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Research Article

Interferon-Stimulated-Gene 15 as a Prognostic Marker of Atopic Dermatitis

Mazen Almehmadi[1,2]* and Alaa Shafie[1,2]

[1]*Collage of Applied Medical Sciences, Taif University, Taif city, Saudi Arabia*

[2]*High-Altitude Research Centre, Taif University, Taif city, Saudi Arabia*

***Corresponding Author:** Mazen Almehmadi, Collage of Applied Medical Sciences, Taif University, Taif city, Saudi Arabia.

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Abstract

Introduction: Atopic dermatitis is resulted from immunological system disparity and genetic predisposition, it is a chronic inflammatory disorder affecting the skin of the patients leading to itching and damaging of the epidermal barrier. ISG-15 has an essential role in human immune system. ISG-15 perform protein-conjugation in a process like ubiquitylation and this process is termed ISGylation.

Materials and Methods: samples were collected from 42 atopic dermatitis patients and 40 healthy donors. ELISA were used to detect the levels of serum-ISG15 in atopic dermatitis patients and healthy control.

Results: serum ISG-15 is elevated in atopic dermatitis patients than healthy control, also, atopic dermatitis males have higher levels than healthy controls.

Discussion and conclusion: ISG-15 increase in AD and can be used as a prognostic maker, the findings are consistence with other research and the expansion in serum ISG15 levels can be due to Th1 response and/or due to cells damage in atopic dermatitis.

Keywords: Interferon Stimulated Gene 15 (ISG-15); Atopic Dermatitis; Eczema

Abbreviations

ISG-15: Interferon Stimulated Gene 15; AD: Atopic Dermatitis; USP-18: Ubiquitin Specific Peptidase 18.

Introduction

Atopic dermatitis (AD) also called atopic eczema is resulted from immunological system disparity and genetic predisposition, it is a chronic inflammatory disorder affecting the skin of the patients leading to itching and damaging of the epidermal barrier [1,2]. The incidence of AD is rapidly increasing and the etiology for this autoimmune disorder is not quite clear [2]. AD exacerbation is three to five times in patients per year [3], generally, eczema is subdivided into two categories atopic and non-atopic eczema, this is due to the fact that part of eczema patients show the disorder without the atopic clinical signs [2]. The effect of AD can progress in patients and leads to bronchial asthma and damaging the respiratory system, in addition it can progress to affect other organs in the body such as the urinary tract and digestive system [3-5]. AD is characterized by itchy, dry skin, and flexural dermatitis, usually symptoms started when the patients was 2 years old with first degree relative that has the same symptoms [1].

The immune system effect of AD in the skin lesions is dominated by Th2 CD4+ T-cells rather than Th1 cells during the acute phase and Th1 rather than The 2 in chronic phase [6]. The activation of Th2 phenotype leads to damaging the skin of the patients, also, Th2 activates B-cells isotype switching toward the production of IgE [3,7]. CD3+ T-cells of AD patients principally express ETEA gene more than healthy control which have an essential role in regulating T-cells and eosinophils toward resisting the apoptosis, also, dendritic cells activate T-cells which promote the

pathophysiology of AD [1,8]. Eosinophilia is detected in majority of AD patients were 70% on total patients show elevation of IgE in the serum [3]. Keratinocytes also participate in the pathology of AD, they release cytokines and chemokines such as IL-22, TNF-α, IL-13 and IL-4 that assist in the pathology of AD and inducing the damage to the cutaneous surfaces [9]. IFN-α serum levels were significantly low in atopic dermatitis patients compared to health control [10], a study stated this can indirectly affect keratinocytes as IFN-α can induce the expression of IL-2Rγ that is expressed by keratinocytes [9]. IL-10 cytokines family like IL-22 is a potent inducer of keratinocytes, this activity is also detected with IL-24, IL-20 and IL-19 [9,11].

ISG-15 protein is about 17 kDa, up-regulation of ISG-15 gene increase rapidly due to Type I IFN, moreover, ISG-15 has an essential role in human immune system, Type-I-IFNs can induce ISG-15 expression and it has been elevated in cases like viral infection and tumors [12-15]. ISG-15 perform protein-conjugation in a process similar to ubiquitylation and this process is termed ISGylation [16]. This protein has gained the interest of many researches in the past decade to identify the potential biological functions. This protein can be detected in blood and urine and induce many immunological functions of CD3+ T-cells [17] and the free form can induce IFN-γ [18]. Our recent findings showed an essential role of ISG-15 in major-depressive-disorder [13], also, serum ISG-15 is elevated in Taif residents with influenza than Makkah [19]. This work has investigated and compared the levels of serum ISG-15 in AD patients and healthy individuals. Taif is a high-altitude city with about 1800 meter above sea levels.

Materials and Methods

Study group

Serum samples were obtained from a panel of 82 individuals (42 who have atopic dermatitis and 40 healthy control) in Taif university aged between 18 and 45 years (42 men and 40 women), following written informed consent. In figure 1 AD is clear on the foot of one of the participants. All subjects are free from malignant or viral infection. About 3 ml of blood was taken into red-tube and centrifuged at 1500 rpm, and then serum was collected and stored at -20°C for serum ISG-15 analysis. Ethical approval was provided from Taif university ethical committee.

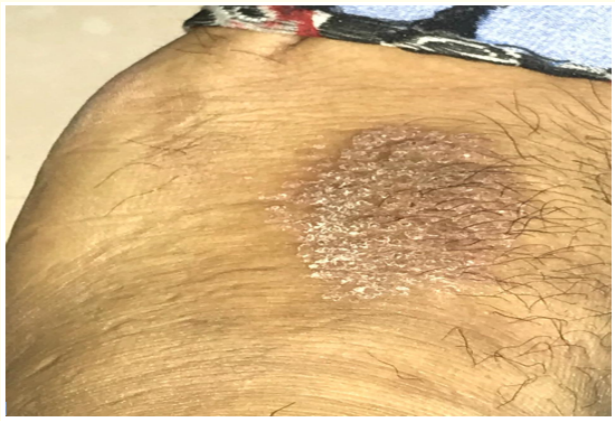

Figure 1: Atopic dermatitis is observable as skin damage is visible on the foot of one of the participants in this study.

ISG-15 serum levels

ISG-15 serum levels have been analyzed using ELISA kit for assay of serum-ISG-15 levels, the kit was purchased from BT-laboratory cat number E1988Hu, the detection sensitivity between 10 ng to 3000 ng. The analysis was performed on Bio-Rad xMark™ micro plate spectrophotometer.

Statistical analysis

ISG-15 serum levels have been compared using t-test, levels of expression have been compared between healthy and AD individuals, age groups of AD patients and between men and women. Results were compared by Paired t-test via GraphPad prism 5.03.

Results and Discussion

Demographic analysis

This study included 82 participants classified as 42 AD and 40 healthy subjects. In table 1 the demographic of participants is demonstrated. 22 AD patients were males their age ranging from 18 to 45. Number of females were 20 and their age groups started from 18 to 43 years. Healthy controls were 20 males and 20 females and their age groups were 20 to 45 and 18 to 45 respectively. All of AD participants are using different types of cortisone medications for this disease.

	AD		HEALTHY	
	Male	Female	Male	Female
Number of participants	22	20	20	20
Minimum	18.00	18.00	20.00	18.00
Median	23.50	26.50	26.50	31.00
Maximum	45.00	43.00	45.00	45.00
Mean	27.82	27.80	29.95	30.40
Std. Deviation	9.338	8.806	7.844	7.430
Std. Error	1.991	1.969	1.754	1.661

Table 1: Demographic analysis of participants of this study.

Serum ISG-15 levels

This study has measured the levels of serum-ISG-15 in AD and healthy control. In figure 2 the mean levels of AD were significantly higher than healthy individuals (P value < 0.0001). Mean levels of AD is 271.1 and 245.5 in healthy controls. In table 2 the statistical analysis of participants is illustrated.

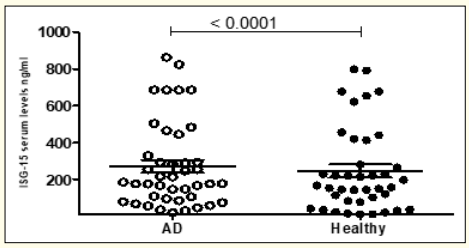

Figure 2: serum ISG-15 levels comparison between healthy and AD patients (P value <0.0001).

	AD	Healthy
Number of participants	42	40
Minimum	20.00	11.00
25% Percentile	92.50	78.75
Median	181.5	162.5
75% Percentile	358.0	380.0
Maximum	863.0	799.0
Mean	271.1	245.5
Std. Deviation	230.3	228.8
Std. Error	35.54	36.17

Table 2: Statistical analysis of the participants showed AD mean and median were higher than healthy participants.

Serum ISG-15 between age groups

The levels of serum ISG-15 was compared between the age groups of AD patients. No significant value detected even though 18-25 age group showed higher levels of serum ISG-15 than the other two groups (figure 3).

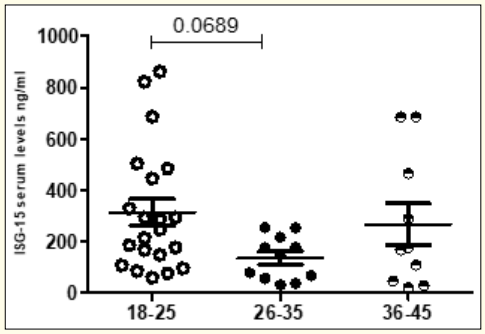

Figure 3: Levels of serum ISG-15 between age groups of AD patients.

Serum ISG-15 between genders

The levels of serum ISG-15 was compared between both genders. Male AD patients have shown significantly higher levels of serum ISG-15 than healthy males (P value < 0.0001) (figure 4).

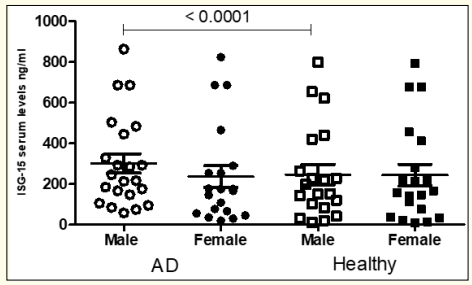

Figure 4: Serum ISG-15 was compared between genders. AD males have higher levels of ISG-15 than healthy males. Mean of AD was 301.9 while healthy males were 246.9.

Discussion

AD incidence has increased rapidly, studies indicated more than 2% of Chinese children have AD, while in developed countries like USA, Australia the prevalence reach 20% [1]. The cause of AD can be related to environmental factors and genetical predisposition. Moreover, hygiene hypothesis can explain the reason of the higher

incidence in urban areas. Interestingly, dietary of the pregnant mother can be related to AD and avoiding some types of food can help to avoid development of AD in their offspring [1,20,21]. Skin lesions of AD is marked by CD4+ T-cells infiltration and several other immune-cells labelled by IgE [6,22]. The role of CD4+ T-cells was acknowledged when αβ-T-cells-lacking mice have not developed any skin lesion when they induced by antigens [23]. AD is accompanied by cutaneous infections such as staphylococci, streptococci, herpes simplex virus, papilloma [24]. Interestingly, a study stated that T-bet continuous expression can lead to Th2 cells mimic Th1 cytokines production in AD, this study finding may change the idea of who is the main response Th1 or Th2 that controls AD [25]. Factors that support the idea of Th2 response effect in AD is marked by the higher levels of IgE and eosinophilia, this followed by detecting eosinophils-derived products and the higher levels of IL-4, IL-13 and IL-5 cytokines of Th2 cells [6].

Our study has found significantly higher levels of serum ISG1-15 in AD than healthy participants. Correspondingly, healthy males showed significantly lower levels than Male-AD participants. In the age groups the higher expression was detected in the younger-age group 18-25 years than the rest. This can be explained as most of young AD patients outgrow this disorder. Our research is inconsistence with study which tested the expression of mRNA of ISG-15 with several other genes in the skin lesions of AD and psoriasis patients, this study has not detected any overexpression of mRNA in skin of AD, however, this study was performed in USA and tested the expression of mRNA on skin but not on serum and there are several forms of ISG-15. our study has found ISG-15 protein expression expand in the serum of AD patients [26]. However, Our finding is consistence with other studies who have found ISG-15 mRNA and protein are elevated in AD and also in other chronic skin disease psoriasis than healthy control [27]. Our patients are from Taif which a high-altitude city, the weather is dry, cold and hypoxia can increase the complications of AD.

According to a study done by Dolen., *et al.* in [10] type-I-IFN α is undetected in AD patients serum, and type-I-IFN is a potent inducer of ISG-15 expression, however, our study have found that serum ISG-15 is higher in AD than healthy control. Th2 response is the dominant during the acute phase of AD during this phase cytokines of Th2 response are higher than those of Th1, thus, in the chronic phase due to bacterial and viral infection [24] the immune system will polarize toward Th1 response to fight these infections. This can explain the higher levels of ISG-15 in the serum of AD patients than healthy control. The role of ISG-15 and ISGylation is acknowledged in fighting infection [29-31] and our recent finding supported this role [19]. However, the role of ISG-15 in AD require more research as this role can be protective or induce the pathogenesis and the skin damage in those patients. Higher levels of serum ISG-15 are not clear if they provide protective role of not, or they are released by cells that have been damaged on the skin by AD like keratinocytes.

Conclusion

Overall, this study has confirmed that serum ISG-15 is elevated in AD patients and can be used as a prognostic marker for AD. ISG-15 has many functions and involved in the ISGylation cycle. The exact role of ISG-15 in AD require more studies to reveal this role. Particularly, research that investigate the levels of USP-18 and IFN-α. Also, as Taif city is a high-altitude city comparing ISG-15 between Taif and a low-altitude city is required. Expression of T-bet and Gata-3 by CD4+ T-cells is also required.

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