautious assessment of MetS parameters in AGA patients. The objective of the present research was to investigate the correspondence between MetS prevalence and AGA.

MATERIAL AND METHODS

The study was conducted on patients attending the Dermatology Clinic of Imam-Reza Hospital, Mashhad, Iran. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences. A total of 102 male subjects (aged 35-55 years) were enrolled in the study. Fifty two AGA cases with a mean body mass index (BMI) < 27 and with alopecia stage ≥ 3 according to the Ebling's Scale [22] were in the study group. The 50 control subjects had a mean BMI < 27 and no AGA. Exclusion criteria were scarring alopecia, alopecia areata, congenital adrenal hyperplasia, Cushing's disease or glucocorticoid treatment within the previous six months or any other systemic disorders. The BMI was calculated by dividing the body weight by the square of the height (kg/m^2). Waist circumference was measured using a tape measure at the midpoint of the narrowest part between the top of the iliac crest and the bottom of the rib cage while the participant was standing erect with the abdomen relaxed, feet together and arms at the sides. Blood pressure was measured in all the study subjects. After an overnight fast, blood samples were obtained from each subject for the measurement of serum glucose (FBS), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG).

MetS was determined based on the NCEP ATP III by the presence of three or more criteria as follows [4]: (a) FBS ≥ 110 mg/dL, (b) TGs value ≥150 mg/dL, (c) HDL-C <40 mg/dL in males, (d) waist circumference ≥102 cm in males and (e) BP ≥ 130/85 mmHg.

Further investigated were the association between the Ebling's Scale, systolic blood pressure (SBP), diastolic blood pressure (DBP), the levels of glucose, TC, triglycerides, LDL-cholesterol, and HDL-cholesterol in the AGA group.

Data were analyzed using IBM SPSS software package version 15.0. Statistical differences in baseline characteristics among groups by the prevalence of AGA, were evaluated by means of chi-square test or Fisher exact test for categorical variables and Student *t* test for continuous variables. Shapiro–Wilk test for normality and Levene homogeneity of variance test were conducted prior to *t* test. Multivariate logistic regression was assessed to find the factors affecting AGA independently. Statistical significance of the obtained results was judged at the level of 5%.

RESULTS

A total of 102 participants were enrolled in the present research. The patient group involved 52 male subjects and the control group comprised 50 healthy male subjects. The mean age of the participants in the patient and control group was 42.65 ± 6.07 and 45.60 ± 6.33 years, respectively. The age difference between the groups was significant (p = 0.018). The groups were compared in terms of weight, height, BMI, FBS, systolic and diastolic blood pressure, LDL-c, and HDL.

There was a statistically significant difference between the two groups (AGA and Control) regarding waist circumference (P <0.0001), SBP (P = 0.003) and TC (P = 0.017). The comparison between the two groups with respect to TG, HDL-C, LDL-C, FBS and DBP, shows no statistically significant difference. (Table 1)

The percentage of smoking was 44.2% (n=23) in AGA group and 21.3% (n=10) in the control group, with a P value of 0.008. There was a significant correlation between smoking and androgenetic alopecia.

In view of the relationship between age and smoking with androgenetic alopecia and metabolic syndrome, these two variables (age and smoking) were considered as confounding variables and adjusted by multiple logistic regression.

According to the Ebling's scale, 26 (50%) patients were classified as grade III, 18 (34.6%) as grade IV, and 8 (15.4%) as grade V. The overall prevalence rate of metabolic syndrome among the 102 participants was 31.4% (n = 32). With respect to MetS frequency, 24 (46.2%) patients in the AGA group and 8 (16.0%) participants in the control group were found to have MetS, and the difference was statistically meaningful (p < 0.05) (Table 2).

The prevalence of MetS regardless of the effect of age and smoking was 46.2% in AGA group and 16.0% in the control group (P=0.001); however, after taking into account the two factors, it was calculated to be 51.3% and 17.8%, respectively (P=0.003). The association between AGA and MetS was still significant after considering age and smoking status. (Table 3)

After taking into consideration the effect of age and smoking, the odds ratios of developing MetS were respectively 5.957, 8.286, and 1.563 among grade III, grade IV, and grade V Androgenetic Alopecia compared to the control group (Table 4). The odds ratio for grade V androgenetic alopecia was not statistically significant in comparison with control group (probably due to the small sample size).

DISCUSSION

As mentioned before, there are several studies investigating the association of AGA and MetS with inconsistent results.

It has been pointed out that there are more androgen receptors in the scalp of the patients with severe AGA and higher levels of serum total and free testosterone [19,23]. Higher levels of androgens lead to atherosclerosis and increase the susceptibility to hypercholesterolemia and hypertension [24]. A relationship between AGA and hypertension, irrespective of age, has also been shown [8].

Fifty two AGA cases and 50 controls were investigated for MetS parameters such as hyperlipidemia, hypertension, fasting blood glucose levels, and different grades of AGA according to the Ebling's score. All the patients were subjected to blood testing for TC, LDL-c, HDL-c, TG, and FBS.

To the best of our knowledge, this is the first comparative study in Iranian population to evaluate the correlation of AGA and MetS.

A similar age group distribution was observed by Arias-Santiago *et al.* In their study, the distribution of alopecia according to the Ebling's scale was as follows: grade III: 31.4%, grade IV: 45.7%, and grade V: 22.9%. Unlike our study, there was no association between alopecia severity and metabolic syndrome in Arias *et al.*

In the present study, the relationship between AGA and SBP was statistically significant. The increase in the levels of serum androgens in AGA patients [25] contributes to smooth muscle cell proliferation in vessels [26] and thus augmentation of the susceptibility to hypertension [24].

In our research, as opposed to most previous studies, the mean value of TC in the control group (176.68±36.09) was higher compared to the AGA group (157.46±43.65) (P=0.017). This indicates the need for further research in our country.

We observed that the correlation between waist circumference and AGA was statistically significant in comparison to the controls (P<0.001). Similar results were reported in studies conducted by Acibucu *et al.* [27] Arias-Santiago *et al.* [14] and Ola Ahmed Bakry *et al.* [28].

Regarding our patients, MetS was significantly associated with AGA. The prevalence of MetS in cases (46.2%) was statistically significant as compared to the control group (16%) (P< 0.05). Similar results were reported by Arias-Santiago *et al.* [14], Acibucu *et al.* [27], Chakrabarty, *et al.* [29], and Ola Ahmed Bakry, *et al.* [28]. However, Mumcuoglu, *et al.* [19] (20)showed (20) no statistically significant difference between the cases and controls.

Other MetS parameters such as diastolic BP, TG levels, FBS levels, HDL-c levels, LDL-c levels were not statistically significant.

In our study, the comparison of MetS prevalence was statistically significant when grade III (46.2%) cases were compared to grade IV (55.6%) (P<0.05). The prevalence of MetS in grade V cases was lower than other grades (probably due to the small sample size). However, it is to be noted that MetS is still more prevalent in comparison to the control group.

CONCOLUSION

MetS was more prevalent in AGA patients compared to the control group, showing a significant association between AGA and MetS. Therefore, early detection could be beneficial for early intervention in order to reduce the incidence of MetS and further complications.

Conflict of Interest: None declared.

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Carotid doppler ultrasound evaluation in patients with lichen planus

Zeinab Aryanian, MD [1,2]
Hosein Shahabandaz, MD [3]
Meysam Abdollahzadeh Sangrody, MD [4]
Azar Shirzadian, MD [2]
Soodabeh Tirgartabari, MD [5]
Ali Bijani, MD [6]
Shabnam Fahim, MD [7]
Ifa Etesami, MD [7]
Arghavan Azizpour, MD [1]
Azadeh Goodarzi, MD [8*]

1. *Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran*
2. *Department of Dermatology, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
3. *Department of Radiology and Radiotherapy, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
4. *Student Research Committee, Babol University of Medical Sciences, Babol, Iran*
5. *Clinical Research Development Center, Shahid Yahyanezhad Hospital, Babol University of Medical Sciences, Babol, Iran*
6. *Department of Statistic and Epidemiology, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
7. *Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran*
8. *Department of Dermatology, School of Medicine, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran*

**Corresponding Author:*
Azadeh Goodarzi, MD
Department of Dermatology, Rasoul Akram Hospital, Sattarkhan St., Tehran
1449614535, Iran
Tel: 00989123882448
Email: goodarzi.a@iums.ac.ir, azadeh_goodarzi1984@yahoo.com

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Background: Lichen planus is a chronic inflammatory disease associated with an increased risk of subclinical atherosclerosis and cardiovascular diseases. This study aimed to evaluate patients with lichen planus using carotid Doppler ultrasound parameters.

Methods: Forty patients with lichen planus and 40 controls were included in this study. Common carotid artery intima-media thickness (CIMT) and the number of atherosclerotic plaque were measured and compared to the control group. Total cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were measured. Leptin level (Pg/ml) was measured using the enzyme-linked immunosorbent assay (ELISA) method (Leptin ELISA kit, Orgenium, Finland).

Results: Significant difference was found between the groups in terms of CIMT (P=0.005). The median range for blood leptin level, triglyceride, cholesterol, and LDL was higher for lichen planus patients than for controls. We found a significant difference between the severity of LP and CIMT (P=0.035). No statistical difference was found between LP and the number of atherosclerotic plaque.

Conclusions: Our study suggested that measurement of the mean intima media wall thickness of the common carotid artery could be beneficial as a valuable method for early diagnosis of atherosclerosis in lichen planus.

Keywords: lichen planus, common carotid artery, doppler ultrasound

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INTRODUCTION

Lichen planus (LP) is a chronic and T cell mediated inflammatory mucocutaneous disease, which is not known yet in term of etiology and pathogenesis. Owing to chronic inflammatory condition, it can enhance the formation of atherosclerotic plaques, and causes disturbances in lipid metabolism [1].

Several cytokines are involved in lichen planus pathogenesis, and some major independent risk

factors— for cardiovascular diseases in Lp— could suggest it as a component of the metabolic syndrome [2]. In addition, the current literature considers endothelial dysfunction and carotid intima-media thickness (CIMT) important markers of subclinical atherosclerosis and cardiovascular diseases [3].

Few studies have shown evidence of subclinical atherosclerosis in LP patients than in controls as indicated by increased CIMT, and there are conflicting findings regarding the relationship between LP, its severity or duration and subclinical atherosclerosis risk.

The main objective of this study was to evaluate patients with lichen planus regarding carotid Doppler ultrasound parameters.

PARTICIPANTS AND METHODS

Participants and study design

A total of 40 patients with lichen planus, presented to a dermatology clinic, were included in this study— based on inclusion criteria. Additionally, 40 age, gender matched healthy controls were selected amongst hospital staff, without any known dermatologic and nondermatologic disease. Inclusion criteria for the study group were presence of lichen planus affecting the skin or mucosa that was confirmed according to clinical and biopsy findings. Informed consent was obtained from all included patients before participation as one of the inclusion criteria.

Patients with renal and hepatic, neurologic disorders, lichenoid drug eruption, a history of cardiovascular, cerebrovascular diseases or collagen vascular diseases, smoking habit, thyroid dysfunction, hypertension, diabet mellitus, pregnancy, malignancy, receiving any systemic lichen planus treatment, steroid, immune-suppressive treatment, lipid-lowering therapy, antihypertensive or hormonal, and anticoagulant drugs were excluded from the study. The participants were recruited from Rohani Hospital of University of Medical Sciences, Babol, Iran, from 2017 to 2018. Demographics and clinical characteristics of patients with lichen planus and healthy controls were assessed.

After 12-hour fasting, 5 cc of blood was taken from each participant. Serum samples were prepared after coagulation and centrifugation of the whole blood at 1500 ×g for 10 minutes. They were frozen and preserved at −80 °C. Biochemical parameters such as serum cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) were measured using the photothermic auto analyzer method. Serum leptin level was assessed using the ELISA Kit for the quantitative determination of leptin in the human serum (Leptin ELISA, ME E-0300).

Ultrasound measurement of the mean intima-media wall thickness of common carotid artery was assessed by an ultrasound specialist blinded to the patients' data. All participants were examined in a supine position— neck extended and the head was slightly tilted toward the opposite of the examined side.

A magnified image was recorded from the angle, showing the greatest distance between the interface of lumen–intima and media–adventitia. From this offline image, at least three measurements of the common carotid artery wall were taken approximately 10 mm proximal to the bifurcation (the arterial segment 1 cm proximal to the carotid bulb) to derive the mean intima-media wall thickness of common carotid artery. Ultrasound scanning was performed using carotid duplex high-resolution B-mode equipment (Ultrasound, Diagnostic, Samsung Medison, Sonoace X8, Gyeonggi-do, South Korea) with a 12-MHz linear-array transducer (axial resolution of at least 0.3 mm). The final intima-media wall thickness value represents an average of the intima-media wall thickness resulting from three different points on the right side. Atherosclerotic plaque was diagnosed with a carotid artery wall thickness exceeding 1.5 mm. Both left and right common carotid artery (CCA)s were depicted. The reproducibility of intima-media wall thickness and plaque detection has been well documented.

Statistical methods

Chi-square test and Fisher's exact test, wherever appropriate, were performed for data analysis. Mann–Whitney U-test was used for comparison between serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and leptin level. Furthermore, Spearman's correlation test

was used to assess the association between mean intima-media wall thickness and other continuous variables. Statistical analyses were conducted using the SPSS Statistics software. P values< 0.05 were considered statistically significant.

Ethical considerations

The written informed consent was obtained from all participants.

RESULTS

Forty patients and 40 healthy controls were included in this review. Table 1 presents the patients' demographical, clinical and biochemical parameters. The patients in the two groups were well balanced in terms of age and body mass index. Although the average level of TG, cholesterol, LDL and leptin was higher in LP patients than in controls, it was not significant. The average level of HDL was lower in the LP group. There was a significant difference between the groups in terms of CIMT (0.68± 0.14 mm vs. 0.59± 0.12 mm, p=0.007). The average right and left CIMT was significantly higher in LP patients than in controls. The number of atherosclerotic plaques in CCAs was higher in the patients. There was a correlation between CIMT and age. No correlation was found between CIMT, BMI and duration of disease.

Statistical differences were found between CIMT and the severity of LP. CIMT was higher in moderate and severe diseases (P=0.035). In the subgroup analysis regarding involvement of LP, CIMT was higher in mucocutaneous type (70±0.12) and lower in mucosal LP (0.65± 0.16). The number of atherosclerotic plagues was higher in cutaneous LP (P=0.152) (Table 2, Figure 1,2).

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DISCUSSION

The metabolic syndrome is a factor resulting in global epidemics of cardiovascular diseases. Early identification of individuals with MS can help them to prevent the mortality and morbidity of cardiovascular diseases.

Based on the results of research, psoriasis and

Table 1. Demographic, clinical and laboratory characteristics of patients with lichen planus and healthy controls

	Patients with lichen planus (n=40)	Healthy controls (n=40)	*P*-value
Age (years) Mean±SD	44.2±12.4	43.1±9.2	0.656
Females/ males, n (%)	16 (40)/ 24 (60)	14 (35)/ 26 (65)	
BMI* (Kg/m^2)	27.5±4.4	27.3±3.2	0.795
Diastolic blood pressure, mmHg	117±12.2	112±12.8	0.111
Systolic blood pressure, mmHg	72±10.2	69±9.3	0.231
Abdominal circumference (cm)	97.5±12.3	92.6±15	0.116
Severity of disease, n (%)			
Mild	9 (22.5)		
Moderate	19 (47.5)		
Severe	12 (30)		
Clinical type, n (%)			
Cutaneous	30 (75)		
Mucosal	2 (5)		
Mucocutaneous	8 (20)		
Duration of disease (years)	3-30		
Mean	2.98		
Lipid profile (mg/dl)			
TG	160.4±144.5	154.1±150.9	0.849
Cholesterol	182.6±39.2	177.2±36.5	0.522
LDLc	102.7±31.3	101.4±27.6	0.835
HDLc	44.2±10.3	44.3±6.7	0.928
Leptin (ng/ml)	32.6±23.2	28.7±20.3	0.429

*Body mass index
Scoring system for lichen planus was based on the extension of skin involvement (generalized involvement; severe type, one localized involvement; mild type, others; moderate type), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL)

Table 2. CIMT and carotid plaque prevalence in patients and controls

	Patients with lichen planus (n=40)	Healthy controls (n=40)	*P*-value
The right CIMT*, mm Mean±SD	0.67±0.15	0.59±0.12	0.012
The left CIMT, mm Mean±SD	0.69±0.16	0.59±0.13	0.005
The number of atherosclerotic plaques in CCAs#			
Right	0	0	0
Left	3	0	0.241
Severity of disease			
Mild	0.59±0.13		
Moderate and severe	0.71±0.15		0.035

* Carotid intima-media thickness
# Common carotid artery

cutaneous LP are associated with a significant level of risk for metabolic syndrome [4]. Although the exact mechanism of the relationship between cutaneous LP and metabolic syndrome is unknown, the chronic inflammation is considered the potent mechanism. Upregulation of inflammatory ligands, presence of effector cytotoxic T-cells and plasmacytoid dendritic cells [5], various cytokines such as interleukins, TNF-α, IFN-α, IFN-γ (5,6), Leptin, Adiponectin, and other Adipocytokines produced by Adipocytes [7,8], oxidative stress and a disorder in the elimination of reactive oxygen species (ROS) [9-11] due to the lymphocytotoxic process, play a role in the pathogenesis of LP. This chronic pro-inflammatory condition possibly can explain the correlation between LP, dyslipidemia and metabolic syndrome [12]. To the best of our knowledge, there are few studies on the association between dermatologic conditions and subclinical atherosclerosis. Recent studies have indicated that average CIMT values were increased in patients with LP who had no clinical evidence of heart

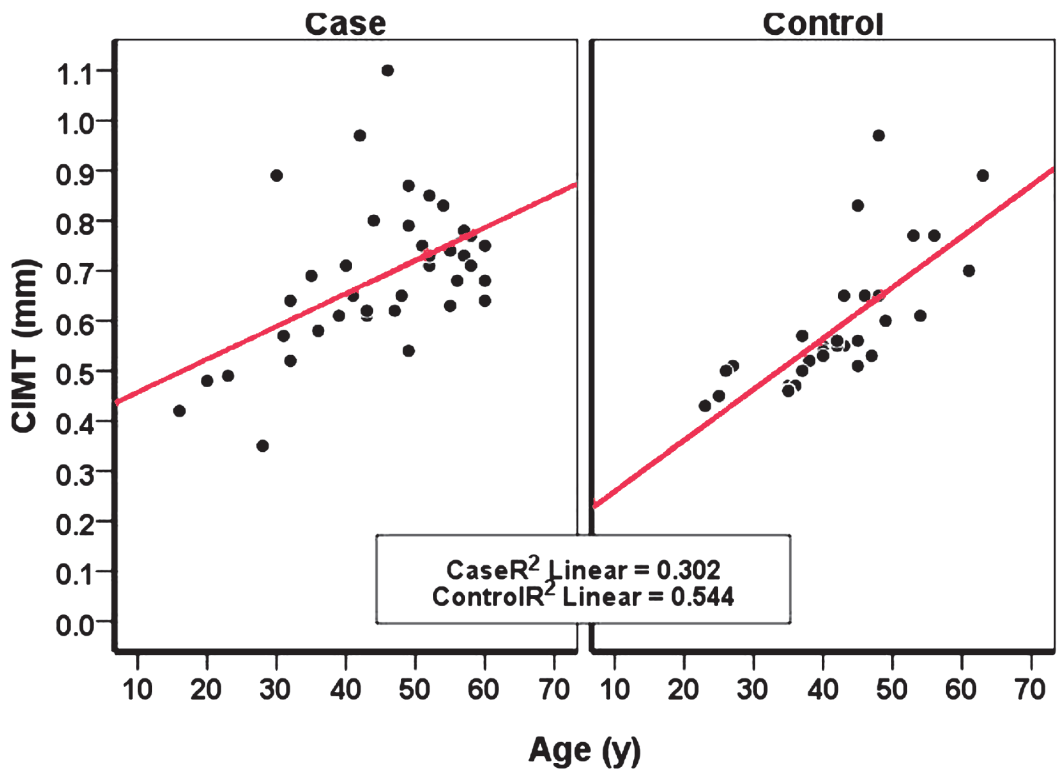

Figure 1. The correlation between CIMT and age

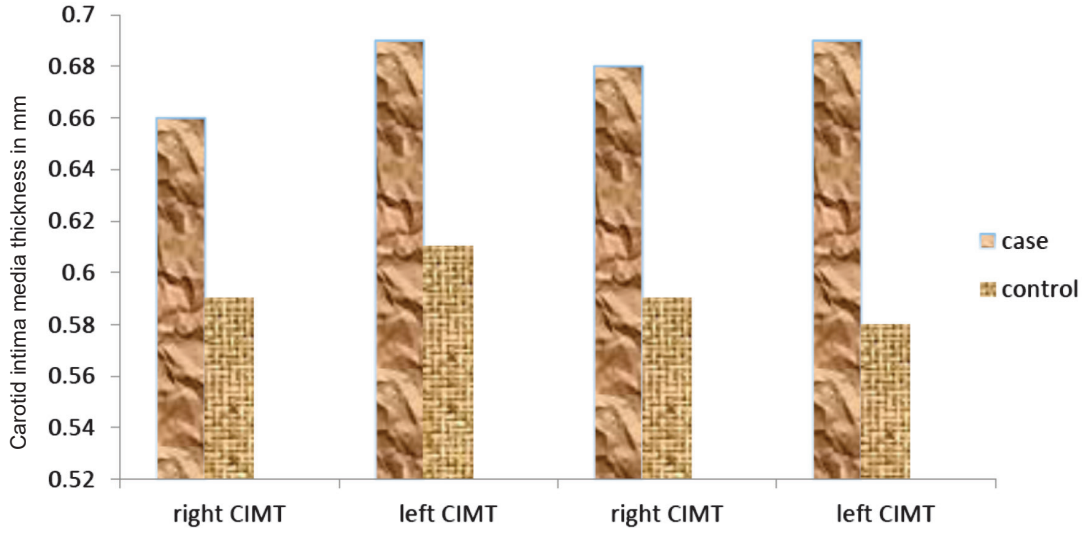

Figure 2. Carotid intima media thickness in the patients and controls

diseases [13]. Impaired levels of flow-mediated dilatation (FMD) and increased CIMT are the sensitive predictors of early endothelial dysfunction and structural changes in patients with LP [14]. The present research aimed to study the association of cutaneous LP with carotid intima-media thickness (CIMT) and the number of atherosclerotic plaques in CCAs in patients with LP not known to have CVD cardiovascular disease (CVD) risk factors and smoking habits. Although in some studies, CIMT was correlated with the longevity of LP [15], others were not correlated, like ours [13,14].

Carotid IMT adjusted for variables was significantly associated with the PASI score in psoriasis [16].

In our study, a significant correlation was found between the severity of disease and atherosclerotic variables. According to previous studies, there was a significant correlation between age and CIMT in LP patients, like our study [13,14].

The participants did not have any cardiovascular risk factors. To make conflicting factors least, we excluded individuals with smoking habits, then we could find out closely whether LP was a dependent predictor of increased CIMT.

In studies on carotid Doppler ultrasound evaluation in patients with Lichen planus, carotid plaque prevalence was not evaluated. Only Troitzsch *et al.* could demonstrate that psoriasis was associated with mean CCA-IMT, but not with carotid plaque prevalence [17]. We assessed the number of atherosclerotic plaques in patients with LP, but there was no significant difference.

Our study has some limitations. The overall sample was restricted by the rigid inclusion criteria; moreover, financial constraints were another limitation.

Subclinical atherosclerosis and cardiovascular morbidity are more frequent and considerably challenging. For better prophylaxis, early diagnosis of atherosclerosis or lipid profile monitoring is important in patients with lichen planus. Measurement of the mean intima media wall thickness of the common carotid artery could be beneficial as a valuable method for the mentioned reason.

Undoubtedly, CIMT in LP is correlated with some inflammatory cytokines and complicated pathogenic and proatherogenic pathways. We suggest that future studies be conducted to clarify the connection of atherogenesis to cytokines in LP.

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Validity and reliability of Persian version of infants' dermatitis quality of life index (IDQOL) questionnaire

Saman Mohammadi, MD [1]
Saeedeh Farajzadeh, MD [2]
Hossein Safizadeh, MD [3]
Maryam Khalili, MD [1]
Mahin Aflatoonian, MD [1*]
Rezvan Amiri, MD [1]
Elham Mohammadrezakhani, MD [4]

1. Department of Dermatology, Afzalipour Hospital, Kerman University of Medical Sciences, Iran
2. Leishmaniasis Research Center, Kerman University of Medical Sciences, Iran
3. Social Determinants of Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
4. Kerman University of Medical Sciences, Iran

**Corresponding author:*
Mahin Aflatoonian, MD
Department of Dermatology, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
Tel: +00989125987542,
Fax: +983433257477,
Postal code: 7616913911,
Email: maaflatoonian@gmail.com

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Background: Atopic dermatitis is the most common inflammatory skin disease in children. Severe itching may lead to an impaired quality of life in the patients. In this study, we evaluated the validity and reliability of Persian version of a questionnaire regarding the infants' dermatitis quality of life in children suffering from atopic dermatitis.

Methods: When the original authors approved of the Persian version of the questionnaire, the parents completed the questionnaire for their 98 children with atopic dermatitis aged less than four years. We analyzed the data by SPSS 16. Cronbach's alpha and inter-item and calculated the correlations to evaluate the reliability and validity via Kaiser criterion and scree plot.

Results: The calculated mean score of questionnaire was 9.65±5.41. The first (itching and scratching) and eight questions (treatment problems) obtained the highest and lowest scores, respectively. There was a strong, positive correlation between the severity of the disease and the quality of life score in the patients. Cronbach's alpha was calculated as 0.88 which is a sign of good internal consistency of the items. The inter-item correlative coefficients varied between -0.004 to 0.87. We used Kaiser's criterion and scree plot to evaluate the validity and achieve a two-factor solution.

Conclusion: Persian version of infants' dermatitis quality of life index questionnaire was valid and reliable.

Keywords: validity, reliability, Persian, dermatitis, quality of Life Index

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INTRODUCTION

Atopic dermatitis (AD) is the most common dermatologic disease among the children with a chronic and relapsing course. Approximately 5%-20% of the children suffer from AD worldwide, as it occurs during the first 5 years of life in 90% of the cases [1,2]. The prevalence of AD in children aged 2 to 7 in Kerman has been reported to be 13.52% [3]. Genetic, immunologic, and functional defects in skin barrier are three contributing factors in the pathogenesis of AD.

Depending on the duration of the disease and patient's age, the clinical symptoms of AD may vary. Scaling, erythema, skin dryness, increased skin thickness, crust and erosion formation are

some of the most common symptoms [3,4].

Severe itching is a significant feature of AD that can lead to irritability, disturbance in sleep, and fatigue during day, and mood alteration. Moreover, limitation in day time activities, leisure, sports, considerable change in life style including type of dressing, bathing and eating habits can damage the impaired quality of life (QoL) of the patients [5,6].

Previous studies demonstrate high incidence of impaired behavior and attention deficit hyperactivity disorders (ADHD) in AD patients [7]. In order to evaluate the treatment response, it is necessary to measure the disease severity, impact of disease on QoL, and psychological aspects of life [5].

In order to evaluate the QoL in children less than 4 years old affected with dermatitis, infantile dermatology quality of life (IDQOL) questionnaire developed by Lewis Jones and Finlay in 2001 [8].

In this study, we decided to evaluate reliability and validity of Persian version of this questionnaire in infants with AD.

MATERIAL AND MEHODS

IDQOL questionnaire has been designed to evaluate dermatitis effects on various aspects of life since a week ago in the children less than 4. This questionnaire encompasses 10 items concerning itching and scratching, mood alteration, treatment problems, the interaction of the disease with hobbies, physical, familial activities, and necessary changes in bathing, dressing, eating and sleep patterns. Each item includes four options with scores ranging from zero to three. The final score is calculated by adding scores of the items that can vary from zero to 30. Higher score represents greater effect of the disease on QoL.

In order to prepare the Persian version of IDQOL, first we received permission from original developers of the questionnaire. Then the original version of questionnaire was translated to Persian by two native bilingual expert translators whose mother tongue was Persian. After concluding an agreement on final version of Persian translation, it was translated back to English by two other trained bilingual English translators. We repeated the process until the original developers officially approved the Persian version.

In order to evaluate the comprehensiveness and clarity of the questionnaire, we asked ten parents whose children suffered from atopic dermatitis to complete it. After the understandability of the questionnaire was confirmed, we began to assess its validity and reliability. This study was performed in Afzalipour Hospital, Kerman University of Medical Sciences from November to august of 2016. 98 children under four participated. The study included the children diagnosed with AD based on UK working party criteria and those whose parents could read and write the Persian language [9]. It also excluded the children affected with other diseases that could change QoL of patients. After obtaining informed consent from the parents, we recorded sex, age and disease severity based on SCORAD in AD patients and the history of atopy, socioeconomic status, and educational level of the parents [4]. Finally, the parents were requested to complete the IDLQOL questionnaire.

Data analysis was conducted via SPSS 16. Cronbach's alpha and inter-item correlation were calculated to evaluate reliability and Kaiser criterion and scree plot were conducted to assess the validity of the questionnaire. The independent T test was employed to compare SCORAD and QOL score. Pearson correlation test was used for inter-item correlation.

RESULTS

We enrolled 98 children with AD under 4 with a minimum age of three weeks and maximum of 52 months. 50 percent of the patients were male. Minimum and maximum duration of the disease were between zero to 36.5 months. We found acute, subacute, and chronic dermatitis in 41%, 40% and 14% of the cases, respectively. The most and the least prevalent sites of involvement were head and neck (75.5%) and genitalia (8.2%). 80 percent of questionnaires were completed by mothers and 20% by fathers.

IDQOL

The obtained mean score was 9.65±5.41 (minimum=0, maximum=28). The highest and the lowest obtained scores belonged to question 1 (itching and scratching) and question 8 (treatment problem). 50 percent of participants achieved the score of nine or less. Nearly 1% of participants acquired floor effect (the least achievable scores),

but none of them obtained the highest achievable score (ceiling effect).

Percentage of scores among the participants in the highest level (ceiling effect) for all of the questions was the least, except for the question 3. Furthermore, percentage of scores in the lowest level (floor effect) for all of the questions was more than 25%, except for question one and two. The mean score, ceiling, and floor effects have been demonstrated in Table 1.

SCORAD

Mean of SCORAD was 40.1±17.01 (minimum=11.8, maximum=84.1). Based on SCORAD the severity of AD was categorized to three groups of mild (less than 25), moderate (between 25 and 50), and severe (more than 50). Mild disease was observed in 21.4% of the patients. Also, 52.04 % and 26.5% of them had moderate and severe disease respectively. We found a strong and positive relationship between the obtained QoL scores and SCORAD (r=0.66, P<0.001).

Reliability

In order to evaluate reliability, we calculated Cronbach's alpha that was 0.88 representing a suitable internal consistency among the questions (Table 2). Also, the inter-item correlation coefficient was between _0.004 to 0.87 (Table 3). The least coefficient belonged to question number 3 that was lower than 0.3 (the least range of acceptable coefficient). Also, after deletion of this question,

Table 3. Corrected item-scale and Cronbach's Alpha

Question number	Corrected item-total correlation	Cronbach's alpha if item was deleted
Q1	0.410	0.883
Q2	0.722	0.861
Q3	0.184	0.912
Q4	0.627	0.869
Q5	0.829	0.854
Q6	0.845	0.854
Q7	0.749	0.860
Q8	0.491	0.878
Q9	0.745	0.860
Q10	0.716	0.862

Table 1. Mean score of each item, ceiling and floor effects, and percentage of response rate to each answer

Question number	Subject	Mean±SD	Ceiling effect	Floor effect	Percent of response rate to answers			
					Very much	A lot	A little	Not at all
1	Itching & scratching	1.68±0.60	5.10	2.04	5.1	60.2	29.6	2
2	Child mood	1.16±0.82	8.16	18.37	8.16	18.4	54.1	18.4
3	Time to go to sleep	1.17±1.04	17.35	28.57	17.3	11.2	40.8	28.6
4	Sleeping problems	0.68±0.75	2.04	46.94	2	11.2	38.8	46.9
5	Hobbies disturbance	0.84±0.74	2.04	34.69	2	14.3	48	33.7
6	Family activities disturbance	0.81±0.70	2.04	33.67	2	10.2	53.1	33.7
7	Mealtimes problems	0.82±0.76	2.04	37.76	2	15.3	44.9	37.8
8	Treatment problems	0.58±0.69	1.02	52.04	1	5.1	33.7	49
9	Dressing problems	0.95±0.82	2.04	33.67	2	24.5	39.8	33.7
10	Bath time problems	0.96±0.77	2.04	29.59	2	21.4	46.9	29.6

Table 2. Inter-item correlation coefficients of questions

Question number	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Q1	1.000									
Q2	0.377	1.000								
Q3	0.304	0.221	1.000							
Q4	0.322	0.534	0.335	1.000						
Q5	0.368	0.620	0.145	0.570	1.000					
Q6	0.343	0.667	0.132	0.626	0.873	1.000				
Q7	0.298	0.590	0.145	0.524	0.728	0.763	1.000			
Q8	0.100	0.378	0.002	0.239	0.512	0.473	0.519	1.000		
Q9	0.239	0.597	0.023	0.408	0.717	0.741	0.662	0.549	1.000	
Q10	0.304	0.612	0.004	0.438	0.708	0.692	0.546	0.472	0.846	1.000

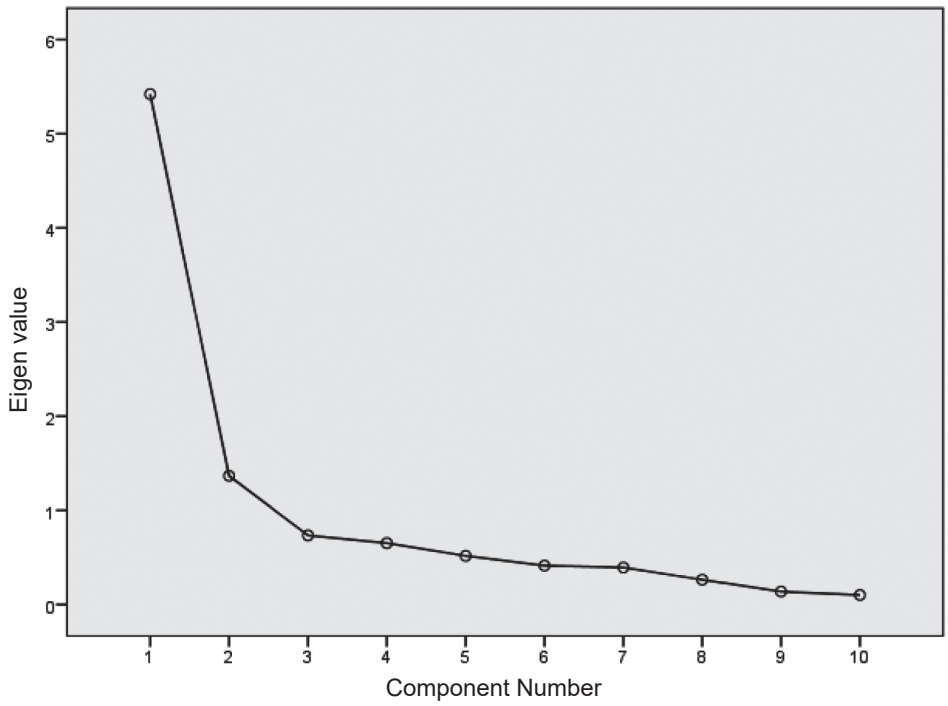

Figure 1. Scree plot and Kaiser's criterion

Cronbach's alpha was increased from 0.87 to 0.92.

Validity

To show the validity, Kaiser's criterion and scree plot were employed with two-factor solution, explaining 67.88% of the variance (Figure 1). The factor loading for each item is shown separately in table 4.

DISCUSSION

Atopic dermatitis is a chronic inflammatory dermatologic disease with a negative impact on psychological aspects and QoL of patients [5,8,10].

Table 4. Factor loading of each item

Question number	Factor one	Factor two
Q1	0.92	
Q2	0.87	
Q3	0.86	
Q4	0.85	
Q5	0.79	
Q6	0.73	
Q7	0.67	
Q8		0.86
Q9		0.63
Q10		0.53

Previous studies indicated that children with severe eczema have more impairment in QoL than children with other chronic diseases such as asthma, epilepsy, diabetes mellitus, and renal disease [11].

IDLQOL is a specific QoL questionnaire that evaluates QoL in children under four years old. To date, this questionnaire has been translated to 21 different languages and used in 18 different countries [12].

In this study, Cronbach's alpha for Persian version of the questionnaire has been estimated as 0.88, representing an acceptable correlation in line with other studies in Italy conducted by Baranzoni (α>0.7) and Neri (α=0.89) [13,14]. The evaluation of inter-item correlation coefficient showed an acceptable connection between the questions except for question 3 with negative coefficient in one item and coefficient of less than 0.2 in five items. Moreover, according to corrected item-scale calculation, question 3 had the correlation coefficient of less than 0.3 (0.184), and after the deletion of question number 3, Cronbach's alpha was increased to 0.92. Regarding to high first Cronbach's alpha (0.88), we finally decided to preserve question 3 in the results with no change.

In one study by Alzolibani in Saudi Arabia on 370 infants with AD, Cronbach's alpha was

reported 0.87 that was compatible with our results [15]. However, unlike our study, the rate of corrected item correlation in all of the questions was more than 0.3 and Cronbach's alpha would be nearly equal to the first Cronbach's alpha, if each item were deleted. In the current study, the evaluation of validity based on factor analysis led to two-factor solution explaining 67.88% of the variance. According to this analysis, question 1, and 3 are situated in different factor loading from other questions.

Lewis-Jones *et al.* estimated the Mean score of QoL in AD infants as 7.89±5.74 which was less than our results (9.65±5.40) [8]. This difference can be explained by higher severity of AD of patients in our study. The higher acquired score in descending order belonged to question 1(itching and scratching), question 3 (average time to sleep), question 2 (child's mood) and the lowest score belonged to question 8 (treatment problems). In most of previous studies, itching, mood alteration and sleep disturbance were the most common symptoms leading to the impairment of QOL that was nearly compatible with our results [12-14].

In our study, there was no correlation between sex of the patients and QoL that was compatible with Ganemo, Kim and Alanne studies [16-18]. Other studies have confounding results, while in some of which a lower QoL has been found in girls, others have the opposite results [12,19]. For example, Ražnatović *et al.* in Belgrade demonstrated that items such as itching, disturbance in familial activities, and time for sleep have more significant effects on QoL in female infants than male infants, while Ang in Singapore has reported more impairments in the familial activities of the male infants [20,21]. This discordance might be explained by cultural difference.

In our study, we observed,a strong and positive relationship between QoL score and severity of the disease based on SCORAD (P<0.001), that was compatible with other studies [22-24].

Our results confirmed validity and reliability of Persian version of IDLQOL. Therefore, it can be used to evaluate QoL of infants in patients with atopic dermatitis. The limitation of our study was the absence of healthy infants as control group to compare the QoL of AD children with healthy ones.

Conflict of interest: None declared.

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Pattern of pediatric dermatoses and seasonal variations in a tertiary referral center in central India

Sarika Pawar, MD
Vaishali H. Wankhade, MD*
Bhagyashree B. Supekar, MD
Rajesh Pratap Singh, MD

Department of Dermatology, Venereology and Leprology, Government Medical College & Hospital, Nagpur, Maharashtra, India

** Corresponding author:*
Vaishali H. Wankhade, MD
Department of Dermatology, Venereology and Leprology, Government Medical College & Hospital, Nagpur, Maharashtra, India
Email: vshingade73@yahoo.com

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Background: Skin diseases in the pediatric population are common worldwide, including rural and urban areas. There is a variation in the pattern and presentation of dermatoses, with eczemas being the most common skin disorder in developed countries and infestations in the developing countries. To study pattern, age-gender wise distribution and seasonal variations of various pediatric dermatoses.

Methods: All children in the age group of 1-12 years of either sex were recruited in the dermatology outpatient department from November 2014 to October 2016.

Results: Infections and Infestations were the most common dermatoses (46.3%), followed by dermatitis and eczema (20.24%). Among, the most common types of infections and infestations were scabies (33.49%), followed by viral (30.4%), and bacterial (23.3%) infections. Impetigo (P<0.001), furunculosis (P=0.025), molluscumcontagiosum (P<0.001), hand foot mouth disease (P=0.004) and atopic dermatitis (P=0.003) were significantly higher in the age group of 1-4 years. We also found a significant association between the seasonal variation and the bacterial infections, pediculosis and varicella.

Conclusion: In our study, skin infections and infestations outnumbered other pediatric dermatoses. These are potentially controllable and hence strategies that target infections and infestations may be a key to an efficient child health care program.

Keywords: Pediatric dermatoses, seasonal variations, central India

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INTRODUCTION

Associated with significant morbidities, skin diseases are of the major health problems among children [1]. Dermatological problems constitute at least 30% of all outpatient visits to pediatric clinics and 30% of all visits to dermatology clinics [2,3]. The prevalence of pediatric dermatoses in various parts of India has ranged from 8.7% to 35% in school-based surveys [4]. The pattern of skin diseases relies in various factors such as poverty, malnutrition, overcrowding, poor hygiene, illiteracy, and social backwardness in many parts of India [5]. The direct effects of climate on the skin may play a minor but significant role in determining the geographical and seasonal variation of many dermatoses [6]. Pediatric dermatoses requires a separate view from adult dermatoses, as there are important differences in clinical presentation, treatment, and prognosis.

MATERIALS AND METHODS

The aim of study was to determine the pattern of pediatric dermatoses and their seasonal variations. To this end, we obtained the institutional ethical committee clearance. We recruited all children between age group 1–12 years of either sex, attending dermatology department during the

period of November 2014 to October 2016. Wherever needed, we recorded a detailed history, a complete skin examination, along with routine examinations in the predesigned pro forma.

Statistical analysis

Categorical variables were expressed in frequencies and percentages. Pearson's chi2 test and Fisher exact test were performed to find correlation of skin diseases with age, sex and seasonal variation. All the tests were two sided. P<0.05 was considered as statistical significance.

Ethical considerations

The written informed consent was obtained from all participants.

RESULTS

In this study, a total of 800 children in age group of 1-12 years were included, among whom 466 (58.25%) were girls and 334 (41.75%) were boys with ratio being 1.39:1. The majority of patients (286; 35.75%) belonged to the age group of 1-4 years. A total of 820 dermatoses were recorded in the patients. As depicted in Table 1, infections and infestations (380, 46.34 %), were the most common type of dermatoses found followed by eczematous dermatoses (166, 20.24 %), papulosquamous disorders (51, 6.21%), pigmentary disorders (43, 5.24%), and genetic disorders (29, 3.53%). In the skin infections, bacterial infection was the leading presentation (n=120), followed by infestations (n=109), viral (n=107) and fungal infections (n=40). Among bacterial infections, impetigo (54, 45%) was most common form followed by secondary pyoderma (41, 34.16%). The prevalence of impetigo was more prevalent in boys (p=0.16) and in the age group of 5-8 years (P<0.001) which was statistically significant (Figure 1)

The most common viral infections include molluscum contagiosum (MC), varicella and herpes

Table 1. Distribution of dermatoses according to sex

Type of dermatoses	Boys	Girls	Total (%)
Infections and infestations	162	218	380 (46.34%)
Eczema and dermatitis	68	98	166 (20.24%)
Papulosquamous disorders			
Psoriasis	8	8	51 (6.21%)
Pityriasis rosea	4	7	
Other	13	11	
Pigmentary disorders			
Vitiligo	14	25	43 (5.24%)
Postinflammatory hyperpigmentation	1	3	
Genetic disorders			
Nevi	8	16	29 (3.53%)
Icthyosis	1	2	
Neurofibromatosis	1	1	
Papular urticaria/ Insect bite reaction	11	17	28 (3.41%)
Nutritional disorders	11	13	24 (2.92%)
Hair disorders	08	14	22 (2.68%)
Urticaria	03	12	15 (1.82%)
Polymorphic light eruption	07	06	13 (1.58%)
Acne vulgaris	01	09	10 (1.21%)
Drug reactions	01	01	02 (0.24%)
Miscellaneous			
Palmoplantar keratoderma	4	0	37 (4.51%)
Connective tissue disorders	1	2	
Mastocytosis	0	2	
Juvenile xanthogranuloma	1	0	
Linear porokeratosis	0	1	
Other	12	14	
Total	341	479	820 (100%)

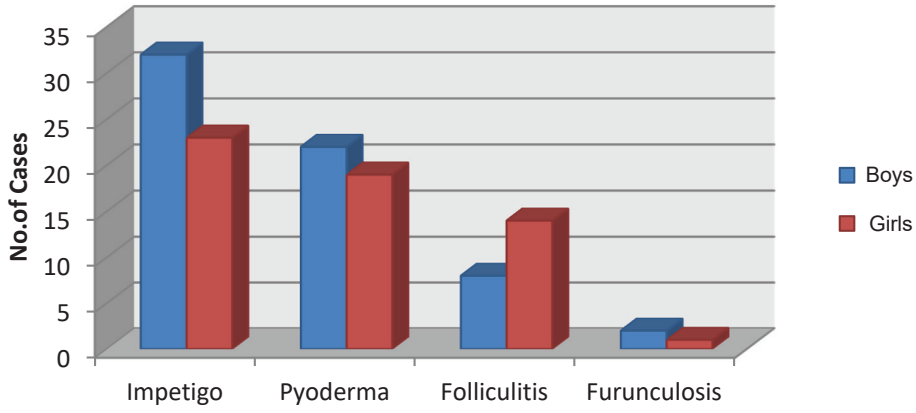

Figure 1. Sexwise distribution of bacterial infections

zoster. The majority of MC patients belonged to age group of 1-4 and 5-8 years which was statistically significant (P<0.001). All the six cases of hand-foot-and-mouth disease occurred in the age group of 1-4 years (P=0.004; Table 2).

After other eczematous eruptions including asteatotic eczema, nummular eczema, and xerosis, the most common condition, in eczema and dermatitis, was atopic dermatitis. Most children with atopic eczema were in the age groups of 1-4 and 5-8 years, which was statistically significant (P=0.003; Table 2). Scabies was most common form of infestations (n=109) followed by pediculosis. Pediculosis which was more frequently recorded in girls than boys (P=0.008). Tinea corporis and tinea capitis accounted for the largest group of fungal infections. Its prevalence among boys showed statistically significant associations (P=0.034; Table 3).

In the present study, the majority of dermatoses were recorded in summer (331; 41.37%), winter (267, 33.37%) and rainy season (202, 25.25%) (Figure 2). Maximum cases of impetigo, secondary pyodermas and folliculitis were documented in summer and rainy seasons (Figure 1). Varicella was the most common viral infection in summer. Scabies was noted predominantly in winter, while pediculosis (P=0.015) was seen more frequently in summer. In this study, fungal infections were observed throughout the year with no statistical difference. The prevalence of eczemas and pityriasis alba was higher in winter. (Table 4)

Table 3. Sexwise distribution of fungal infections and infestations

Infections and infestations	Boys	Girls	Total	*P*-value
Dermatophytoses	21	14	35	0.034
Intertrigo	0	3	3	0.270
Pityriasis versicolor	1	1	2	1.000
Scabies	33	51	84	0.628
Pediculosis	4	21	25	0.008

Table 2. Distribution of viral infections, eczema and dermatitis according to age

Viral infections, Dermatitis & Eczema	1-4 yrs	5-8 yrs	9-12 yrs	Total	*P*-value
Molluscum contagiosum	34	16	8	58	<0.001
Varicella	10	11	9	30	0.960
Herpes zoster	0	3	3	6	0.179
Hand-foot-mouth disease	6	0	0	6	0.004
Warts	1	2	1	4	0.925
Herpes labialis	0	1	0	1	0.492
Other eczematous eruptions	28	26	21	75	0.949
Atopic dermatitis	17	14	1	32	0.003
Pityriasis alba	8	12	8	28	0.627
Contact dermatitis	8	4	5	17	0.529
Pompholyx	6	2	1	9	0.144
Keratolysis exfoliativa	0	3	0	3	0.061
Seborrheic dermatitis	0	1	1	2	0.565

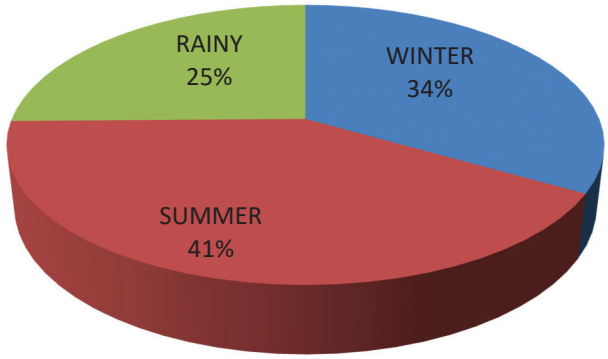

Figure 2. Seasonal variation in pediatric dermatoses

DISCUSSION

The pattern of skin diseases differs from one country to another and within various regions of the same country. Low socio-economic status, malnutrition, overcrowding, and poor standard of hygiene are important factors responsible for the distribution of skin diseases in developing countries such as India [7]. Various climatic factors that may affect the incidence of skin diseases include coldness, heat, light, sunshine, and humidity. The type and prevalence of the disease in each community may be directly or indirectly affected by the climate.

In this study, the majority of patients (286; 35.75%) belonged to the age group of 1-4 years, in line with the observations recorded by Patel *et al.* [8], Jawade *et al.* [9], Karthikeyan *et al.* [10] and Hassan *et al.* [11]. This can be explained on the basis that the infants are mostly confined to their household whereas preschool children are prone to skin infections due to increased environmental exposure. The girls outnumbered 466; 53.25 %) the boys (334; 41.75%) with a girl: boys ratio 1.39: 1 which is comparable with the study by Nageswaramma *et al.* [12]. In this study, infections and infestations were the most common group (380; 46.34%) followed by eczemas and dermatitis (166; 20.24%). A similar pattern of dermatoses has been reported in the study conducted by

Table 4. Seasonal variations in infections, infestations, dermatitis and eczema

Infections/infestations	Winter	Summer	Rainy	Total	*P*-value
I) Bacterial infections				120	
Impetigo	7	16	31	54	<0.001
Secondary pyoderma	7	16	18	41	0.008
Folliculitis	1	8	13	22	<0.001
Furunculosis	1	1	1	3	0.925
II) Viral Infections				107	
Mollusum contagiosum	16	29	13	58	0.377
Varicella	7	19	4	30	0.042
Herpes zoster	0	5	1	6	0.092
Hand-foot-mouth disease	2	3	1	6	0.431
Warts	0	1	3	4	0.062
Viral exanthema	2	0	0	2	0.135
Herpes labialis	1	0	0	1	0.368
III) Fungal Infections				40	
Dermatophytosis	12	15	8	35	0.815
Intertrigo	1	1	1	3	0.919
P. versicolor	1	1	0	2	0.702
IV) Infestations				109	
Scabies	35	33	16	84	0.177
Pediculosis	6	13	0	25	0.015
V) Mycobacterial infections	0	1	3	4	0.062
VI) Dermatitis and eczema					
Atopic dermatitis	11	17	4	32	0.195
Pityariasis alba	17	9	2	28	0.004
Contact dermatitis	10	7	0	17	0.372
Pompholyx	2	5	2	9	0.662
Keratolysis exfoliativa	1	2	0	3	0.542
Seborrheic dermatitis	1	2	0	3	0.542
Other eczema	49	24	2	75	0.001

Karthikeyan *et al.* [10] and Nageswaramma *et al.* [12].

Bacterial infection (124; 15.12%) was the most common entity followed by viral (107; 13.04%) and fungal (67; 4.8%) infections. In the infestations group, scabies accounted for the maximum number of cases (109; 13.29%). These results are consistent with studies conducted by Patel *et al.* [8], Karthikeyan *et al.* [10] and Balai *et al.* [13].

In the viral infections, the most common entity was MC (58; 7.07%) followed by varicella (30; 3.65%) and hand- foot-and-mouth disease (6; 0.73%). Similar observations have been reported in several studies [8,13,14]. The hand-foot-and-mouth disease has recently been rising due to the probable mass immunization programs in India. Polio vaccination has eliminated polio viruses from the gut to increase the chances of coxsackie and echovirus infections [15]. Tinea corporis was the most frequent fungal infection followed by tinea capitis, tinea faciei, and tinea manuum. The fungal infections were more frequently encountered in boys in the age group of 5-8 years. These results are in accordance with the study conducted by Roy *et al.* [16] and Sharma *et al.* [17] The fungal infections can be attributed to the hot and humid climate and recent changes in dermatophyte flora. Large families, sharing of towels, clothing, and hair accessories with infected individuals may lead to the spread of fungal infections [18].

We recorded 4 boys with Hansen's disease. Dogra *et al.* reported the similar results. (0.4%) [7]. Jawade *et al.* found childhood leprosy in 2.02% [9]. Despite the statistical elimination of leprosy in this region, childhood leprosy cases continue to present in alarming numbers. It indicates that familial contacts play a significant role in the development of the disease.

Eczema and dermatitis were the second most common group of dermatoses in our study constituting 20.24% of the total cases. Other eczematous eruptions including winter dermatitis, nummular eczema, and xerosis constituted the majority of cases followed by atopic dermatitis, pityriasis alba and contact dermatitis, which were consistent with the study by Bhatia *et al.* [19] The increased incidence of atopic dermatitis may be associated with environmental pollution, exposure to agricultural chemicals, early weaning from breast feeding and increased awareness.

In our study, psoriasis followed by pityriasis rosea accounted for the largest number of patients with papulosquamous disorders. Karthikeyan *et al.* [10], and Roy *et al.* [16] reported the prevalence of psoriasis as 1.4% and 2.17 %, respectively. Similar to Roy *et al*, 4.75% of patients had vitiligo in our study [16]. Papular urticaria and insect bite reaction followed by urticaria were the most common hypersensitivity disorders. Similar findings have been reported in the studies by Roy *et al.* [16], Sardana *et al.* [20] and Sayal *et al.* [21]. The high prevalence of papular urticaria can be explained by the fact that most of these children are from rural or semi-urban areas and are prone to insect bites due to weather conditions, lack of suitable clothing. Our study also reported a few number of patients with phrynoderma. Karthikeyan *et al.* [10] and Jawade *et al.* [9] studies showed an incidence of 2.8% and 2.70% respectively, who had nutritional dermatoses.

Acne was documented in 10 adolescent patients. The incidence of acne in the present study was low since this condition mainly a dermatosis of adolescents and young adults whereas our study was limited to the age group of 1-12 years. Roy *et al.* [16] and Bisht *et al.* [22] reported an incidence of 3.5% and 0.69%, respectively.

In this study, hair disorders constituted 1.58% of the total cases. Alopecia areata was the most common followed by diffuse hair loss which is comparable to the studies conducted by Bisht *et al.* [22] and Sharma *et al.* [23] Genetic disorders had been reported in 3.53% of our study. We also reported two cases of drug reactions, angioedema in one case and maculo-papular eruption in another one.

The prevalence of certain dermatoses may be affected by seasonal and climatic changes. This was quite evident in our study in which impetigo, secondary pyodermas and folliculitis were most frequently noted in summer and rainy seasons. Scabies was noted predominantly in winters while pediculosis and varicella were observed more frequently in summer and winter. Although dermatophytos were more prevalent in summer, they have been reported throughout the year. The studies conducted by Patel *et al.* [8], Balai M *et al.* [13], Bisht *et al.* [22], and Banarjee *et al.* [24] have reported that the bacterial infections are more common in the summer and rainy seasons, while scabies and pityriasis alba were more reported in the winter. On the other hand, fungal infections were more

frequent in summer while popular urticaria was seen in rainy season. High temperature and humidity in the summer and rainy seasons lead to rapid proliferation of pyogenic bacteria, and therefore high prevalence of bacterial infections. Scabies were more prevalent in winter, which may be because people spend more time indoors and in closer proximity to each other at this time of year.

CONCLUSION

The study emphasizes the importance of recognizing pediatric dermatoses at an early stage so that one can prevent their long term consequences on children, parents, and society. This study concluded that infections and infestations outnumbered other pediatric dermatoses in India. The incidence of skin infections can be reduced by raising awareness about nutrition, sanitation, and personal hygiene. Further studies are required in different regions to evaluate the actual magnitude of skin disorders in pediatric group.

Conflict of interest: None declared.

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A comprehensive review on vitamin D receptor (VDR) gene polymorphism in immune-related diseases with emphasis on dermatologic disorders

Azadeh Goodarzi, MD*

Department of Dermatology, Rasoul Akram Hospital, Iran University of Medical, Tehran, Iran

**Corresponding author:*
Dr. Azadeh Goodarzi, MD
Rasoul Akram Hospital, Sattarkhan Street, Tehran 1449614535, Iran
Tel: +98 9123882448
Email: goodarzi.a@iums.ac.ir

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There are many immune mediated disorders with the corroborated role of vitamin D or Vitamin D Receptor (VDR) gene polymorphisms in their pathogenesis, immunologic regulation, and disease characteristics. Therefore, in this review, we searched PubMed data base in regard to the role of VDR gene polymorphisms in common autoimmune disorders, emphasizing on dermatologic diseases.

Keywords: vitamin D, genetic polymorphism, autoimmune diseases

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INTRODUCTION

Numerous studies have evaluated the association between the inheritance of VDR gene polymorphisms such as FokI polymorphism and genetic susceptibility to various illnesses, including cancers, and infectious, inflammatory, and immunogenic disorders. There are many studies on such type of association in autoimmune or immune-related disorders such as type 1 diabetes mellitus [1-10], multiple sclerosis [11-14], autoimmune thyroid diseases [15-22], autoimmune hepatitis and liver diseases [23], inflammatory bowel diseases [24,25], collagen vascular disorders [26-29], and many specific dermatologic entities, including psoriasis [30-37], alopecia areata [38-40], recurrent aphthous stomatitis [41], vitiligo [42], and skin cancers [43-47]. Despite the body of work done on this subject, an obvious and conclusive association is yet to be identified. There are no similar studies focused on immunobullous disorders in the field of dermatology.

There are many studies regarding vitamin D levels and their association with different aspects of immunobullous disorders such as pemphigus vulgaris; however, we did not find any studies on the relationship between vitamin D receptor gene polymorphisms and these entities. In some studies, lower levels of vitamin D were found in pemphigus vulgaris patients irrespective of their age, BMI, and sun exposure. This could be associated with disease severity and worsening. Or vitamin D deficiency could be a predisposing factor in PV through affecting immune system (TGF-β/IL-17), particularly regulatory T cells. However, an inverse association was also reported between vitamin D levels and severity of immunobullous disorders (these patients had hypovitaminosis D, increased rate of vertebral fracture, and normal BMD) [48-53]. There are many articles regarding VDR gene polymorphisms in psoriasis [30-37]. Moreover, a recent meta-analysis showed that circulating 25(OH) D levels were lower in patients with psoriasis, and there was a small statistically significant and negative correlation between psoriasis severity and 25(OH)D levels [54].

METHOD

In this review, summarized in Table 1, the role of vitamin D receptor gene polymorphism in immune-related non-dermatologic and dermatologic disorders was studied. PubMed data base in

Table 1. The role of Vitamin D Receptor gene polymorphism in common immune-related non-dermatologic and dermatologic disorders

Disorder	Study	Findings
Common autoimmune disorders		
Diabetes mellitus [2,3, 5-10, 55-66]	Fassbender et al., 2002	There was a correlation between the TT genotype and diabetes in Germans. No difference was found in bone turnover markers.
	Mohammadnejad et al., 2012	VDR TaqI polymorphism was connected with DM type 1 in an Iranian population.
	Sahin et al., 2012	FasL -843C/T and VDR FokI gene polymorphisms and type 1 diabetes were associated in Turkey but not Fas -670A/G.
	Pani et al., 2000	There was a linkage between VDR or a nearby gene and DM type 1 susceptibility in Germans.
	Nejentsev et al., 2004	Common sequence variation of VDR gene had no major effect on DM type 1.
	Zemunik et al., 2005	An association was reported between VDR FokI polymorphism and several VDR and IL-1-R1 haplotypes in DM type 1 in Dalmatians.
	Capoluongo et al., 2006	There was slight increase in the prevalence of “ff” VDR genotype in DM type 1.
	Chang et al., 2000	Vitamin D receptor gene polymorphisms were correlated with type 1 diabetes in a Taiwanese population.
	Turpeinen et al., 2003	No association was seen between single nucleotide polymorphisms in VDR gene and type 1 diabetes in a Finnish population.
	Abd-Allah et al., 2014	VDR BsmI and FokI polymorphisms were associated with vitamin D deficiency in DM type 1 in Egyptian children.
	Boraska et al., 2008	There existed relationships between specific VDR gene variants and DM type 1 in South Croatia.
	Lemos et al., 2008	Single nucleotide polymorphisms of the VDR gene had no significant role in DM type 1 in a Portuguese population.
	Mauf et al., 2015	Genotypes of the VDR and CYP24A1 in susceptibility to DM type 1 might influence the immune modulatory effects of 25 (OH) D3.
	Morán-Auth et al., 2015	A more balanced T cell immunity could be beneficial for patients with DM type 1 carrying the “FF” genotype as an adequate vitamin D therapy.
	Mory et al., 2009	No relationships were found between VDR polymorphisms and beta-cell autoimmunity. However, age and remaining beta-cell function were correlated in Brazilian individuals with DM type 1.
	Panierakis et al., 2009	FokI, BsmI, ApaI, and TaqI polymorphisms of the VDR gene were associated with DM type 1 prevalence in a southern European population.
	Qin et al., 2014	VDR BsmI B allele, bb genotype was correlated with DM type 1 risk in Asians, and bb genotype was associated with its risk in the overall populations.
	Skrabić et al., 2003	VDR polymorphisms had a relationship with increased risks of DM type 1 in a Dalmatian population of South Croatia.
	Tizaoui et al., 2014	In DM type 1 pathogenesis, VDR polymorphisms interacted with each other and the environmental factors.
	Zhang et al., 2012	BsmI polymorphism was associated with increased risks of DM type 1, particularly in Asians.
Diabetes mellitus and Thyroid dysfunction [67]	Mory et al., 2016	The VDR FokI polymorphism (rs10735810) was associated with the persistence of GADA (glutamic acid decarboxylase antibody), TPOA positivity (TPO Antibody) and TD (thyroid dysfunction) in Brazilians with DM type 1. Positivity to TPOA and VDR polymorphism FokI was greatly associated with the concurrence of DM type 1 and TD.
Thyroid dysfunction [15-22, 68-70]	Feng et al., 2013	The cumulative effect of BsmI or TaqI polymorphisms in VDR had a meaningful association with AITD (autoimmune thyroid diseases).
	Ban et al., 2000	There was a relationship between Graves’ disease and a VDR polymorphism in the Japanese; also, a VDR-FokI polymorphism might affect bone mineral metabolism as a predictor of osteoporosis risk as a complication of Graves’ disease in remission.
	Abd El Gawad et al., 2012	BsmI, ApaI, and TaqI polymorphisms in the VDR gene were associated with susceptibility to GD (Graves’ disease) whereas BsmI, ApaI, and TaqI polymorphisms were not correlated with serum levels of 1,25 (OH)2D3.

Table 1. Continued

Disorder	Study	Findings
	Zhou et al., 2009	ApaI, BsmI and FokI polymorphisms in the VDR gene were associated with susceptibility to GD (Graves' Disease) in Asian populations while ApaI, BsmI, TaqI, and FokI polymorphisms had no correlation with GD in Caucasian populations.
	Chen et al., 2007	The VDR-FokI T/C polymorphism could possibly be employed as a genetic marker for predicting the likelihood of (Graves' disease) development.
	Ramos-Lopez et al., 2005	An association was seen between VDR gene polymorphisms and Graves' disease in the German and Polish populations, but not in the Serbian ones. VDR polymorphisms were differentially distributed in the three populations. Therefore, VDR polymorphisms analysis should be interpreted according to the population background.
	Stefanić et al., 2005	There was a relationship between VDR gene BsmI/ApaI/TaqI polymorphisms and Graves' disease susceptibility in a subset of patients from Eastern Croatia. The ApaI, BsmI "AA", "BB" genotypes, and combined "BBAAtt" genotype were revealed to allow protection against Graves' disease; however, ApaI "aa" and TaqI "TT" genotypes were associated with an increased risk of GD.
	Ban et al., 2000	There was an association between the VDR gene and Graves' disease in a Japanese population; therefore, VDR gene could be a non-HLA-linked gene predisposing an individual to GD.
	Lin et al., 2006	Chinese patients in Taiwan carrying the C/C homozygote of the VDR-FokI gene polymorphism in exon 2 could run a higher risk of HT (Hashimoto's thyroiditis).
	Stefanić et al., 2008	Common haplotypic variants within the VDR gene 3'-region, previously linked with VDR mRNA expression and allelic imbalance, could also be associated with Hashimoto's thyroiditis in the general population and disease pathogenesis.
	Yazici et al., 2013	VDR gene TaqI TT and FokI FF genotypes were associated with increased risks of Hashimoto's thyroiditis in Turkish patients. BbAaTtFf genotype seemed to be protective for HT disease in our population.
Multiple sclerosis [11-14, 71-77]	Huang and Xie, 2012	The VDR Apa-I, Bsm-I, Fok-I and Taq-I polymorphisms were not associated with MS risk.
	Sioka et al., 2011	Aq-I and Bsm-I polymorphisms of the VDR gene were not related to MS risk, BMI, or BMD in the studied Greek population.
	Orton et al., 2011	There was no direct connection between vitamin D metabolism genes and MS susceptibility despite the large sample size and comprehensive gene coverage.
	Smolders et al., 2009	No association existed between the Fok-I VDRG polymorphism and MS.
	Agliardi et al., 2011	There was interaction between the major genetic (HLA-DRB*15) and environmental (vitamin D) factors associated with MS onset.
	Bettencourt et al., 2017	There was a relationship between FokI ff genotype and MS susceptibility, but not its form or progression.
	Čierny et al., 2015	They found a weak association between VDR SNP FokI, and the MS risk in women
	Cox et al., 2012	There was a weak evidence of an association between a common variation within the VDR gene and MS in the largest study reported to date.
	García-Martín et al., 2013	VDR rs2228570 and rs731236 polymorphisms were not related to the risk of MS; therefore, there was no interaction between these VDR SNPs and HLADRB1 regarding MS risk.
	Kalman and Toldy, 2014	It was revealed that there were very complex molecular networks underlying inflammatory demyelination disorder and the roles of vitamin D and other environmental factors.
	Yamout et al., 2016	No connection was observed between serum vitamin D or A or VDR genotypes and MS. HLA-DRB1*15 was the major factor leading to more than 3-fold higher risks for developing MS among a Lebanese population.
Liver disorder [23,107-110]	Fan et al., 2005	A genetic connection existed between VDR polymorphisms and autoimmune liver diseases such as AIH (autoimmune hepatitis) and PBC (primary biliary cirrhosis) in Chinese patients.
	Fan et al., 2003	There was a significant correlation between FokI polymorphism and AIH as well as between the BsmI polymorphisms and PBC in a Chinese population.

Table 1. Continued

Disorder	Study	Findings
	Kempinska-Podhorodecka et al., 2017	The ApaI polymorphisms in VDR might impact disease-related symptoms and the quality of life in patients with PSC (primary sclerosing cholangitis).
	Tanaka et al., 2009	The genotype 'BB' and 'B' allele at BsmI polymorphism of the VDR gene could affect the risk of PBC development.
	Vogel et al., 2002	There existed a link between genetic of VDR polymorphisms and autoimmune liver diseases such as PBC and AIH in German patients.
Inflammatory Bowel Disease (IBD) [24,25,82-88]	Simmons et al., 2000	There was a genetic association between Crohn's disease susceptibility and Vitamin D receptor gene polymorphisms such as TaqI polymorphism.
	Naderi et al., 2008	There existed the likelihood of a relationship between Fok I polymorphism in VDR receptor gene and Crohn's susceptibility in an Iranian population.
	Hughes et al., 2011	Common variations in the VDR gene alone had no significant effect on the predisposition to IBD in an Irish population.
	Wang et al., 2014	ApaI polymorphism might increase the risk of CD (Crohn's disease); in contrast, TaqI polymorphism might reduce the risk of UC, particularly in Caucasians.
	Xia et al., 2014	Their study showed that genetic polymorphism of VDR (Fok I, Bsm I, Apa I, Taq I) and the serum levels of 25 (OH) D were significantly linked with UC (ulcerative colitis). Mutation of VDR (Bsm I) was a protective factor for UC. Moreover, mutant genotype (TC/CC) of VDR (Fok I) and vitamin D deficiency might exert synergistic effects on the susceptibility to UC.
	Xia et al., 2015	The mutation of FokI gene influenced the severity of the disease in UC patients. The AAC haplotype formed by the VDR BsmI, ApaI and TaqI gene might reduce UC attack risk.
	Xia et al., 2016	Vitamin D receptor (BsmI, ApaI, and TaqI) mutations and lower 25 (OH)D levels were correlated with CD in Chinese patients. VDR (FokI, ApaI, and TaqI) mutations and vitamin D deficiency might have a combined impact on CD.
	Xue et al., 2013	The meta-analysis showed a major increase in CD risk in Europeans carrying TaqI tt genotype and a significant decrease in CD risk in all carriers of the ApaI "a" allele. Regarding Asians, the VDR FokI polymorphism was shown to present susceptibility to UC. Concerning males, the TaqI tt genotype was associated with susceptibilities to both UC and CD.
	Zheng et al., 2017	VDR polymorphisms and 25 (OH) D level were significantly connected with UC risk and severity in a Chinese Han population.
Collagen vascular disorders [26-29,89-94]	Lee et al., 2011	This meta-analysis showed that the VDR FokI polymorphism might confer susceptibility to RA in Europeans. Furthermore, associations were found between the VDR BsmI polymorphism and susceptibilities to SLE and LN (lupus nephritis) in Asians.
	Mao and Huang, 2014	BsmI B allele might be a risk factor for SLE onset among the overall populations and Asians; also, FokI FF genotype was a risk factor for SLE susceptibility in Asians.
	Xiong et al., 2014	BsmI and FokI polymorphism were related to increased risk of SLE, especially in an Asian population.
	Zhou et al., 2015	BsmI B allele and bb genotype, Fok1 f allele and ff genotype were connected with the risk of SLE in the overall populations; in Asians, however, these associations were not reported in Caucasians.
	Hitchon et al., 2012	VitD receptor polymorphisms might affect the high prevalence of RA in North American Native populations.
	John et al., 2017	An association was observed between rs1544410 and RA in Pakistani samples.
	Kamal et al., 2016	VDR gene polymorphisms were significantly associated with Behçet's disease in Egyptian patients.
	Maalej et al., 2005	F allele and F/F VDR genotypes were associated with RA.
	Song et al., 2016	The meta-analysis suggested that the VDR FokI polymorphism was associated with susceptibility to RA in European populations.
	Tizaoui et al., 2015	TaqI and FokI VDR polymorphisms were significantly related to RA risk.
Dermatologic Disorders		

Table 1. Continued

Disorder	Study	Findings
Psoriasis [30-37]	Acikbas et al., 2012	Certain haplotypes of VDR were important in resistance to vitamin D3 therapy and the onset of psoriasis.
	Polić et al., 2012	None of the analyzed polymorphisms was individually associated with the risk of psoriasis, diabetes or combined phenotype development.
	Liu et al., 2013	In this meta-analysis, ApaI and TaqI polymorphisms in VDR gene were revealed to be associated with psoriasis in Caucasians.
	Lee et al., 2012	VDR ApaI polymorphism contributed to susceptibility to psoriasis in a Turkish population. In addition, a relationship was found between the BsmI polymorphism and susceptibility to psoriasis in Asians and between the Fok I polymorphism and psoriasis in a Turkish population.
	Zuel-Fakkar et al., 2011	There was no significant prevalence of ApaI and TaqI genotypes of vitamin D receptor in Egyptian patients with psoriasis.
	Park et al., 1999	Allelic variance in the vitamin D receptor gene itself or other genes in linkage disequilibrium with this gene could make to prone to the development of psoriasis.
	Stefanic et al., 2013	No VDR gene variant showed a robust and reproducible correlation with risk for psoriasis.
	Vega-Hernandez et al., 2015	Polymorphisms FokI, ApaI, BsmI, and TaqI in the VDR gene were not connected with the risk of presenting psoriasis in a Mexican population; however, the TT (ff) genotype of the FokI polymorphism was significantly more prevalent in patients with the late onset of PsV (after age 40) and those without nail affection.
Alopecia areata [38-40]	Akar et al., 2007	No association was observed between VDR gene polymorphism and alopecia areata.
	Akar et al., 2004	No relationship was found between VDR gene polymorphism and AA, the VDR FokI polymorphism.
	Ates, 2017	VDR gene polymorphisms could not contribute to determin genetic susceptibility to AA.
Recurrent Aphthous Stomatitis (RAS) [41]	Bazrafshani et al., 2002	The inheritance of specific gene polymorphisms for TNF-alpha, TNF-beta or VDR did not seem to be a major factor in determining susceptibility to minor RAS.
Vitiligo [42, 95, 96]	Li et al., 2012	There was a connection between VDR polymorphisms and 25 (OH)D levels, and there existed a genetic predisposition for vitiligo in a Chinese population.
	Aydıngöz et al., 2012	VDR TaqI gene polymorphism and the haplotype BsmI/ApaI/ TaqI/FokI/ Cdx2 GCCCG might be considered as a novel risk factor in vitiligo.
	Doss et al., 2015	Vitamin D deficiency had an effect on the extent of vitiligo and might have a role in the pathogenesis of vitiligo through its immunomodulatory role and its role in melanogenesis.
Skin cancer [43-47, 97-107]	Hutchinson et al., 2000	Polymorphisms of the VDR gene, which might lead to impaired function, were related to susceptibility and prognosis in melanoma.
	Li et al., 2007	Genetic variants (TaqI t protective allele and FokI f risk allele) in VDR might change the risk of melanoma.
	Randerson-Moor et al., 2009	Vitamin D and VDR seemed to slightly but potentially contribute to melanoma susceptibility, and putatively play a greater role in disease progression.
	Mocellin et al., 2008	There was a connection between 1 VDR gene polymorphism (BsmI) and the risk of developing melanoma.
	Burns et al., 2017	Benefits of early treatment and prevention of NMSC with chemopreventive agents (for those with the BsmI SNP) were shown. A screening for the BsmI SNP might confirm the importance of sun protection and assist skin cancer prevention, thereby reducing skin cancer burden.
	Lee et al., 2015	This meta-analysis demonstrated that the VDR BsmI polymorphism was associated with susceptibility to melanoma in Europeans, suggesting that carrying the VDR BsmI B allele might be a protective factor against melanoma development.
	Orlow et al., 2012	The VDR might greatly contribute to melanomagenesis.
	Orlow et al., 2016	VDR gene might affect melanoma survival; however, the mechanism by which VDR exerts its effect did not seem to be run by tumor aggressiveness.

Table 1. Continued

Disorder	Study	Findings
	Santonocito et al., 2007	BsmI polymorphism might play a role as a possible risk marker for MM and its aggressiveness.
	Zeljic et al., 2014	FokI and TaqI polymorphisms in the VDR gene might be potential biomarkers for melanoma susceptibility.
	Denzer et al., 2011	Vitamin D endocrine system (VDES) was important for pathogenesis and progression of MM and other skin cancers.
	Han et al., 2007	The polymorphisms were likely to have a role in MTHFR and VDR interacting with dietary intakes of folate and vitamin D in skin cancer development, particularly regarding SCC.
	Köstner et al., 2012	VDR polymorphisms were shown to be of importance for the development of BCCs and cutaneous SCCs.
	Lesiak et al., 2011	Certain VDR and MTHFR gene polymorphisms increased the risk of BCC development in individuals of Polish origin.
	Liu et al., 2005	VDR f and t alleles and their genotypes might protect against SCC of the head and neck.
	Reichrath et al., 2013	This study showed how vitamin D endocrine system (VDES) could be associated with tumorigenesis, prevention, and treatment of NMSC.

regard to the role of VDR gene polymorphisms in common autoimmune disorders, emphasizing on dermatologic diseases was searched.

RESULTS AND DISCUSSION

In this review, summarized in Table 1, the role of Vitamin D Receptor gene polymorphism in immune-related non-dermatologic and dermatologic disorders was studied.

CONCLUSION

There are many articles about the role of VDR gene receptor polymorphisms in common immune-mediated dermatologic and non-dermatologic disorders. These articles may propose various genetic susceptibilities to these disorders and their better management. There are no studies focused on this type of polymorphism; however, the role of vitamin D level have been frequently evaluated regarding different aspects of these diseases.

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Treatment of varicella skin scars with sequential punch elevation, autologous fat injection and fractional CO_2 laser

Reza Kavoussi, MD [1]
Hossein Kavoussi, MD [2*]

1. Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran
2. Dermatology Department, Hajdaie Dermatolgy Clinic, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran

**Corresponding Author:*
Hossein Kavoussi, MD
Dermatology Department, Hajdaie Dermatolgy Clinic, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran
Tel: 00988334276301
Fax: 00988334274623
Email: hkavoussi@gmail.com
hkawosi@kums.ac.ir

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Varicella is a common viral infection that occasionally results in scar. Despite a number of measurements taken to combat this infection, they have all been either impractical or limited.The current study presents a 28-year-old woman diagnosed with varicella 10 years ago which caused her to have several depressed skin scars over the face. She was subjected to sequential treatment of punch elevation, fractional CO_2 laser therapy, and autologous fat injection in one session. Over two years of postoperative follow-up, remarkable aesthetic improvements were observed in her face. This method had some advantages including high speed, convenience, application of conventional medical devices, and the minimal manipulation. The only limitation of our method was mild-to-moderate improvement of the previous hyperpigmentation of the scar.

Keywords: varicella scar, punch, autologous fat, CO_2 laser

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INTRODUCTION

Varicella is a common viral infection with skin lesions in children which occasionally results in skin scar. It is usually induced due to the immunodeficiency, secondary infection of skin lesions, severe form and the onset of the disease in adulthood [1-3].

Skin scars, caused by varicella, has various forms but usually induce boxcar scar type [2,3].

Several optional treatments with variable outcomes have been suggested for the revision of this type of scar [2-8].

Herein, we reported a female patient with several sparse boxcar scars over the face, showing a significant improvement by punch elevation, autologous fat injection, and fractional CO_2 laser therapy in one session.

CASE REPORT

A 28-year-old woman presented with several boxcar scars with variable sizes ranging from 1.5 mm to 5 mm on the face (Figure 1).

She had a severe form of varicella 10 years ago. In spite of the systemic intake of anti-viral and antibiotic therapies, she noticed multiple depressed scars on her face several weeks after the infection.

Our patient had received several treatments to treat her skin scars. These treatments include chemical peeling, long-term topical tretinoin therapy, radiofrequency, various laser therapies, punch elevation, subcision and filler injection alone or in combination during the past 8 years. However, none of the mentioned treatments were satisfactory.

After giving information to and obtaining written

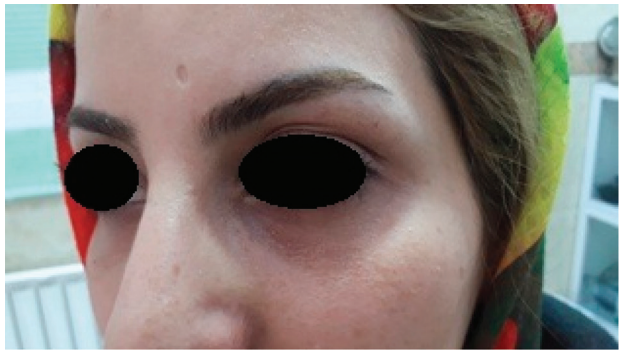

Figure 1. Patient with two scars on the forehead and nose

consent from the patient, she was subjected to a planned procedure.

In this procedure, the scarred area was prepared in a sterile manner, followed by injection of lidocaine 2% with epinephrine. Initially, we used sharp and disposable punches based on the skin scar size. During the punching stage, we applied a moderate tension perpendicular to the relaxed skin tension line (RSTL). Then, autologous fat, which was harvested from the lower abdomen, was injected into the area in different levels of subcutaneous tissue so that the depressed scar area could be slightly elevated from the surrounding tissue.

Finally, the scar area was subjected to fractional CO_2 laser therapy (Jeisys, Edge, Korea) with a density of 6%, pulse energy of 30 mJ and total fluence of 13.5 J/cm2 with 120 µm spot size. (Figure 2).

After the procedure, we prescribed a repair cream and sunscreen on the treated area for a few weeks and later we recommended a combination of tretinoin and bleaching cream on the area for several weeks. What was observed after one session in a two-year follow-up, was a significant improvement along with patient satisfaction (Figure 3).

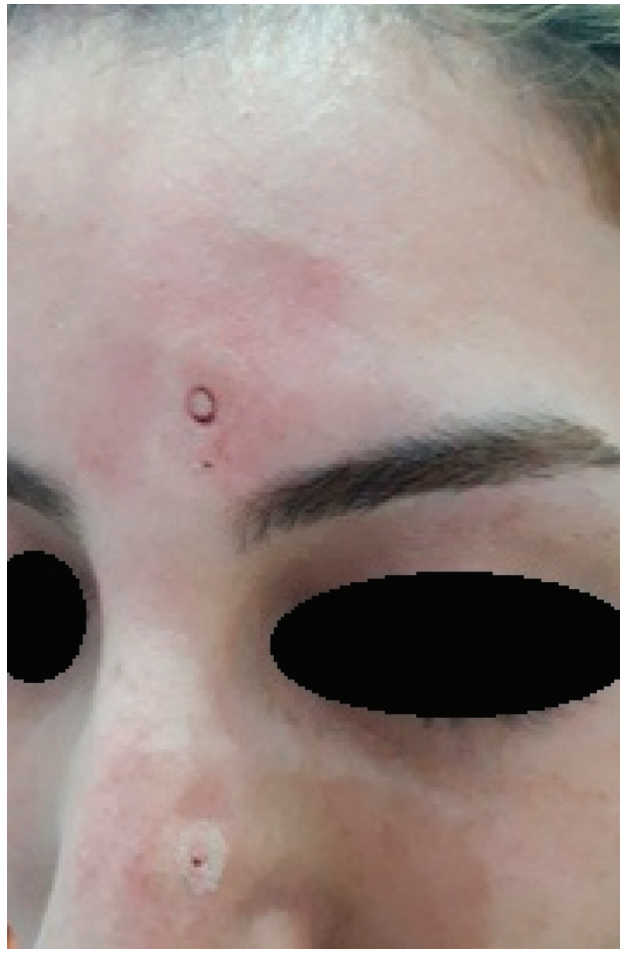

Figure 2. Scar areas treated with punch elevation, fractional CO_2 laser and autologous fat injection

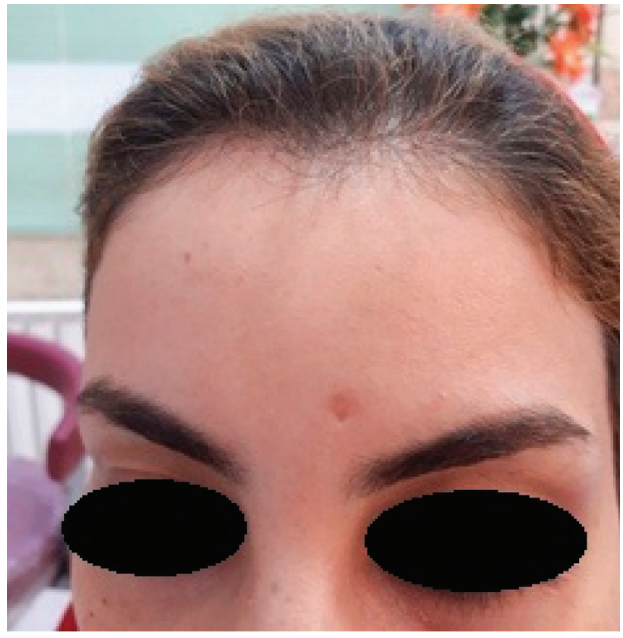

Figure 3. Significant improvement in the scar areas after one session

DISCUSSION

The severity of varicella skin scars (VSS) is most probably associated with the individual skin repair, severity of varicella, and superimposition of secondary infection [1-3]. Deep and boxcar VSS induce an unpleasant appearance, which makes the patients ask for appropriate treatments.

Several optional treatments have been suggested, including chemical peeling, long-term topical tretinoin, excisional surgery, subcision, various laser treatments alone or in combination, which have multifarious outcomes, limitations, and

complications [2-4].

Most of the mentioned treatment modalities cost a lot and require advanced medical equipment, high experience, skilled hands, and multiple sessions.

In a study, 46 patients with various types of atrophic skin scar, including VSS were treated by combined subcision-suction method. Sixty to 90% of the patients showed improvement in the depth and size of scars. This method required multiple sessions, high experience and skilled hands [3].

Costa *et al.* [4] reported the successful treatment of a dark-skinned teenage girl who suffered from multiple round, varicella depressed scars up to 0.5 cm in diameter on the face by multiple sessions of microneedling. Although this method is very simple and easy, it may require several sessions and not be appropriate for deep skin scars. It also needs to be performed in many cases to confirm its effectiveness.

Lee *et al.* [2] reported that 3 patients with multiple boxcar scars were successfully improved by a combination of intracision and 2940-nm Er:YAG laser therapy. The laser used in this study was not generally available to most dermatology clinics, and intracision required a high experience.

In two studies, a high concentration of trichloroacetic acid (TCA) was used to treat VSS [5,6]. Barikbin *et al.* [5] and Agarwal *et al.* [6] reported a significant improvement in 41% and 69% of patients with VSS, respectively, after multiple treatment sessions over several months of follow-up.

TCA resulted in the modification and improvement of VSS by producing connective tissue through greater collagen construction and fragmentation of elastin fibers in the upper dermis [5].

Therefore, TCA is suitable for deep VSS and not appropriate for other types of VSS and Fitzpatrick skin types IV- VI.

In a single-center, open-label study [7], injectable Poly-L-lactic acid (PLLA) was effective in the treatment of patients with acne scar and VSS.

Because of adhesions due to the presence of numerous fibrotic bundles beneath the scar area, especially the deep type, filler injection alone cannot eventuate the bulging of scar regions.

In a study, 3 (2 teenagers and 1 young) patients were subjected to low-dose oral isotretinoin for revision of VSS a few months after varicelle involvement [8]. A marked improvement was observed in pigmentation, size and depth of VSS area.

This treatment is sufficient for the early course after the improvement of acute infection. Moreover, oral isotretinoin is a drug with abundant adverse effects; therefore, it is not used by patients and their parents.

Punch instrument is a simple device used for the removal of benign skin tumors and improvement of rolled skin scars [9]. For achieve better outcomes, we suggest a disposable and sharp punch with different sizes based on VSS and a moderate tension perpendicular to the RSTL during the punching step.

Autologous fat is the safest filler which is effective for skin rejuvenation and some facial defects [10]. We injected the fat in different levels of scar until the treated area became bulger than the surrounding tissue.

CO_2 laser is currently an ordinary device used in most outpatient dermatology clinics. It treats the scars and improves the dyspigmentation of many skin lesions through contour modification, collagen re-biosynthesis and remodeling, and alteration of dermal melanophage [11,12].

Our therapy protocol exerts multiple synergic effects through improvement of dyspigmentation, collagen remodeling, contour change and appropriate and permanent elevation of the deep VSS.

CONCLUSION

This procedure is a simple and rapid-responding method, which does not require a very advanced device, but a minimal manipulation. The only limitation of this procedure was the mild-to-moderate improvement of the previous post-inflammatory hyperpigmentation in the scar area for which we suggest that this procedure be conducted on more cases with different types of VSS.

Conflict of Interest: None declared.

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