Evaluation of Expression of Tissue Interleukin 17 in Atopic Dermatitis Compared to Normal Control before and after Topical Mometasone Fumarate Cream: A Case Control Study

Section A-Research paper

Evaluation of Expression of Tissue Interleukin 17 in Atopic Dermatitis Compared to Normal Control before and after Topical Mometasone Fumarate Cream: A Case Control Study

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intense itching and eczematous lesions. Interleukin 17 (IL-17) has been implicated in the pathogenesis of AD, but its expression in the skin tissues of AD patients compared to normal controls remains to be fully elucidated. Understanding the role of IL-17 in AD is crucial for the development of targeted therapies and improved management strategies. This study aimed to assess the level of tissue IL-17 in AD compared to normal control before and after topical mometasone fumarate cream.

Methods: This diagnostic interventional case-control study was carried out on 30 patients with AD (Group A) and 30 age and sex-matched healthy subjects (Group B) as controls. Comprehensive assessments were performed, including evaluation of disease severity using the SCORAD index and measurement of subjective symptoms. Skin tissue biopsies were collected before and after the application of topical mometasone fumarate. IL-17 levels were assessed through histopathological examination.

Results: Before treatment, AD patients had significantly higher tissue IL-17 when compared with controls (314.51 ± 19.60 vs 146.39 ± 15.75 pg/ml; $p<0.001$). After treatment, AD patients had significantly higher tissue IL-17 when compared with controls (209.19 ± 21.49 vs 146.39 ± 15.75 pg/ml; $p<0.001$). The mean IL-17 in tissue significantly decreased after treatment with topical mometasone furoate when compared with before treatment (209.19 ± 21.49 vs 314.51 ± 19.60 pg/ml; $p<0.001$).

Conclusions: The present study revealed significant elevation of tissue IL-17 in patients with AD when compared with controls. In addition, treatment with topical mometasone furoate had a significant lowering effect on tissue IL-17 in AD patients.

Keywords: Atopic Dermatitis; Borgasone; Tissue Interleukin 17; Topical Mometasone Fumarate

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Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, characterized by eczema and itchiness. It typically starts in infancy and is associated with lichenification. AD has been linked to asthma, food allergies, and allergic rhinitis. The prevalence of AD has been increasing in recent decades. The development of AD involves a complex interplay of genetic and environmental factors, resulting in epidermal and immune system abnormalities [1].

AD is one component of the atopic triad, which also includes allergic rhino-conjunctivitis and asthma. These conditions may manifest simultaneously or in a sequential manner known as the "atopic march." Patients with the atopic triad exhibit impaired barriers in their skin, upper respiratory tract, and lower respiratory tract, which contribute to their symptoms. If one parent is affected by atopic conditions, there is a greater than 50% likelihood of their children developing atopic symptoms. When both parents are affected, the risk increases to as much as 80% for their offspring [2].

Filaggrin, an epidermal protein that breaks down into natural moisturization factor, has been found to be affected by genetic abnormalities. AD patients with filaggrin mutations are up to 30% more likely to suffer from the condition. One in every ten to one in every thirty people with AD has food hypersensitivity. Eggs, milk, peanuts, soy, and wheat are responsible for 90% of these reactions [3].

Th2-mediated pathology with high serum immunoglobulin E levels was originally assumed to be the cause of AD, according to previous theories (IgE). The Th1, Th22, and Th17 cells have also been implicated in the aetiology of AD, according to study. Th17 cytokines, such as interleukin-17 (IL-17) and IL-22, have been found in the skin of people with AD who have had their immune systems damaged. In total, there are six IL-17s in the family (IL-17A through IL-17F). For example, IL-17A (or IL-17) is the first and most investigated member because of its extensive distribution in the body [4].

IL-17A is a cytokine, chemokine, adhesion molecule, and growth factor regulator in a variety of immunologic and inflammatory reactions. But its role in the control of IgE-mediated allergy reactions is uncertain in several animal models. IL-17 levels in the peripheral blood and skin biopsies of patients with AD vary widely, according to studies [5].

To date, however, the only report on the presence of IL-17 in AD shows that, although IL-17 expression is enhanced in acute lesions in AD skin compared with uninvolved skin, IL-17 levels are not enhanced in chronic skin lesions. Although it cannot be excluded that IL-17 is involved in the onset of the disease through its actions on fibroblasts, infiltrating cells and keratinocytes, it seems that if at all, IL-17 has a different role in AD than in other chronic inflammatory diseases, which do exhibit enhanced IL-17 levels in the chronic phase [6].

Therefore, we aimed to assess the level of tissue IL-17 in AD compared to normal control before and after topical mometasone fumarate cream.

Subjects and Methods:

This diagnostic interventional case-control study was carried out at the Dermatology Department of 6-October University between October 2022 and April 2023. The study included patients who met the inclusion criteria: those aged 18 years or older, of both genders, and diagnosed with acute and subacute AD.

Exclusion criteria were Patients who had received topical or systemic therapy, including phototherapy, for at least 4 weeks prior to study enrollment. Additionally, patients with systemic diseases such as autoimmune diseases, blood diseases, malignancy, and other dermatological diseases (e.g., psoriasis).

The study population was divided into two equal groups: Group A consisted of 30 patients with AD, and **Group B** included 30 healthy subjects matched for age and sex, serving as the control group. The control group was recruited from individuals attending plastic surgery for abdominoplasty.

The study obtained approval from the ethics committee of the faculty of medicine, with approval number PMC-Me 2212041. Agreement for the study was also obtained from the hospital's ethical committee. Informed written consent was obtained from all participants before their inclusion in the study. Patients were fully informed about the potential complications of biopsy, such as bleeding, bruising, scarring, and infection. The confidentiality and anonymity of participants' data were strictly maintained.

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All participants were subjected to a) Complete history taking: Comprehensive medical histories of all participants were collected, including relevant information related to their dermatological condition. **b) Complete dermatological examination:** Thorough physical examinations were conducted to assess the participants' dermatological condition. **c) General examination:** Vital signs, such as blood pressure, temperature, heart rate, and respiratory rate, were recorded. Signs of pallor, cyanosis, jaundice, and lymph node enlargement were also evaluated. **d) Evaluation of disease severity:** The severity of AD was assessed using the SCORAD (SCORing Atopic Dermatitis) index, as established by Stalder et al. in 1993 [7]. The index utilizes a six-area, six-sign scoring system, considering the extent and intensity of symptoms. The areas evaluated include the head and neck, upper limbs (left and right), lower limbs (left and right), anterior trunk, back, and genitals. The intensity of signs such as redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), and dryness were graded as none (0), mild (1), moderate (2), or severe (3).

e) Evaluation of subjective symptoms: Subjective symptoms, including itch and sleeplessness, were assessed using a visual analogue scale ranging from 0 (no itch/sleeplessness) to 10 (worst imaginable itch/sleeplessness). Patients were evaluated at the initial visit and were subsequently treated with topical mometasone fumarate cream (Borgasone®) for two weeks. After this treatment period, patients' SCORAD scores were reassessed.

f) Histopathological examination: A 3 mm punch skin biopsy was performed on all participants under local anesthesia during the first visit. Another biopsy was taken from patients two weeks later during the second visit. All samples were processed as follows: Tissue was rinsed in ice-cold PBS to remove excess blood. Weigh the tissue before homogenization. The tissue was finely minced and homogenized with a tissue homogenizer on ice in PBS and sonicate the cell suspension. Centrifuge for 5 min at $5000 \times g$ to remove any precipitates. The supernatant was transferred into a clean tube and analyze immediately or stored at 4°C (up to one week), -20°C (up to one month) or -80°C (up to two months). Freeze-thaw cycles were avoided. Samples were brought to room temperature before carrying out the assay.

The study aimed to investigate the primary outcomes, including the assessment of Interleukin 17 skin tissue levels in AD patients both before and after the application of topical mometasone fumarate (Borgasone®), as well as the comparison of Interleukin 17 levels between AD patients and the control group. **Additionally, the secondary outcome parameters** were assessing the correlation between the severity of AD, as measured by the SCORAD index, and the level of Interleukin 17 in the skin tissues of patients.

Statistical analysis

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (≤0.05) level. Chi-Square test was used to compare qualitative data between groups as appropriate. Mann Whitney U test was used to compare between 2 studied groups for non-normally distributed data. Wilcoxon signed Rank test, Friedman test were used to compare between more than 2 studied periods. Paired t test was used to compare 2 paired readings for normally distributed data.

Results

In the current study, 30 patients with acute and subacute AD who were attending to 6 October university dermatology department were included and were compared with 30 age and sex matched healthy subjects as control group.

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Regarding the demographic data of studied groups: No significant difference was reported between cases and controls regarding age or gender. **Table 1**

Table 1: comparison of sociodemographic characteristics of the studied groups

	Cases group n=30	Control group n=30	test of significance
Age / years median (range)	7.5 (1-45)	10 (1-45)	z=0.822 p=0.411
Sex Male Female	21 (70) 9 (30)	18 (60) 12 (40)	χ^2=0.659 p=0.417

Z: Mann Whitney U test, χ^2: Chi-Square test

Regarding family history and disease duration in studied cases: Positive family history was reported in 73.3% of patients with AD. Median disease duration in studied cases was 7 months ranging between 1 and 108 months.

Clinical data of cases:

Regarding the site of lesion among studied cases, upper limbs were the most commonly reported site of lesion in 24 (80%) patients followed by back which was reported in 16 (53.3%) patients. The least common sites were face and hand each was reported in 6 (20%) patients. **Fig. 1**
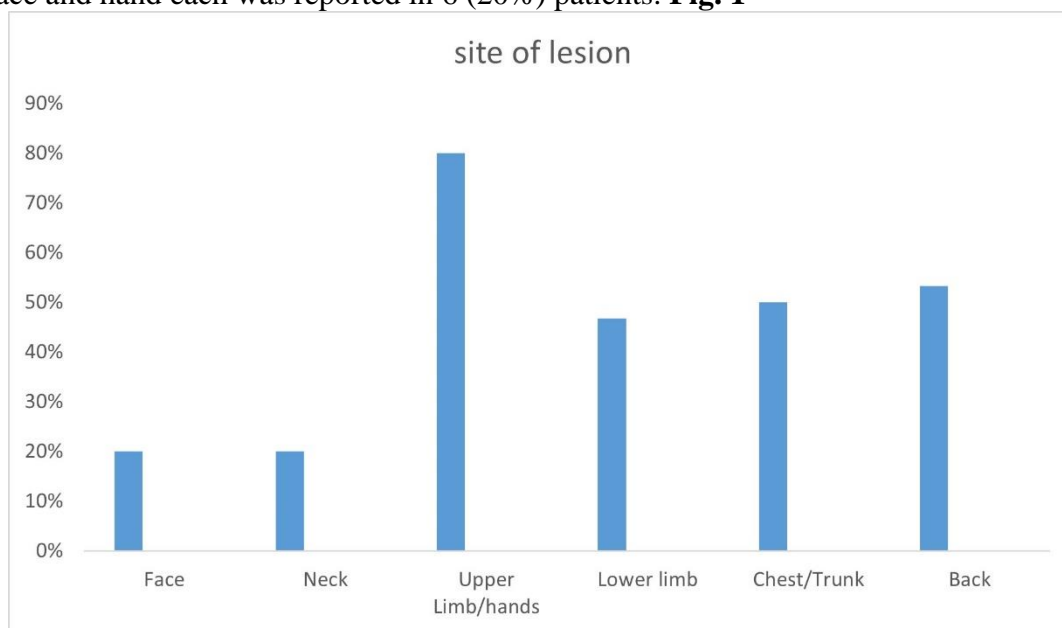

Figure 1: Site of the studied lesion

Regarding the extent of lesion, duration and recurrence distribution among studied cases: The median body surface area was 19, ranging between 8 and 60. The median disease duration was 16 years ranging between 7 and 21 years. Recurrence was reported in all studied cases. **Regarding the exacerbating factors:** The most common exacerbating factor was dryness in 27 (90%) patients, followed by exposure to sun in 25 (80%) patients. The least common exacerbating factor was sweating in 6 (20%) patients. **Regarding the treatment history:** Systemic steroids were previously prescribed for 10 (33.3%) patients. Topical cortisone and anti-histaminic drugs were prescribed for 24 (80%) patients while topical antihistaminic drugs were prescribed for 6 (20%) patients. **Regarding comorbidities:** The most common comorbidity was rhinitis which was reported in 28 (93.3%) patients, followed by asthma which was reported in 25 (83.3%) patients and eye disease which was reported in 21 (70%) patients. Food allergy was reported in 18 (60%) patients. The least common comorbidities were diabetes, hypertension and cardiac diseases, each was reported in 2 (6.7%) patients. Hepatitis was reported in 3 (10%) patients. **Regarding the cutaneous signs:** Pallor was found in 20 (66.7%) patients. LN enlargement was reported in 10 (33.3%) patients. **Table 2**

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Table 2: Extent, duration, recurrence, presence of Exacerbating factors, treatment history and cutaneous signs distribution among studied cases

		n=30	%
BSA (extent) Median (min-max)		19 (8-60)	
Duration (years) Median (min-max)		16 (7-21)	
Recurrence		30	100.0
Exacerbating factors			
Spring		11	36.7
Sweating		6	20
Winter		25	83.3
Dryness		28	93.3
Sun		25	80
Treatment history			
Systemic steroids		10	33.3
Other medications Topical cortisone and anti-histamine		24	80
Topical antihistamine		6	20.0
Phototherapy		0	0.0
Comorbidities			
Non allergic	Diabetes	2	6.7
	Hypertension	2	6.7
	Cardiac disease	2	6.7
	Hepatic disease	3	10.0
Allergic	Eye disease	21	70.0
	Rhinitis	28	93.3
	Asthma	25	83.3
	Food allergy	18	60
	Urticaria	6	20
Cutaneous signs			
Pallor No Yes		10 20	33.3 66.7
LN enlargement No Yes		20 10	66.7 33.3

In comparison of IL-7 between studied groups: Before treatment, patients with AD had significantly higher tissue IL-17 when compared with controls (314.51 ± 19.60 vs 146.39 ± 15.75 pg/ml; $p<0.001$). After treatment, patients with AD had significantly higher tissue IL-17 when compared with controls (209.19 ± 21.49 vs 146.39 ± 15.75 pg/ml; $p<0.001$). **Table 3**

Table 3: comparison of tissue IL-7 between studied groups

	Cases group n=30	Control group n=30	test of significance
IL-17 Before (pg/ml)	314.51 ± 19.60	146.39 ± 15.75	t=4.28 **p<0.001***
IL-17 after (pg/ml)	209.19 ± 21.49	146.39 ± 15.75	t=12.91 **p<0.001***

t: Student t test, *statistically significant, IL: interleukin

Comparison of skin manifestations before and after treatment with topical mometasone furoate: There was significant improvement of all skin manifestations including redness, swelling, crustation, scratch marks, Lichenfication, dryness, and pruritis after treatment with topical mometasone furoate when compared with before treatment ($p<0.001$ for all). **Table 4**

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Table 4: Comparison of skin manifestations before and after treatment with topical mometasone furoate

	Before treatment		After treatment		test of significance
	n	**%**	**n**	**%**	
Redness					
No	0	0.0	18	60.0	
Grade 1	9	30.0	12	40.0	z=4.85
Grade 2	15	50.0	0	0.0	**p<0.001***
Grade 3	6	20.0	0	0.0	
Swelling					
No	0	0.0	25	83.3	z=5.11
Grade 1	19	63.3	5	16.7	**p<0.001***
Grade 2	11	36.7	0	0.0	
Crustation					
no	19	63.3	26	86.7	
Grade 1	7	23.3	4	13.3	z=3.13
Grade 2	2	6.7	0	0.0	**p=0.002***
Grade 3	2	6.7	0	0.0	
Scratch marks					
no	5	16.7	21	70.0	
Grade 1	14	46.7	9	30.0	z=4.24
Grade 2	7	23.3	0	0.0	**p<0.001***
Grade 3	4	13.3	0	0.0	
Lichenification					
no	29	96.7	30	100	z=1.0
Grade 1	1	3.3	0	0.0	p=0.317
Dryness					
no	0	0.0	14	46.7	z=4.71
Grade 1	4	13.3	13	43.3	**p<0.001***
Grade 2	26	86.7	3	10.0	
Pruritis median (range)	7 (5-9)		2 (0-6)		z=4.8 **p<0.001***

Z: Wilcoxon signed rank test, *statistically significant

Comparison of SCORAD score before and after treatment with topical mometasone furoate: The median SCORAD score significantly decreased from 37.08 (range: 12.45-72.05) before treatment to 10.8 (range: 0-32.1) after treatment (p<0.001). **Fig. 2**
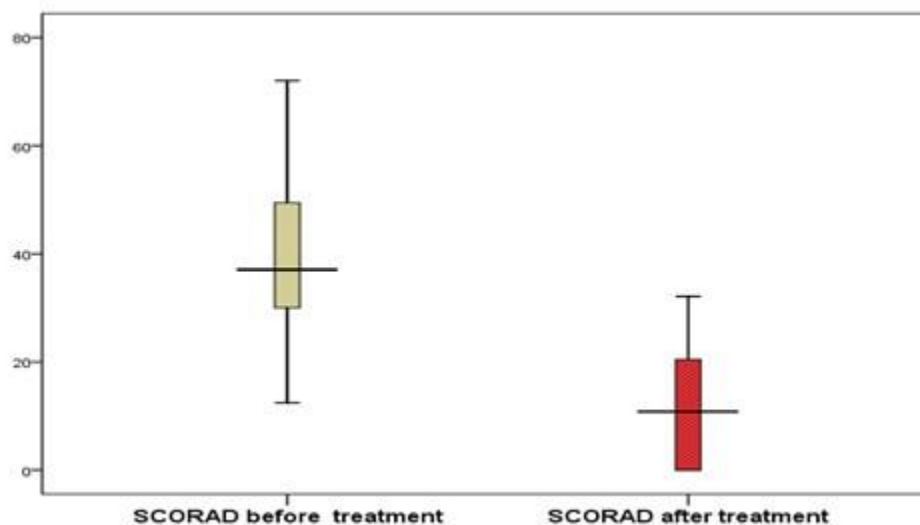

Figure 2: Box and Whisker plot showing median SCORAD before and after treatment

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Comparison of IL-17 before and after treatment with topical mometasone furoate: Mean IL-17 in tissue significantly decreased after treatment with topical mometasone furoate when compared with before treatment (209.19±21.49 vs 314.51±19.60 pg/ml; p<0.001). **Fig. 3**
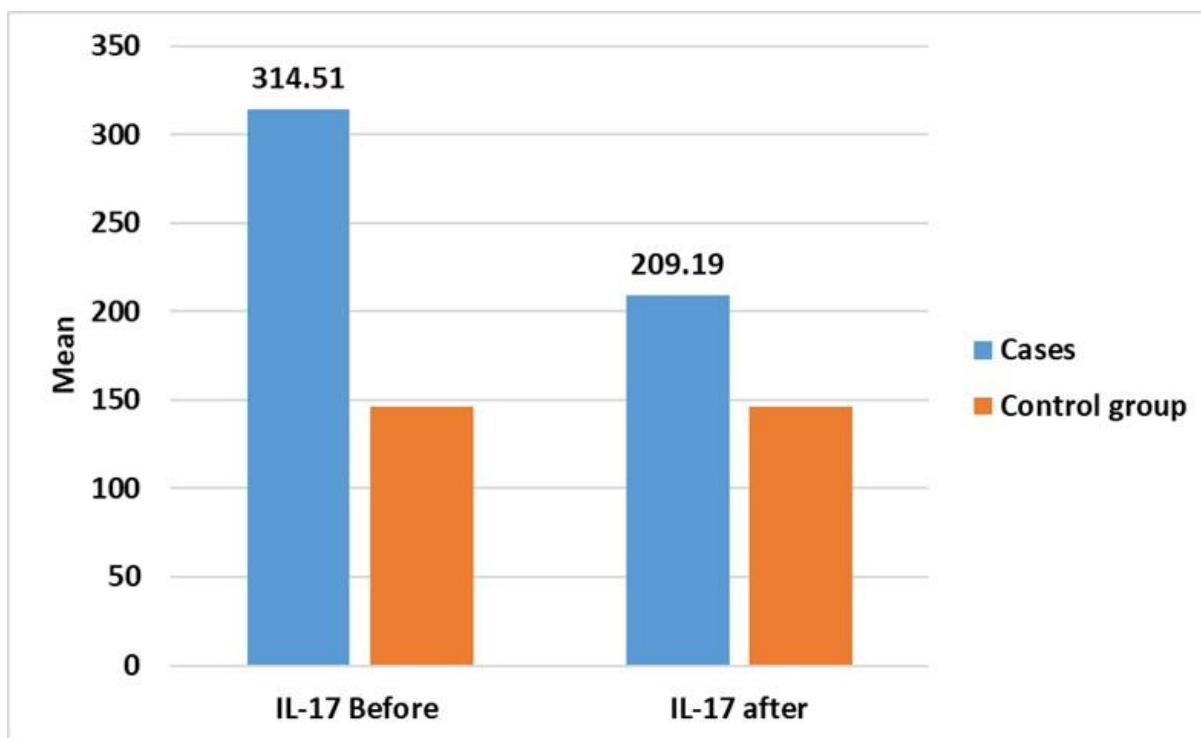

Figure 3: Comparison of IL-17 between cases and control before and after treatment

Correlation between IL-17 with demographic data and clinical findings: No significant correlation was reported between IL-17 level before treatment with age of patient, clinical findings or SCORAD score before treatment. No significant difference was reported between IL-17 level with age of patient. IL.17 after treatment was positively correlated with **Swelling (r=0.420*; P=0.021),** and **Scratch marks after treatment (r=0.494**; P=0.006).** While no significant correlation was reported between IL-17 level after treatment with other clinical findings or SCORAD score after treatment. **Table 5**

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Table 5: correlation between IL-17 before and after the treatment with demographic data and clinical findings

		IL.17 before treatment
Age (years)	r	0.222
	p value	0.239
Duration (months)	r	0.114
	p value	0.548
Family history	r	-0.044
	p value	0.819
Redness before treatment	r	0.084
	p value	0.659
Swelling before treatment	r	0.140
	p value	0.459
Crustation before treatment	r	0.027
	p value	0.887
Scratch marks before treatment	r	0.262
	p value	0.162
Lichenification before treatment	r	0.054
	p value	0.777
Dryness before treatment	r	-0.131
	p value	0.491
Sleepiness before treatment	r	0.352
	p value	0.057
Pruritis before treatment	r	0.196
	p value	0.299
SCORAD before treatment	r	0.325
	p value	0.080
		IL.17 before treatment
Age (years)	r	0.263
	p value	0.160
Duration (months)	r	-0.034
	p value	0.858
Family history	r	0.070
	p value	0.713
Redness after treatment	r	0.103
	p value	0.589
Swelling after treatment	r	**0.420***
	p value	**0.021**
Crustation after treatment	r	0.046
	p value	0.811
Scratch marks after treatment	r	**0.494****
	p value	**0.006**
Dryness after treatment	r	0.117
	p value	0.537
Sleepiness after treatment	r	0.217
	p value	0.250
Pruritis after treatment	r	0.188
	p value	0.320
SCORAD after treatment	r	0.276
	p value	0.140

r: Spearman correlation co-efficient

Receiver Operating characteristics (ROC) of IL-7 in differentiating cases and control group: ROC revealed that cut off point 290.6 pg/ml of IL-17 had significant discriminative ability to differentiate between cases with AD and controls with area under curve 1 (P<0.001) with 90% sensitivity and 100% specificity. **Table 6**

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Table 6: validity of IL-17 in differentiating between cases and control groups

	AUC (95% CI)	P value	cut off point	Sensitivity %	Specificity %
Il -17 (pg/ml)	1.0 (1.0-1.0)	**<0.001***	290.6	90%	100.0

AUC: Area under curve

Discussion

The current study aimed to assess the level of tissue IL 17 in acute and subacute AD compared to normal control before and after topical corticosteroid therapy mometasone furoate (Borgasone ® 1% cream). To achieve this aim, 30 patients with acute and subacute AD who were attending to 6 October university dermatology department were included and were compared with 30 age and sex matched healthy subjects as control group.

Positive family history was reported in 73.3% of patients with AD in our study. In line with our study, results of **Ng and Chew** meta-analysis revealed that a family history of atopic diseases was the most reported non-modifiable factors for AD, suggesting the involvement of genetics in AD pathogenesis [8].

The present study reported that the most common exacerbating factor was dryness in 90% of patients, followed by exposure to sun in 80% of patients. Meanwhile, **Murota et al.** study revealed that typical exacerbating factors of AD were irritant dermatitis, food allergy, sweating, and psychological stress in adults [9].

The least common exacerbating factor in our study was sweating in 20% of patients. In their study, **Sugawara et al.** showed that patients with AD had significantly reduced levels of sodium, potassium, lactate, urea, and pyrrolidone carboxylic acid in their sweat than healthy controls. This suggests that impaired sweating might reduce the levels of natural moisturizing factors and cause dry skin in patients with AD [10].

Systemic corticosteroids are commonly used as a first-line systemic treatment of AD [11]. In the present study study, systemic steroids were previously prescribed for 33.3% of patients. In many patients with moderate-to-severe AD, disease activity requires systemic treatment to achieve adequate disease control. Data from routine clinical care suggest that more than 10% of all patients with AD receive systemic anti-inflammatory treatment [12].

Topical glucocorticosteroids are the first-line anti-inflammatory treatment in AD [13]. Topical cortisone and anti-histaminic drugs were prescribed for 80% of our patients while topical antihistaminic drugs were prescribed for 20% of patients.

Phototherapy was not reported to be used for AD patients in our study. Phototherapy has been considered an option, based on narrow-band UVB or UVA ultraviolet light [14]. This type of treatment is not free from adverse effects, including photodamage or in long-term effects skin carcinogenesis mainly due to the application of UV light [15].

The most common comorbidity in our study was rhinitis which was reported in 93.3% of patients, followed by asthma which was reported in 83.3% of patients. Food allergy was reported in 60% of patients. Similarly, AD was reported by **Silverberg.** to be associated with and may predispose to higher risk of other atopic disorders, including asthma and food allergy [16].

Before treatment, patients with AD had significantly higher tissue IL-17 when compared with controls (314.51±19.60 vs 146.39±15.75pg/ml; p<0.001). After treatment, patients with AD had significantly higher tissue IL-17 when compared with controls (209.19±21.49 vs 146.39±15.75 pg/ml; p<0.001).

In agreement with our finding, IL 17 tissue expression was previously reported to be significantly elevated in AD patients when compared with controls. In a study on 87 children with AD and 60 healthy control subjects, **Tan et al.** reported that IL-17 tissue expression was significantly increased in the skin lesions of subjects with AD [5]. Moreover, **Ma et al.** in a study on 181 AD patients and 218 healthy control subjects, showed that

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IL-17 mRNA level was elevated in AD patients [17]. Also, **Koga et al.** indicated that IL-17 participate in the development of AD; as on immune-histochemical examination, IL-17+ cells infiltrated in the papillary dermis of atopic eczema more markedly in the acute than chronic lesions [18].

There was significant improvement of all skin manifestations including redness, swelling, crustation, scratch marks, Lichenfication, dryness, and pruritis after treatment with topical mometasone furoate when compared with before treatment (p<0.001 for all).

In agreement with our study, in **Khan et al.** study on 60 patients with AD, topical mometasone furoate 0.1% cream showed a significant improvement in mean scores of erythema, excoriation and papules among patients with AD (p<0.05) [19].

Median SCORAD score significantly decreased after treatment with topical mometasone furoate when compared with before treatment (10.8 vs 37.08; p<0.001). In agreement with our finding, in **Dähnhardt et al.** study which included 20 patients with AD reported that mean local SCORAD significantly decreased in the mometasone furoate treatment group [20]. Additionally, **Khan et al.** reported that topical mometasone furoate 0.1% cream showed a significant improvement in mean SCORAD index (p<0.05) [19].

Mean IL-17 in tissue significantly decreased after treatment with topical mometasone furoate when compared with before treatment (209.19±21.49 vs 314.51±19.60 pg/ml; p<0.001).

In line with our study, the effect of mometasone furoate on IL-17 was previously reported in allergic diseases. For example, in a study on 50 children with allergic rhinitis, **Meng and Ying.** reported that mometasone furoate nasal spray can effectively decrease IL-17 levels [21]. Moreover, in ex vivo human nasal mucosal tissue model, **Zhang et al.** reported that the use of mometasone furoate decreased the secretion of IL-17 [22].

IL.17 after treatment was positively correlated with Swelling (r=0.420*; P=0.021), and Scratch marks after treatment (r=0.494**; P=0.006). Supporting our finding, **Ma et al.** showed that IL-17 mRNA level was correlated with the severity of AD [17].

In the present study, we didn't report significant correlation between IL-17 and SCORAD index. In contrast, **Dewi.** found a robust positive correlation between IL-17 serum level and SCORAD index in adult patients which suggests IL-17 as a potential targeted therapy to cure AD and a prognostic biomarker to evaluate disease severity [23].

No significant difference was reported between males and females in our study regarding IL-17 in tissue. In contrast, men with multiple sclerosis had higher IL-17 concentrations than women patients in **Ghaffari et al.** study on 135 patients with multiple sclerosis. This difference may attribute largely to the effect of sex hormones. In a number of experimental models of inflammatory diseases, it has been indicated that the frequency of Th17 lymphocytes was higher in male as compared with female gender and this phenomenon has been attributed to the inhibitory effects of estrogen on the Th17 cells differentiation [24].

Regarding the ROC analysis, our study revealed that IL-17 is a strong biomarker for identifying cases of AD, with a sensitivity of 90% and specificity of 100%. In a study conducted by **Baioumy et al.** they also investigated the predictive ability of IL-17A for disease severity [25]. However, their findings indicated that IL-17A alone had a poor predictive ability. However, when combined with total IgE, the predictive ability for disease severity improved.

CONCLUSION

Taken together, the present study revealed significant elevation of tissue IL-17 in patients with acute and subacute AD when compared with controls. In addition, treatment with topical mometasone furoate had significant lowering effect on tissue IL-17 in patients with AD.

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Section A-Research paper

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