Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://dx.doi.org/10.21608/zumj.2020.14566.1323 Volume 28, Issue 5, September 2022(1029-1035)

Manuscript ID ZUMJ-1907-1323 (R6)
DOI **10.21608/zumj.2020.14566.1323**

ORIGINAL ARTICLE

Association of total IgE with both atopic and nonatopic asthmatic patients A case-control study

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Submit Date 2019-07-17
Revise Date 2020-02-03
Accept Date 2020-02-05

ABSTRACT

Background: Asthma is a chronic lung disease that inflames and narrows the airways. Asthma was considered an allergic disease and allergen specific IgE antibodies, mast cells, T helper 2 (Th2 cells) and their cytokines contribute to pathophysiology of atopic asthma. But nonatopic asthma is not associated with symptoms of allergy. The aim of this study was to determine total IgE level in both atopic asthma and nonatopic asthma and assess its relation to disease severity and assess the role of total IgE in diagnosis of atopic asthma.

Methods: This study was carried out on 55 subjects who classified into 5 groups: 11 mild atopic, 11 severe atopic, 11 mild nonatopic asthmatic, 11 severe nonatopic asthmatic, 11 healthy controls. The asthma patients were divided into atopic and nonatopic based on skin prick test. Asthma severity was determined by Forced Expiratory Volume (FEV1), then total IgE level was determined by Enzyme Linked Immunosorbent Assay (ELISA).

Results: There was statistically significant difference ($p<0.05$) of Predicted FEV1(%) between asthmatics and healthy controls (HCs). There was insignificant difference ($p>0.05$) in total IgE level between atopic asthmatics, nonatopic asthmatics and healthy controls ($p=0.64$). There was also statistically insignificant difference ($p>0.05$) of total IgE level between mild atopic asthmatics and severe atopic asthmatics.

Conclusion: Total IgE levels plays a role in asthma regardless of type of asthma either atopic or nonatopic. Total IgE levels are not associated with asthma severity.

Keywords; Asthma; total IgE level; atopic and nonatopic asthma.

INTRODUCTION

Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning **[1]**.

Symptoms and airway limitation have a great variation. They may resolve spontaneously or in response to medications and may sometimes be absent for weeks or months. Asthma is usually associated with airway hyperresponsiveness and chronic airway inflammation in response to direct or indirect stimuli **[2]**.

Asthma may be closely related to the various factors such as: history of allergy, genetic factors, respiratory infections, and environmental factors. There are occupational asthma and exercise induced asthma also **[3]**.

The most common phenotypes of asthma are atopic and nonatopic. The atopic asthma often commences in childhood and is usually associated with a past history or family history of allergic disease such as allergic rhinitis, or food or drug allergy. There is esinophilic airway inflammation. Asthma with this asthma phenotype usually respond well to inhaled corticosteroids (ICS) treatment. While the nonatopic asthma usually occurs in adulthood. The cellular profile of the sputum of these patients may be neutophilic, esinophilic or contain only a few inflammatory

cells. Patients with this asthma phenotype respond less to inhaled corticosteroids **[4]**.

Serum levels of allergen-specific and total IgE are strongly associated with the degree of sensitization and disease severity in atopic patients. Determination of total serum IgE levels is used as a screening method for atopy, and an upper limit of 120–180 U/L is generally accepted as a threshold for distinguishing atopics from non-atopics**[5]**.

In this study, we aimed to determine total IgE level in both atopic asthma and nonatopic asthma and assess its relation to disease severity and assess the role of total IgE in diagnosis of atopic asthma.

SUBJECTS AND METHODS

This case-control study was carried out over 13 months from April 2018 to May 2019 at Microbiology &Medical Immunology Department, the Allergy and Immunology Unit and Chest diseases Department, Faculty of Medicine, Zagazig University after review and approval by the Institutional Review Board (IRB) committee at Faculty of Medicine. Five groups were included in this study: 11 mild atopic, 11 severe atopic, 11 mild nonatopic asthmatic, 11 severe nonatopic asthmatic, 11 healthy controls. The healthy group included age and sex-matched subjects, serving as controls. While the cases included adult patients more than 20 years old had clinical history of asthma with intermittent chest symptoms such as wheezing, dyspnea, chest tightness and cough. The diagnosis of asthma in these patients was confirmed by pulmonary function tests including spirometry. Spirometry was used to determine forced expiratory volume in first second (FEV1). The predicted value of pulmonary function test was adjusted for age and sex. The classification was done according to the 2008 Global Initiative for Asthma (GINA) guidelines which categorize asthma severity as mild, moderate, or severe. Severity is determined according to frequency of symptoms and forced expiratory volume in first second (FEV1). The asthmatic patients were classified into atopic and nonatopic according to skin prick test. Skin prick test depends on the presence and degree of cutaneous reactivity as a representative marker for sensitization within target organs. It produced a wheal and flare response after about 15 minutes which could be quantitated **[6]**. Pediatric age group, subjects with malignancy and subjects with chronic inflammatory diseases were excluded from the study. All subjects were subjected to full history taking, clinical examination and laboratory investigations including total serum IgE concentration. Total serum IgE concentration was determined by Enzyme Linked Immunosorbent Assay (ELISA) (chemux bioscience Inc.)

Two mL of peripheral blood were obtained from each study subject by venous puncture under complete aseptic conditions. The blood was incubated for 30 min at 37 ºC then centrifuged at 2,000-3,000 rpm for 5 min. Serum was collected from the supernatant, aliquoted and stored at -20 ºC**.** The IgE Quantitative Test Kit based on a solid phase enzyme- linked immunosorbent assay was used according to the manufacturer's protocols **[7]**.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis: The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 20.0. Armonk.

RESULTS

Socio-demographic characteristics of Asthmatic patients (Atopic, non- atopic and control included in this study. Non-atopic asthmatic patients age per year ranged between 21-62 with mean± SD (42.3±13.2),while atopic asthmatic patients age per year ranged between 19-63 with mean± SD (40.2±14) and control group ranged between 33-62 with mean± SD (47.5±9.3) There was statistically insignificant difference $p>0.05$ of age between atopic patients, nonatopic patients and control group. Males among non-atopic asthmatic patients is 45.5%, 54.4% among atopic asthmatic patients and 72.7% among control participants. There was statistically insignificant difference $p>0.05$ of sex between atopic patients, nonatopic patients and control group **(Table 1).**

100% of atopic asthmatic patients have family history of allergy, while all nonatopic asthmatic patients don't have family history of allergy and also controls don't have family history of allergy except one. There was statistically highly significant difference $p<0.05$ of family history of allergy between atopic asthmatic patients, nonatopic asthmatics and control group.100% of atopic asthmatic patients have positive skin test, while all nonatopic asthmatics have negative skin test and also controls have negative skin test exept one.There was statistically highly significant difference of skin test ($p<0.05$) between atopic asthmatic patients, nonatopic asthmatics and control group (**Table 2).**

Predicted FEV1(%) in nonatopic asthmatic patients ranged between 45-85 with mean± SD (65±14),while Predicted FEV1(%) in atopic

asthmatic patients ranged between 45-85 with mean± SD (62.6±14) and Predicted FEV1(%) in healthy control ranged between 80-95 with mean± SD (91±5.4). There was statistically highly significant difference (p<0.05) of Predicted FEV1(%) between atopic asthmatics and healthy controls. And there was also statistically highly significant difference (p<0.05) of Predicted FEV1(%) between nonatopic asthmatics and healthy controls**(Table 3).** On the other hand, Predicted FEV1(%) in nonatopic asthmatic patients ranged between 45-85 with mean± SD (65±14),while Predicted FEV1(%) in atopic asthmatic patients ranged between 45-85 with mean± SD (62.6±14). There was statistically insignificant difference (p>0.05) of Predicted FEV1(%) between nonatopic asthmatics and atopic asthmatics **(Table 5).** In nonatopic asthmatic patients total IgE level (IU/ml) ranged between 7.213-190.6 with mean± SD (60.3±60.8) ,while total IgE level (IU/ml) in atopic asthmatic patients ranged between 11.8-208.2 with mean± SD (78.8±64.5) and in control participants total IgE level (IU/ml) ranged between 11.3-112.1 with mean± SD (61±43). There was statistically insignificant difference p>0.05(p=0.64) of total IgE level between atopic asthmatics, nonatopic asthmatics and healthy controls**(Table 3).**

Predicted FEV1(%) in asthmatic patients ranged between 45-85 with mean± SD (64±14), while Predicted FEV1(%) in healthy control ranged between 80-95 with mean± SD (91±5.4). There was statistically significant difference (p<0.05) of Predicted FEV1(%) between asthmatics and healthy controls **(Table 4).**

Predicted FEV1(%) in mild atopic asthmatic patients ranged between 60-85 with mean± SD (74±10), while Predicted FEV1(%) in severe atopic asthmatic patients ranged between 45-56 with mean± SD (51.2±4.7). There was statistically significant difference (p<0.05) of Predicted FEV1(%) between mild atopic asthmatics and severe atopic asthmatics. In mild atopic asthmatic patients total IgE level (IU/ml) ranged between 11.8-101.6 with mean± SD(60±32.3) ,while total IgE level (IU/ml) in severe atopic asthmatic patients ranged between 14.5-208.2 with mean± SD (97.5±83).There was statistically insignificant difference (p>0.05)of total IgE level between mild atopic asthmatics and severe atopic asthmatics **(Table 6**).

Predicted FEV1(%) in mild nonatopic asthmatic patients ranged between 65-85 with mean± SD (78±5.6), while Predicted FEV1(%) in severe nonatopic asthmatic patients ranged between 45-55 with mean± SD (52±4.7). There is statistically significant difference (p<0.05) of Predicted FEV1(%) between mild nonatopic asthmatics and severe nonatopic asthmatics. In mild nonatopic asthmatic patients total IgE (IU/ml) ranged between 7.213-190.6 with mean± SD (60.3±68.2) ,while
total IgE (IU/ml) in severe nonatopic asthmatic patients ranged between 19.3-146.7 with mean± SD (60.3±55.8).There is statistically insignificant difference(p>0.05) of total IgE level between mild nonatopic asthmatics and severe nonatopic asthmatics **(Table 7**).

Table 1: Socio-demographic characteristics of asthmatic patients (atopic and non- atopic) and controls

	Studied groups			Test of sig	P
	Non-atopic (No=22)	**Atopic (No=22)**	**Control (No=11)**		
Age per years Mean ±SD median(min-max)	42.3±13.2 46(21-62)	40.2±14 36(19-63)	47.5±9.3 49(33-62)	F=1.16	0.32
Sex no(%) Male Female	10(45.5) 12(54.5)	12(54.5) 10(45.5)	8(72.7) 3(27.3)	$\chi 2$ =2.2	0.33

$\chi 2$ = Chi square test (F)= ANOVA test

Table 2 : Allergic characteristics of asthmatic group(non-atopic, atopic) and controls

	Studied groups			χ^2	P
	Non-atopic (No=22)	**Atopic (No=22)**	**control (No=11)**		
Family history of allergy yes no	0 22(100)	22(100) 0	1(9.1) 10(90.9)	51	0.0001(HS)
Skin test positive negative	0 22(100)	22(100) 0	1(9.1) 10(90.9)	51	0.0001(HS)

χ^2 = Chi square test HS=highly significant

Table 3: Predicted FEV1, total IgE (iu/ml) of asthmatic groups (non-atopic and atopic) and controls

	Studied groups			F Test	P
	Non-atopic (No=22)	**Atopic (No=22)**	**control (No=11)**		
Predicted FEV1(%) Mean ±SD median(min-max)	65±14 60(45-85)	62.6±14 58(45-85)	91±5.4 95(80-95)	20.1	<0.0001 (HS)
Total IgE (iu/ml) Mean ±SD median(min-max)	60.3±60.8 32.2(7.213-190.6)	78.8±64.5 68.3(11.8-208.2)	61±43 78.6(11.3-112.1)	0.88^	0.64 (NS)

(F)= ANOVA test ^ = Kruskall Wallius test

FEV1: Forced Expiratory Volume in first second

Table 4: Predicted FEV1 of asthmatic group and control group

	(Asthmatic patients) (No=44)	(control) (No=11)	(t) test	P
Predicted EFV1 Mean ±SD median(min-max)	64±14 58(45-85)	91±5.4 95(80-95)	10.3	<0.0001(S)

(t)= t test

FEV1: Forced Expiratory Volume in first second

Table 5: Predicted FEV1 of non-atopic and atopic asthmatic groups

	Studied groups		t Test	P
	Non-atopic (No=22)	**Atopic (No=22)**		
Predicted FEV1 Mean ±SD median(min-max)	65±14 60(45-85)	62.6±14 58(45-85)	0.56	0.57(NS)

(t)= t test

FEV1: Forced Expiratory Volume in first second

Table 6: Predicted FEV1(%) and total IgE level(iu/ml) of atopic Asthmatic patients as regard severity

	Asthmatic patients –atopic		(t) Test	P
	mild(n=11)	**severe(n=11)**		
Predicted FEV1(%) Mean ±SD median(min-max)	74±10 80(60-85)	51.2±4.7 50(45-56)	**7**	**<0.0001**
total IgE (iu/ml) Mean ±SD median(min-max)	60±32.3 64(11.8-101.6)	97.5±83 118(14.5-208.2)	MW=0.25	0.27

(t)= t test MW= Mann-Whitnney test
FEV1: Forced Expiratory Volume in first second

Table 7: Predicted FEV1 and total IgE levels (iu/ml) of non-atopic Asthmatic patients as regard severity

	Asthmatic patients Non-atopic		(t) Test	P
	mild(n=11)	**severe(n=11)**		
Predicted FEV1(%) Mean ±SD median(min-max)	78±5.6 80(65-85)	52±4.7 55(45-55)	**11.5**	**<0.0001**
total IgE (iu/ml) Mean ±SD median(min-max)	60.3±68.2 22.2(7.213-190.6)	60.3±55.8 32.2(19.3-146.7)	**MW=0.5**	**0.52**

(t)= t test MW= Mann-Whitnney test

DISCUSSION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, such as mast cells, eosinophils, and T lymphocyte. The chronic inflammation is associated with airway hyper-responsiveness. Asthma is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These symptoms appear either at night or in the early morning **[2]**.

Asthma is classified according to the 2008 GINA **[8]**(Global Initiative for Asthma) into: intermittent asthma, mild persistent asthma, moderate persistent asthma and severe persistent asthma.

Intermittent asthma: Symptoms are less than twice a week, flares up are brief and nighttime symptoms are less than twice a month. FEV1 (Forced Expiratory Volume in first second) is 80% or more**.**

Mild persistant asthma**:** Symtoms are 3-6 times a week, flares up may affect activity level and nighttime symptoms are 3-4 times a month. FEV1 (Forced Expiratory Volume in first second) is 80% or more**.**

Moderate persistant asthma: Symptoms are daily, flares up may affect activity level and nighttime symptoms are 5 or more times a month. FEV1 (Forced Expiratory Volume in first second) is above 60% and below 80% of normal value.

Severe persistent asthma: Symptoms are continual and there are frequent nighttime symptoms. FEV1 (Forced Expiratory Volume in first second) is 60% or less of normal value.

In our study there was statistically insignificant difference ($p>0.05$) of sex between atopic patients, nonatopic patients and control group. And, there was statistically insignificant difference ($p>0.05$) of age between atopic patients, nonatopic patients and control group

Spirometry is a method that objectively assesses pulmonary function and is important for evaluating current asthma severity. The FEV1 values and FEV1/FVC ratios are used to assess airway obstruction and usually decrease during asthma attacks **[9]**. In our study there was statistically significant difference ($p<0.05$) of Predicted FEV1(%) between mild atopic asthmatics and severe atopic asthmatics and There was statistically significant difference ($p<0.05$) of Predicted FEV1(%) between mild nonatopic

asthmatics and severe nonatopic asthmatics. This means that Predicted FEV1(%) is an important indicator of severity.

One of the hallmarks of asthma is variation in airflow obstruction. In clinical practice, once an obstructive defect has been confirmed, airway limitation is generally assessed from reduction of FEV1**[10]**. In our study, Predicted FEV1(%) in asthmatic patients ranged between 45-85 with mean± SD (64±14), while Predicted FEV1(%) in healthy control ranged between 80-95 with mean± SD (91±5.4). There was statistically significant difference ($p<0.05$) of Predicted FEV1(%) between asthmatics and healthy controls (HCs). These results were matched with results of the study of Ming-Han et al **[11]** who found that among seventy patients with asthma and twenty age- and sex-matched HCs were enrolled, the percentages of predicted FEV1 were 81.4% ± 19.5% in the asthma patients and 96.2% ± 4.6% in the healthy controls and there was also significant difference ($p<0.05$) of Predicted FEV1(%) between asthmatics and healthy controls (HCs).

Atopy is a condition characterized by inappropriate IgE responses to common environmental antigens or allergens encountered by bronchial mucosa **[12]**. Atopic asthma is triggered by an allergen induced Th2 response, which is correlated with eosinophilia and increased serum IgE levels **[13]**.

Serum levels of allergen-specific and total IgE are strongly associated with the degree of sensitization and disease severity in atopic patients. Determination of total serum IgE levels is used as a screening method for atopy, and an upper limit of 120–180 U/L is generally accepted as a threshold for distinguishing atopics from non-atopics. However, there are studies that supported the existence of a close interrelationship between asthma and total IgE, either atopic or non-atopic. They also found that increased total serum IgE levels was independent of symptoms of allergy.**[5]**

Our study showed that, in nonatopic asthmatic patients total IgE level (IU/ml) ranged between 60-70 with mean± SD (60.3±60.8), while total IgE level (IU/ml) in atopic asthmatic patients ranged between 70-80 with mean± SD(78.8±64.5) and in control participants total IgE level (IU/ml) ranged between 60-70 with mean± SD(61±43). There is insignificant difference $p>0.05$ ($p=0.64$) of total IgE serum level in atopic, nonatopic patients and control group.

According to the National Health and Nutrition Examination Survey 2005-2006 the measurement of total IgE should not be a routine measurement in asthma. Total IgE levels, in the absence of specific IgE, are not associated with asthma. This finding validates the use of specific IgE measurement to determine the atopic asthma **[14]**. But the data collected in this survey did not allow full identification of the subjects.

On the other hand**, Ediva Myriam et al., [5]** supported the existence of a close interrelationship between asthma and total IgE, either atopic or non-atopic. They found increased total serum IgE levels was independent of symptoms of allergy.

Many other studies proved that IgE plays a role in asthma regardless of type of asthma either atopic or nonatopic **[15]**.

Also, **Antoine et al., [16]**. reported that IgE plays a role in the pathogenesis of some of high-IgE asthma phenotypes including nonatopic patients.

CONCLUSION

Total IgE levels plays a role in asthma regardless of type of asthma either atopic or nonatopic. Total IgE levels are not associated with asthma severity.

Conflect of interest:

There is not any financial or personal problems with any author.

Financial Disclosures: no

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To Cite:
helal, N., fathy, F., soliman, M., al shora, A. Association of total IgE with both atopic and nonatopic asthmatic patients A case-control study. *Zagazig University Medical Journal*, 2022; (1029-1035): -. doi: 10.21608/zumj.2020.14566.1323