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Original Article

Dermatology Section

Immunoglobulin E, Interleukin-18 and Interleukin-12 in Patients with Atopic Dermatitis: Correlation with Disease Activity

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disorder. Immunological/inflammatory reactions are reported to play a role in AD but their role in disease activity has not been fully investigated. This study was done to investigate the role of immunoglobulin E (IgE), interleukin (IL)-18 and IL-12 in AD patients with different disease severities.

Materials and Methods: Sera from 50 AD infants with varying levels of disease activity according to the scoring index of atopic dermatitis (SCORAD) index and 30 age-matched healthy controls were evaluated for serum levels of IgE, IL-18 and IL-12/p40.

Results: Serum analysis showed higher levels of IgE, IL-18 or IL-12/p40 in AD patients compared with controls. Interestingly, not only was there an increased number of subjects positive for IgE, IL-18 or IL-12/p40, but also the levels of these parameters were higher among AD patients whose SCORAD scores were higher. In addition, a significant correlation was observed between the levels of these parameters and SCORAD scores.

Conclusion: These findings support an association between IgE, IL-18 or IL-12/p40 and AD. The stronger response observed in serum samples from patients with higher SCORAD scores suggest that IgE, IL-18 and IL-12/p40 may be useful in evaluating the progression of AD and in elucidating the mechanisms of disease pathogenesis.

Keywords: Atopic dermatitis, Disease activity, Immunoglobulin E, Interleukin-18, Interleukin-12

INTRODUCTION

Atopic dermatitis (AD) is a multifactorial chronic inflammatory skin disorder that generally occurs in infancy [1]. AD is characterized by intense pruritus and erythematous lesions with increased transepidermal water loss [2]. The lesions of AD are red, scaly, excoriated and oozing plaques [3]. There is no cure for AD, but its symptoms can be managed with various treatments [4]. The pathogenesis of AD is unknown, but it seems to be the results of genetic susceptibility, immune dysfunction, environmental factors and epidermal barrier dysfunctions [5,6]. Recently, the guidelines for the diagnosis and assessment of AD patients have been revised and updated by Eichenfield et al., [7]. They have addressed the important clinical questions that arise in the management of AD. Not only these, they have also expanded the views on the major risk factors for the onset of AD [7]. Researchers have reported that the pathogenesis of AD is mediated partly by type 2 helper T cells (Th2 cells) expressing interleukin (IL)-4 and IL-13 which induce IgE production. It has now been well reported that the interplay between IgE and mast cells play an important role in the onset of dermatitis by production of numerous inflammatory mediators including IL-1, IL-3, IL-4, IL-5, IL-6, granulocyte macrophage-colony stimulating factor (GM-CSF) and TNF-α [8]. Recently the role of basophils with mast cells has also been reported in the production of these inflammatory mediators by stimulation with IgE [8].

IL-18 is a member of IL-1 superfamily that enhances both innate and acquired immune response and now it is also known as interferon gamma (IFN-γ) stimulating factor [9,10]. IL-18 is produced from numerous cell types including T cells, B cells, natural killer (NK) cells, macrophages, dendritic cells (DC), chondrocytes [9-11]. Moreover, it is well also reported that IL-18 synergistically with IL-12 stimulates the production of IgE and Th2 cytokines [12-15].

IL-12 is a lymphokine produced mainly by monocytes, macrophages, B-lymphocytes and dendritic cells. *In-vivo*, it appears to play a major role in auto-immune diseases in the resistance to bacterial and parasitic infections, in antiviral responses including HIV, in the promotion of antitumor immunity. IL-12 has been shown to be a powerful adjuvant in vaccination.IL-12 induces cell-mediated immunity by up-regulating Th1 cytokines, especially IFN-γ, which inhibits both IgE production and the eosinophil recruitment associated with allergic diseases [16]. IL-18, identified as an IFN-γ-inducing factor, is a pro-inflammatory cytokine that plays an important role in Th1 cell activation [9]. IL-12 and IL-18 have also been shown to affect Th2 function. It is also reported in mouse model that IL-12 effectively suppressed inflammatory airway hyperresponsiveness that was induced by repeated antigen challenge [16]. Not only in AD patients but also in patients with asthma and allergic rhinitis, IL-18 production becomes high [17-19]. It is also reported that IL-18 stimulates antigen-induced eosinophil recruitment in the airways of ovalbumin-sanitized experimental mice [20]. Administration of IL-18 with IL-12 in IFN-γ deficient mice or helminthes infected mice increased production of IgE [21]. This also caused an increase in IgE production, which furtherup-regulates the production of IL-4 and IL-13 by basophils [21]. Moreover, administration of IL-18 alone in both wild-type mice or IFN-γ deficient mice stimulates production of IL-4 and histamine [21]. In view of these important pathogenic roles of IgE, IL-18 and IL-12 in allergic disorders or in the production of numerous inflammatory mediators, we hypothesized that the serum levels of IgE, IL-18 or IL-12 may serve as biomarkers for the diagnosis of AD. To test this hypothesis, the serum levels of IgE, IL-18 and IL-12 were investigated in AD patients and their results were compared with age-matched healthy human controls. Moreover, the relationship of IgE, IL-18 or IL-12 with disease severity of AD was also investigated.

MATERIALS AND METHODS

Human subjects

The study was performed in the College of Medicine, Qassim University, KSA between January 2013 and March 2014. The study group included 26 female patients and 24 male patients with AD (age range 4-72 months, mean±SD age 22.85±14.7 months). All 50 patients were from dermatology clinics of Qassim University and Qassim University affiliated hospitals. Informed consent was obtained from the parents of all participants. An inclusion criterion of the patients was based on the clinical diagnosis of AD as defined by revised guidelines of diagnosis and assessment for AD patients [7]. Exclusion criteria of the patients were based on the following points: Patients who received ultraviolet therapy, immunotherapy, local/systemic therapy in last three weeks, and patients were on any other systemic, allergic, parasitic or dermatologic diseases were excluded. The control group comprised 30 healthy subjects (16 males and 14 females; age range 5-72 months; mean±SD age 28.7±13.1 months). The racial or ethnic compositions of the AD groups were comparable with those of the control group. The study was carried out in accordance with the code of ethics of the World of Medical Association (Declaration of Helsinki) for humans and was approved by the ethical review board committee, College of Medicine, Qassim University.

Assessment of Disease Severity

The severity of AD was evaluated by SCORAD scoring which is a clinical tool for an assessment of the disease severity. The SCORAD index consists of: (i) the interpretation of the extent of the disorder according to the rule of nines (20% of the score); (ii) the measurement of disease intensity by six items including erythema, edema/ papules, effect of scratching, oozing/crust formation, lichenification, and dryness, each graded on a scale of 0–3 (60% of the score); and (iii) assessment of subjective symptoms, e.g. itching or sleeplessness (20% of the score). The most representative lesion was used for scoring purposes rather than the most severe or the mildest lesion. The SCORAD index was rated as severe, moderate or mild.

ELISA for Immunoglobulin E, IL-18 and IL-12

Venous blood samples from the control subjects and AD patients were collected and sera were separated and stored in small aliquots at -70ºC until analyzed further. Total IgE levels were measured in the serum samples by human IgE specific sandwich ELISA according to the manufacturers' instructions (cat. # 20783-72876, GenWay Biotech, CA, USA). Serum IL-18 levels were measured by human Interleukin-18 sandwich ELISA according to the manufacturers'instructions (cat. # KC0181, Invitrogen, CA, USA). The minimal detection level of the cytokine by this method was ≤12.5pg/ml for IL-18 (inter- and intra-assay reproducibility's were 8.54% and 4.93%).Whereas, IL-12 levelsin the serum samples were measured by human IL-12/p40 specific ELISA as per instructions described (cat. # 40056-205023, GenWay Biotech, CA, USA).The minimal detection level using this method was ≤2pg/ml for IL-12/p40 subunit (inter- and intra-assay precisions were 3.9 % and 3.9%).

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS program version 16.0 (SPSS Inc., Chicago, IL, USA). P<0.05 was considered statistically significant. Results are expressed as mean ± SD.

RESULTS

Demographic Characterization of AD Patients

The affected children with AD included 24 (48%) males and 26 (52%) females' children. Their mean age and standard deviation (SD) was 22.85 ±14.7 months, with a median age of 20 months. Approximately 52% of parents of affected children had received a university education and 40% were from moderate socio-economic standard of society.

The mean ± SD SCORAD score was 47.6 ± 23.5 (range 10–74) in the patients. According to the categories of the SCORAD index, 20% (10) of children showed a mild AD (SCORAD <20), 40% (20) a moderate AD (SCORAD 20-40) and 40% (20) a severe AD (SCORAD >40).The control group of children with no complaint of any dermatologic disorders comprised 30 healthy children (16 male (53%), 14 (47%) females. Their mean age and standard deviation (SD) was 23.8±13.1 months, with a median age of 22 months. The demographic characteristics of study population are shown in [Table/Fig-1].

Parameters	AD Patients (n = 50)	Controls (n = 30)
Age		
Mean (SD), months	22.85 ±14.7	23.8±13.1
Median, months	20	22
Gender		
Males	24 (48%)	16 (53%)
Females	26 (52%)	14 (47%)
Parent education		
Primary	4 (8%)	3 (10%)
High school	20 (40%)	12 (40 %)
University	26 (52%)	15 (50 %)
Socio-economic standards		
Low	10 (20%)	5 (16%)
Moderate	20 (40%)	9 (30%)
High	20 (40%)	16 (44%)
Consanguinity		
Yes	22 (44%)	10 (33.3%)
No	28 (46%)	20 (66.7%)
Family history		
Atopic dermatitis	10 (20%)	3 (10%)
Bronchial asthma	16 (32%)	6 (20%)
Allergic rhinitis	2 (4%)	1 (3.3%)

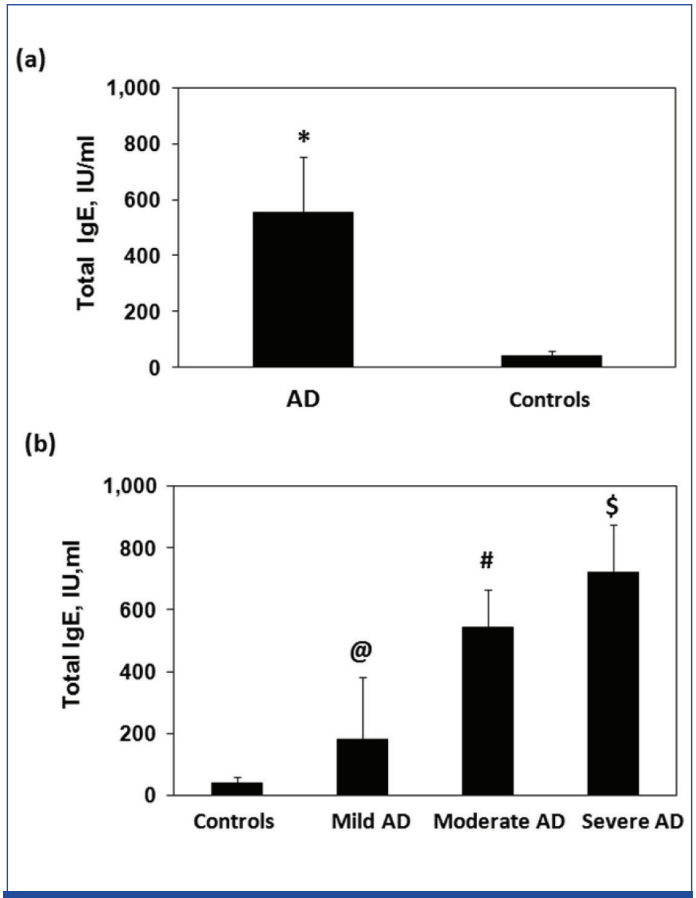
[Table/Fig-1]: Demographic characteristics of the study population
AD, atopic dermatitis; n, number of samples tested

Effect of Immunoglobulin E in the Progress of Atopic Dermatitis

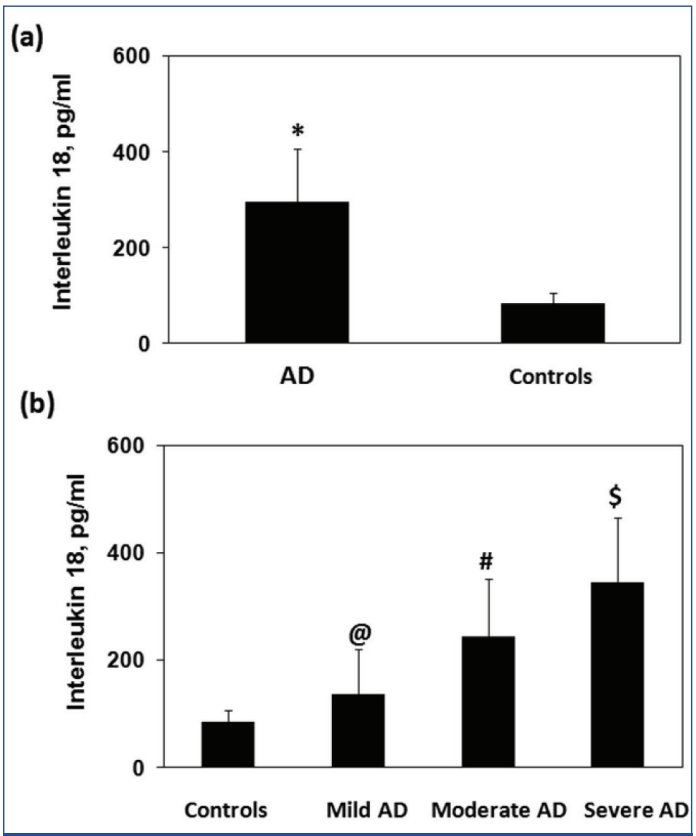
Serum total IgE levels were statistically significantly higher in study group (266-965 IU/mL mean ± SD 556±198IU/mL) than in control group (17–80 IU/mL mean ± SD, 41±19IU/mL) (p<0.001) [Table/Fig-2a]. In addition, we have also determined the role of IgE in the progress of AD. For that IgE levels were estimated in accordance with the disease activity in mild, moderate, and severe AD patients. The average IgE levels (±SD) in the patients' sera with mild, moderate, and severe groups are shown in [Table/Fig-2b]. Our results showed that IgE levels were significantly increased in mild, moderate or severe patients as compared with healthy controls (p<0.05) [Table/Fig-2].

Effect of Interleukin 18 in the Progress of Atopic Dermatitis

Serum levels of IL-18 were determined in all patients in the study groups and also in control group. Serum levels of IL-18 were determined statistically and were found significantly higher in patients (155-566 pg/mL mean ±SD 295±112pg/mL) than controls (44-122 pg/mL mean ±SD 83.7±22.6pg/mL) (p<0.001) [Table/Fig-3a]. We have also determined the role of IL-18 in the progress of AD. IL-18 levels were estimated in accordance with the disease activity in mild, moderate, and severe AD patients. The average IL-18 levels (±SD) in the patients' sera with mild, moderate, and severe groups are summarized in [Table/Fig-3b]. Our results showed that IL-18 levels were significantly increased in mild, moderate or severe patients as compared with healthy controls (p<0.05).



[Table/Fig-2a,b]: Immunoglobulin E in atopic dermatitis. (a) Levels of immunoglobulin E (IgE) in the sera of all studied atopic dermatitis (AD) patients and controls. *p<0.001 versus controls. (b) Levels of IgE in the sera of AD patients with mild, moderate, and those with severe scores and in controls' sera. $p<0.01 versus moderate AD; #p<0.05 versus mild AD; @p<0.01versus control. Each bar shows the mean± SD



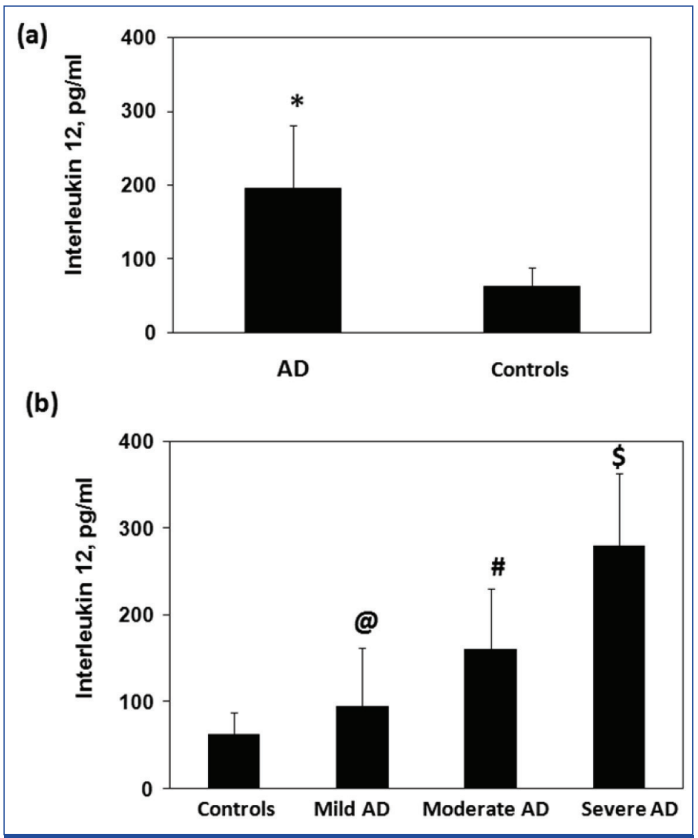
[Table/Fig-3a,b]: Interleukin 18 in atopic dermatitis. (a) Levels of interleukin (IL)-18 in the sera of all studied atopic dermatitis (AD) patients and controls. *p<0.001 versus controls. (b) Levels of IL-18 in the sera of AD patients with mild, moderate, and those with severe scores and in controls' sera. $p<0.05 versus moderate AD; #p<0.05 versus mild AD; @p<0.01versus control. Each bar shows the mean± SD

Effect of Interleukin 12 in the Progress of Atopic Dermatitis

Serum levels of IL-12/p40 were determined in all patients in the study group and also in healthy individualsin the control group. Serum levels of IL-12/p40 were determined statistically and were found significantly higher in patients (60-381 pg/mL, mean ±SD 195.5±84.9pg/mL) than controls (22-120 pg/mL, mean ±SD 62.6±25.3pg/mL) (p <0.001) [Table/Fig-4a]. Similarly IL-12/p40 levels were also estimated in accordance with the disease activity in mild, moderate, and severe AD patients. The average IL-18 levels (±SD) in the patients' sera with mild, moderate, and severe groups are summarized in [Table/Fig-4b]. Our results showed that IL-12/p40 levels were significantly increased in mild, moderate or severe patients as compared with healthy controls.

Correlation of IgE, IL-18 or IL-12 with Disease Activity Using Regression Coefficient

Correlation of IgE, IL-18 or IL-12 with AD activity was further evaluated by using regression coefficient (r) values. A statistically significant relationship between serum levels of total IgE (r=0.90; p<0.001), IL-18 (r=0.85; p<0.001) or IL-12/p40 (r=0.80; p<0.001), and SCORAD in children with AD was determined [Table/Fig-5]. These data also pointing out that the levels of IgE, IL-18 and IL-12 are well correlated with AD severities.



[Table/Fig-4a,b]: Interleukin 12 in atopic dermatitis. (a) Levels of interleukin (IL)-12/p40 in the sera of all studied atopic dermatitis (AD) patients and controls. *p<0.001 versus controls. (b) Levels of IL-12/p40 in the sera of AD patients with mild, moderate, and those with severe scores and in controls' sera. $p<0.05 versus moderate AD; #p<0.05 versus mild AD; @p<0.05 versus control. Each bar shows the mean± SD

Parameters	Statistical values	SCORAD
Total IgE	r p	0.90 <0.001
IL-18	r p	0.85 <0.001
IL-12/p40	r p	0.80 <0.001

[Table/Fig-5]: Relationship between SCORAD values and the serum levels of total IgE, IL-18, and IL-12/p40 in the patients with atopic dermatitis.
SCORAD, SCORing atopic dermatitis; IgE, immunoglobulin E; IL, interleukin; r, regression coefficient; p, probability values.

DISCUSSION

In the present study, we examined the relationship between atopic dermatitisand serum levels of IL-18, IL-12, and IgE levels in a group of young children living in Qassim region of Saudi Arabia.Our results showed that serum IL-18 levels were statistically significantly higher in AD patients as compared with their respective controls group ($p<0.001$). Our results also showed that serum IL-12/p40 levels were also significantly higher in AD patients than in control group ($p<0.001$). IL-18 level was also found to be significantly higher in the patients' sera than of controls. Furthermore, we also determined the SCORAD values and were found to be statistically higher with serum levels of IL-18 and IL-12/p40. An association between SCORAD score and the IL-18 levels was also previously reported in several studies on Turkish [22], Chinese [23], Japanese [19], and Korean [24] populations. In contrast, other studies [22,26] reported no correlation between SCORAD score and IL-18 levels. IgE antibody responses to food and inhalant allergens represent characteristic immunological markers in individuals with atopic dermatitis. Data obtained from longitudinal observational birth cohort studies indicate that in children with atopic dermatitis, elevated serum concentrations of IgE antibodies to inhalant allergens can be considered not only as early markers for atopy, but also as potential predictors for both subsequent allergic airway disease and the long-term persistence of atopic dermatitis [27-30]. Serum IgE level is often increased in allergic diseases, but, a normal serum IgE level does not mean that atopy does not exist. IgE serum level is considered one of the minor diagnostic criteria for AD [7], even though it is not of predictive value for the course of AD or long-term prognosis [31,32]. However, normal IgE serum levels have been reported in up to 20–40% of AD patients, and are related to AD with absence of atopic history [33]. The role of IgE in the pathogenesis of allergic rhinitis and in some forms of allergic asthma has been documented, but its role in AD pathogenesis has been pointed out by few reports only, where serum IgE levels have been correlated with the disease severity [34]. In the present study, the levels of total IgE in the serum samples of all tested AD patients was found to be greater than 200 IU/ml, which was significantly higher than the normal human controls ($p<0.05$).

In addition, our data also pointed out that IgE levels were significantly higher in those AD patients with higher SCORAD scores as compared to the lower SCORAD scores' patients. Similar results were found with IL-18 and also with IL-12 in AD patients and these results were also well correlated with the SCORAD scores. These findings clearly indicated that IgE, IL-18 and IL-12 are increased in AD patients and are well associated with the increased AD disease activity.Similar to our results, Kim et al., [26] and Ando et al., [35] found a correlation between IL-18 and IgE levels, whereas Hon et al., [23] and Shida et al., [33] did not, but their studies had smaller numbers of patients [23,33]. Our data confirmed that IL-18 and IL-12 may prove to be a suitable markers of disease severity in AD; consistent with some of the previous studies [23,24,35] however, other studies [25,26] found no correlation between SCORAD score and IL- 18 or IL-12 levels. Our data also confirmed that SCORAD score correlates with IgE level, again consistent with numerous previous observations [19,26,33]. We also confirmed the finding of an association between IgE levels and eosinophilia in the sera of patients with AD similar to the report of Trzeciak et al., [36], and opposite to the findings of Yoshizawa et al., [19]. In short, this study demonstrated higher levels of serum IgE, IL-18 and IL-12 in AD patients. Interestingly, not only was there an increased number of subjects positive for these tested parameters, but also their levels were significantly higher among AD patients, whose SCORAD scores were higher. Moreover, significant correlation was observed between the levels of these parameters and the SCORAD scores, indicating that IgE, IL-18 and IL-12 play an active role in the progression and/or progress of the disease.

CONCLUSION

Our data clearly show that the levels of IgE, IL-18 and IL-12 were significantly increased in atopic dermatitis patients. More importantly, the results of this study, for the first time to the best of our knowledge, provide evidence of a strong association between serum levels of IgE, IL-18 or IL-12 and atopic dermatitis disease activity. These data clearly conclude that IgE, IL-18 and IL-12 may be useful in evaluating atopic dermatitis activity, and would therefore be helpful for predicting the progression of the disease.

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