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The correlation of serum level and gene polymorphisms of interleukin-33 in atopic dermatitis Iraqi patients

Hiba Dhia Jafer [1], Aseel S. Mahmood [2]
[1,2]Biotechnology department, College of Science, University of Baghdad, Baghdad, Iraq
*Corresponding author:

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ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing inflammatory skin condition. Interleukins-33 (IL-33) are inflammatory cytokines that highly expressed in the keratinocytes of AD-suffering patients. This study aimed to investigate the correlation of the IL-33 serum levels and single nucleotide polymorphisms (SNP) of its gene in the rs10975519. This study includes 100 patients with atopic dermatitis (AD) and 80 healthy controls. The result indicate there was no significant difference when compared between the body mass index (BMI) of patient and control groups. In addition, there were non-significant increase in the concentration of eosinophil in AD patients, in comparison with controls ($p<0.553$). While result of the total Immunoglobulin E (t-IgE) was showed a high significant increase in t-IgE in patients with AD compared with controls ($p<0.001$). The findings showed that serum level of IL-33 was highly increased in patients of AD in compared with controls with ($p<0.001$). Also, no significant variations of IL-33 serum levels (p-value = 0.01), with age, gender, BMI, IgE, eosinophilia and duration of disease. Only age showed a significant correlation with IL-33 among patients and controls ($p<0.001$). SNPs rs10975519 of IL-33 gene was also investigated, and the result indicates that the patients whose carry elevated frequencies of both codominant CT, TT, dominant (CT+TT) or allele T of rs10975519 SNP are more likely infected with AD with odd ratios (2.4, 3.7, 6.2 and 1.8, respectively) among patient and control groups. No significant differences were observed in serum levels of IL-33 with its related-SNPs (rs10975519).

Keywords: *Single nucleotide polymorphism, IgE, Body mass index, alleles, Atopic eczema.*

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INTRODUCTION

Atopic dermatitis (AD) is a chronic disease and its symptoms appear at infancy or early childhood. A 15-20% of individuals suffer from this disease, as well as AD is commonly increased in developed countries and in urban locations. Various factors are play vital role in the eczema development. For instance, family history is considered as a great risk factor, in addition to many factors, such as enough presented to microorganisms in infancy and hyper presented to airborne contamination [1], [2]. In addition to the influence of AD disease on the physical health of individual, this disease can cause a significant emotional risk. Individuals with AD have been suffer from anxiety, depression and disturbances of sleep as well as they have a considerable reduced quality of self-esteem and life [3]. Indeed, that stress aggravated symptoms of atopic dermatitis [4].

Both sexes (Male and female) are affected, however in adults, females are more likely to get the condition, but in children, boys are more likely to have atopic dermatitis [5]. Atopic dermatitis disease is a hereditary condition that runs in families, but there is no obvious line of inheritance, which explains why clinically normal parents could have affected children, ruling out simple dominant inheritance. Other families, on the other hand, may have both parents sick but the children are unaffected, barring a simple recessive trait [6].

Recently, several studies have been paid attention to immune response against the pathogenesis of AD as well as defects of epidermal barrier also, its pathophysiology involves an orchestrated sequence of allergic provocation by IgE-mediated and non-IgE-mediated Th2 responses to allergens. Allergen sensitization precedes the immunopathogenesis. These studies were indicated that many skin disorders were aggravated after releasing of several cytokines, (IL-4, IL-5 and IL-13) which resulting in rise the IgE production, where elevate the skin inflammation and cause weakness in the barrier of skin in AD [7]. As an immune response on the skin of AD patients, lymphocytes such as Th17, Th22 and cytokines such as IL-17, IL-19 and IL-22 are released, as well as functions of modern cytokines, such as IL-16, IL-17, IL-21, IL-22, IL-23, IL-27, IL-31, IL-33 and IL-35 during the inflammation formation in the skin and physical injury of the skin have been explained. The immune response of T cells, with the controlling of cytokines which they secret, are differ significantly in the AD aggravation stage and in the period of remission [7].

Furthermore, the modern studies have noticeable evidences about the role of IL-33 pathway in skin inflammations, including the AD. IL-33 is a member of IL-1 cytokines family [8]. IL-33-encoding genes are impacted by many genetic polymorphisms, where there are many of these genetic polymorphisms have been described with their association to cedar pollinosis and AD, such as the single nucleotide polymorphisms of IL-33 gene (rs1157505, rs11792633, and rs7044343) have been described as a risk factor in formation of AD in Caucasian populations [9]. In this context, this study aimed to investigate the correlation of serum level of Interleukin-33 with its gene polymorphism rs10975519 in atopic dermatitis Iraqi patients.

MATERIAL AND METHOD

Subjects

After obtaining approval by the Ethics Committee in Biotechnology Department, Collage of Science, University of Baghdad and written was taken from all participants, this study was conducted on atopic dermatitis patients in Baghdad, Iraq. The study included 85 patients who were diagnosed with atopic dermatitis with ages ranged between 14 to 80 years, include 48 females and 37 males, who attended the Allergy Specialized Center in Al-Russafa, Baghdad, Iraq from November 2021 to March 2022. Furthermore, there were 40 apparently healthy subjects as controls, with ages ranged between 18 to 62 years, include 22 females and 18 males.The diagnosis of atopic condition was included the history of symptoms, skin symptoms and itchy. While atopic status or allergic case can be recognized by measuring the level of specific- and total-immunoglobulin E in serum or by skin prick testing (SPT) [10].

Sample collection

A 6ml of blood were obtained from each subject by vein-puncture under aseptic technique by syringe.

The blood samples were divided into three parts; the first part was 2 ml of blood were dispensed in a sterile EDTA tube for testing the eosinophils count, second part was 2 ml of blood were dispensed in a sterile EDTA tube for DNA extraction, and the third part was 2 ml of the blood sample dispensed in a sterile gel tube and left for about two hours to clot and then centrifuged at 3000rpm for fifteen minutes at room temperature to separate the serum and dispensed into three sterile Eppendorf tubes which tightly closed and stored at -20°C until assayed.

Anthropometric calculation

The body mass index (BMI) was calculated by considering both weight and height of the body, using following formula [11]:

$$BMI = {Weight\ (in\ Kg)}\Big/{Height^2 (in\ meter)}$$

Immunological studies

The total serum IgE was determined using enzyme-linked immune-sorbent assay technology (ELISA) (Bio Merieux, French). In addition, BioSource USA ELISA kit was utilized for estimation of serum level of IL-33. The hematological examination (eosinophils count) was performed by Beckman Coulter analyzer (German).

Molecular studies

Samples of DNA were collected from peripheral blood, and isolated by utilizing the kit of Blood Mini DNA extraction, based on the instructions of manufacturer (EasyPure Genomic DNA KIT Trans Gene.biotech.EE101-01). Single nucleotide polymorphisms (SNPs) of the IL-33 gene (rs10975519 loci) were evaluated using High Resolution Melt-Real time quantitative PCR (HRM-RT qPCR). The sequences according to their reference sequence in the database of National Center for Biotechnology Information (NCBI), as shown in Table 1. In addition,

TABLE 1: Designed Primers of IL 33 rs10975519 C>T that used in the present study

Primer	Sequence (5′→3′ direction)	Product size (bp)
Forward	ATGCATTCTCTTTCAGATAAGGTG	68
Reverse	CCTGATTCATTTGAGGGGTGT	

TABLE 2: Thermal profile of HRM genotyping

Step	Temperature (ºC)	Duration	Cycles
Enzyme activation	94	60 sec	1
Denature	94	5 sec	35
Annealing	56	15 sec	
Extension	72	20 sec	
HRM	65-95	0.2 sec for 1 degree	

Statical analysis

For summarize the data in this study, different descriptive statistical methods were applied. The mean differences in eosinophil counts between patients and controls were compared using an independent two-sample student one-way ANOVA and T-test. The IL-33 and total serum IgE level was compared using the Mann Whitney test, which employed the Median ± Standard Error to distinguish between different levels of AD severity. A significant p-value of less than 0.05 was used. SPSS ver. 28 was used for statistical processing (SPSS inc, Chicago, Ill). The statistical analysis of SPSS was utilized to assess the significantly variations in the noted allele between collection of genes. A model of logistic regression was utilized to counted the 95% confidence intervals (CIs) and odds ratios (ORs).

RESULTS AND DISCUSSION

Demographic Characteristics

Atopic Dermatitis (AD) patients nominated for the present study were 85 in total. These samples involved 37(43.5%) males and 48(56.5%) females. patients were presented according to their age, gender, duration of disease, BMI, Family history, social status, treatment and other disease. The ages in AD cases and healthy controls (HCs) ranged between (18-62) and age groups were divided into six groups (<20, 20-29, 30-39, 40-49, 50-59 and 60> years). Total AD patients showed a non-significant increased age mean compared to controls p-value = 0.144. The disease duration in AD patients according to such range, the patients were distributed into three groups of disease duration; <1, 1-4 ,5-9 and ≥10 years the Mean± SD (Range) was 6.6±7.7. All information was taken from patients and HCs, as shown in Table 3. There are no significant variations in all parameter, except social status among patients with p>0.001.

TABLE 3: Demographic Characteristics of Subject (patients and controls)

		Atopic dermatitis		Health Controls		p-value
		No.	%	No.	%	
Age (years)	<20years	11	12.9	2	5.0	0.144
	20---29	15	17.6	7	17.5	
	30---39	17	20.0	17	42.5	
	40---49	12	14.1	5	12.5	
	50---59	21	24.7	6	15.0	
	=>60years	9	10.6	3	7.5	
	Mean± SD(Range)	39.4±14.3 (14-65)		37.3±12.3 (18-64)		0.433
Gender	Male	37	43.5	18	45.0	0.877
	Female	48	56.5	22	55.0	
BMI (Kg/m2)	Normal (18.5-24.9)	18	21.2	9	22.5	0.919
	Overweight (25-29.9)	34	40.0	17	42.5	
	Obese (=>30)	33	38.8	14	35.0	
	Mean± SD (Range)	28.2±4.0 (18.50-34.90)		27.9±3.8 (18.60-34.80)		0.737
Social status	Single	15	17.6	18	45.0	0.001
	Married	70	82.4	22	55.0	
Smoking	Yes	14	16.5	5	12.5	0.564
	No	71	83.5	35	87.5	
Treatment	Yes	41	48.2			
	No	44	51.8			
Duration of disease (years)	<1year	30	35.3			
	1---4	23	27.1			
	5---9	7	8.2			
	=>10years	25	29.4			
	Mean± SD (Range)	6.6±7.7 (1M-24Y)				
Other disease	Yes	29	34.1			
	No	56	65.9			
Family history	Yes	27	31.8			
	No	58	68.2			
No.: Number, N: Frequency, % percentage, S.D Standard Deviation, p: probability, BMI: Body Mass Index, kg: Kilogram						

A previous study clarified the 7- to 12-year-old age group, all kinds of allergic diseases (asthma, allergic rhinitis, allergic conjunctivitis, food allergy and drug allergy) were potent [12], [13]. The existing studies detected contradictions, however, most of these studies were revealed that obesity have relationship with AD as well as studies included the obesity in the stage of infancy or childhood (age less than 2 years) and AD were found there is a positive association between them [14]. However, there are contradiction in observations of results from childhood into adulthood, as the more modern studies reported a positive association, but that was not noted in older included studies. It was concluded that overweight and obesity are related with an increased risk of AD [15].

Total IgE and Eosinophil Count

Concentration of Total IgE and Eosinophil in AD patients were observed as shown in Table 4. The result shows that there is a high significant difference in total IgE level of AD patients compared with HCs (157.367±158.276 vs. 14.622±1.853, $p>0.001$). While it showed no significant difference in the eosinophil assay $p\leq 0.553$.

TABLE 4: Total IgE and Eosinophil Count levels in subjects (patients and controls)

		Atopic dermatitis		Controls		P-value
		No	%	No	%	
Total IgE (IU/mL)	<50	39	45.9	40	100	0.0001*
	50	4	4.7	-	-	
	100	5	5.9	-	-	
	150	3	3.5	-	-	
	200	10	11.8	-	-	
	250	8	9.4	-	-	
	=>300	16	18.8	-	-	
Total IgE (IU/mL)	High (=>180)	35	41.2	-	-	0.0001*
	Normal (<180)	50	58.8	40	100	
	Mean±SD (Range)	157.367±158.276 (10.324-487.879)		14.622±1.853 (12.292-19.727)		0.0001#
Eosinophil	High (>4)	17	20.0	7	17.5	0.741
	Normal (1-4)	68	80.0	33	82.5	
Eosinophil	<1.0e	16	18.8	6	15.0	0.695
	1.0---	16	18.8	11	27.5	
	2.0---	22	25.9	10	25.0	
	3.0---	14	16.5	6	15.0	
	4.0---	10	11.8	2	5.0	
	=>5.0e	7	8.2	5	12.5	
	Mean± SD (Range)	2.7±2.0 (0.21-10.15)		2.5±1.5 (0.50-6.26)		0.553

The current study showed a very significant increase in patients with AD. This indicates that IgE may play an important role in AD disease, this is in agreement with a previous study [16] was mentioned that IgE is a key immunoglobulin which involved in acute allergic reactions and chronic allergic disorder. It is the key of allergic type I hypersensitivity reaction, where this immunoglobulin expressed on mast cells after the first exposure to allergen during process named sensitization. Accordingly, after the second exposure to the same allergen, mast cells blow up in order to release many inflammatory mediators, which give rise the allergic cascade [17]. It becomes clears in this study, that there is a significant increase in median of total serum levels of IgE in patients with atopic dermatitis compared with control group (91.64 vs. 49.72 IU/ml). This result has been explained as being caused by the induced Th2 cells that can secrete the cytokine TSLP which mediate stimulate B-cells to secrete specific IgE [18]. In addition, the study indicates that the no significant difference in eosinophil's count of AD patients in compared with HCs.

Eosinophils are circulating granulated leukocytes which have role in pathogenesis of atopic dermatitis. Eosinophils involved in the modification of immune response, as induce the airway hypersensitivity and reconfiguring, distinctive features of asthma [19].

Serum Level IL-33

The current study, IL-33 also shows highly significant difference in patients with AD in compared with HCs (183.897±79.427 vs. 96.377±42.513, p<0.001) respectively.

TABLE 5: Serum level of IL-33 in patients with AD and controls

ELISA		Atopic dermatitis		Controls		P value
		No	%	No	%	
IL-33 (ng/dL)	<50ng/dL	-	-	3	7.5	0.0001*
	50	7	8.2	26	65.0	
	100	31	36.5	8	20.0	
	150	16	18.8	1	2.5	
	200	14	16.5	2	5.0	
	250	9	10.6	-	-	
	≥300ng/dL	8	9.4	-	-	
	Mean±SD (Range)	183.897±79.427 (85.951-427.879)		96.377±42.513 (44.102-234.669)		0.0001#
#At the 0.05 level, the students t-test indicates a statistically significant variation between the independent means of two groups.						
*At the 0.05 level, Pearson Chi-square test (χ2-test) indicates significant difference between percentages.						

The biologically activated IL-33 is expressed on membrane of the epithelial cells, such as keratinocytes, and it is stored in usually in their nuclei. IL-33 is quickly produced in order to stimulate response of innate immunity after exposure to cellular stress or damage [20]. The result did not explain if the IL-33 appearance is a result or a cause of AD, but indicates the IL-33 stimulate severe eczema. The innate immunity may have a key role in the AD-like inflammation that induce IL-33 expression. The human skin-derived ILC2s activated in skin of AD patients as a result of IL-33 expression [21].

This study was found that there was a considerable increase in interleukin-33 when measured in the ELISA system in patients compared to healthy controls with high significant differences. This result explains that disruption epidermal barrier via reversible innate immune response, and catalyze the keratinocytes in order to increase the expression of alarmins, such as IL-33. The results corroborated the findings of a previous study that indicated elevated IL-33 levels in AD cases compared to a control group of healthy persons, but failed to find any statistically significant differences between the two groups [22]. Results are consistent with previous research showing that people with allergies, such as AD, had elevated levels of IL-33 [23], as well as the total IgE was highly significant. This is consistent with the previous study [24] also demonstrated the presence of increased IgE for patients AD. Immunoglobulin E (IgE) has a unique position among immunoglobulins. The concentration of serum may rise many folds as a response to certain triggers. The levels are increased in allergic disorders, such as AD, allergic bronchial asthma and allergic rhinitis. While there was no significant difference when measuring eosinophils for patients compared to healthy controls in the current study. In a previous study, the eosinophils are existed in the infiltration of the mixed perivascular inflammation within the patient's dermis. Both of tissue and blood eosinophilia is correlated with the severity of AD. The appearance of blood eosinophil cells was more evident, if the AD was related with the diseases of respiratory allergy [25].

Correlation of IL-33 with various parameter

Table 6 is explaining the IL-33 correlation with some parameters such as age, gender, BMI, duration of disease, total IgE and eosinophil of patients and healthy subjects. Results show up significant difference with age P<0.001, no significant deference in duration of disease and eosinophil.

TABLE 6: Correlation of IL-33 with various parameters

		Total IgE (IU/mL)	Eosinophil	IL 33 (ng/dL)
Atopic dermatitis (n=85)				
Age (years)		-0.397**	-0.027	-0.163
		<0.001	0.805	0.136
BMI (Kg/m2)		-0.045	-0.066	0.011
		0.682	0.547	0.922
Duration of disease (years)		-0.039	0.067	-0.095
		0.723	0.543	0.386
Total IgE (IU/mL)		-	0.170	0.143
		-	0.119	0.193
Eosinophil		0.170	-	0.037
		0.119	-	0.735
		0.128	0.946	0.841
IL 33 (ng/dL)		0.143	0.037	-
		0.193	0.735	-
Controls (n=40)				
Age (years)		0.272	0.036	-0.368*
		0.090	0.823	0.019
BMI (Kg/m2)		0.177	0.338*	0.005
		0.275	0.033	0.974
Duration of disease (years)		-	-	-
		-	-	-
Total IgE (IU/mL)		-	0.081	-0.262
		-	0.621	0.102
Eosinophil		0.081	-	0.167
		0.621	-	0.304
		0.006	0.037	0.327
IL 33 (ng/dL)		-0.262	0.167	-
		0.102	0.304	-
* At the 0.05 level, significant, ** At the 0.01 level, high significant				

It was also noted in current study that there were no significant differences when comparing interleukin 33 with gender, BMI, IgE and eosinophilia atopic dermatitis patients. In previous studies, they found a relationship with atopic dermatitis, and this is not consistent with the current study. This study include high numbers of participates with the widely range of age, gender and BMI range, the atopy objective markers were included too [26]. The activation marker CD69, the eotaxin receptor CCR3 and the adhesion molecule CD11b are a few of the cell-surface markers that can be upregulated by IL-33 [27]. In study by [28] was demonstrate that IL-33 also synergized with IgE receptor activation of primary human mast cells and basophils. IL-33 amplifies inflammation in both IgE-independent and IgE-dependent responses.

Molecular studies

The SNP of IL-33 gene (rs10975519; located on Chromosome 9p24.1) that presented with three genotypes (CC, CT, TT) and two alleles (C and T). The table (4-9) was showed analysis of Hardy-Weinberg equilibrium (HWE) in atopic dermatitis patient group and healthy control group revealed that the genotypes was consist with the equilibrium, and significant differences were observed between both of codominant CT and TT genotype frequencies in patient and control group with p=0.04. In addition, the dominant (CT+TT) genotype frequencies also were significant in between groups (p=0.02). A significant difference between allele T in patient and control groups with p=0.03. Hence, the patients whose carry elevated frequencies of both of codominant CT, TT, dominant (CT+TT) or allele T are more likely infected with AD with odd ratios (2.4, 3.7, 6.2 and 1.8, receptively).

TABLE 7: The comparison of the genotype and frequencies of allele for rs10975519 SNP of IL33 gene in patient and control groups using law of Hardy-Weinberg equilibrium

IL33 polymorphism rs10975519	Frequencies (%)		P value	Odd ratio (95% CI)
	Control group (n=40)	Patients Group (n=85)		
Codominant				
CC	40.0 % (n=16)	17) % (n=20.0	---	1.00 (Reference)
CT	50.0 % (n=20)	61.2 % (n=52)	0.04	2.4 (1.0-5.7)
TT	10.0 % (n=4)	)% (n=1618.8	0.04	3.7 (1.0-13.6)
Dominant				
CC	40.0 % (n=16)	17) % (n=20.0	---	1.00 (Reference)
CT+TT	60.0% (n=24)	80.0 % (n=68)	0.02	6.2 (1.1-6.0)
Recessive				
CC+CT	90.0 % (n=36)	81.2 % (n=69)	---	1.00 (Reference)
TT	10.0 % (n=4)	)% (n=1618.8	0.2	2.0 (0.6-6.7)
Allele				
C	65.0 % (n=52)	50.5 % (n=86)	---	1.00 (Reference)
T	35.0 % (n=28)	49.5 % (n=84)	0.03	1.8 (1.0-3.1)

The table was show correlation between IL33 serum level and gene polymorphisms. Results observed no significant difference between serum level and gene polymorphisms.

TABLE 8: correlation between IL33 serum level and gene polymorphisms

		IL 33 (ng/dL)			
		Atopic dermatitis		Controls	
		No	Mean±SD	No	Mean±SD
Total IgE (IU/mL)	High (≥180)	35	198.048±75.109	-	-
	Normal (<180)	50	173.991±81.591	40	96.377±42.513
	P value		0.171		
Eosinophil	High (>4)	17	199.540±62.853	7	116.283±36.828
	Normal (1-4)	68	179.987±82.995	33	92.155±42.934
	P value		0.367		0.176
HRM IL33	Wild CC	17	207.373±89.931	16	87.733±26.447
	Mutant TT	16	185.264±68.743	4	125.249±74.609
	Hetero CT	52	175.802±78.818	20	97.519±45.155
	P-value		0.367		0.290

Currently, IL-33 is cytokine induce responses of Th2. The data is recently referring to the significant role of IL-33 in atopic dermatitis exacerbation. In a previous study, they proved genetic polymorphism within the IL33 gene region has been previously reported to have a strong association with AD [29]. The association between IL-33 gene SNP and incidence of atopic dermatitis was investigated. According to the results that reported by [30], most people with the IL-33 rs10975519 SNP had mild to moderate pruritus.

Some genetic association studies indicates that the AD disease is significantly associated with the region of ST2 (−26999G/A) distal promoter of SNP [31]. Furthermore, there is a previous study indicates the presence of 22 SNPs of IL-33 gene, after analyze database of HapMap as well as reported the relation of these SNPs with

pollinosis of Japanese cedar (JC), which considered as the commonly allergic rhinitis form in Japan, as AD, this disease is related with a weakness in pathway of inflammation. According to statistical analysis, there is significantly association between the Japanese rhinitis appearance and the IL-33 gene SNP (rs1929992) existent (p = 0.048) [32].

CONCLUSION

Many researches have been carried out for describe the genetic fundamental information about AD. Currently, findings indicate that the diversity in pathways of immune response may be have a vital role in development of AD, in addition to its significant role in protection of skin barrier work. Several studies inclusively bringing together epigenetic mechanisms and interactions of gene with environment, as well as more demonstration about the genetic factors behind the pathogenesis of AD in order to improve the treatment of this disease in the future. Moreover, the current study explains that there was no correlation between the serum concentration of IL-33 and its single gene polymorphisms, the disease severity and IgE levels. The results conclude that the AD disease is very heterogeneous, where the course of its treatment differs in individuals.

ETHICAL CLEARANCE

The Biotechnology Department's local committee agreed to the experiments mentioned in this research. The study was undertaken by the University of Baghdad team.

CONFLICT OF INTEREST

There are no conflicts of interest between authors.

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