

## Assessment of Total Serum IgE Level and Associated Factors among Asthmatic Patients at University of Gondar Hospital, Gondar, Northwest Ethiopia

Ayenew Assefa\*, Demeke Geremew and Tadelo Wondmagegn

Department of Immunology and Molecular Biology, School of Biomedical and Laboratory Sciences, University of Gondar, Gondar, Ethiopia

### Abstract

**Background:** Asthma is a chronic respiratory disorder having both genetic and environmental underlying risk factors. Immunoglobulin E (IgE) is known to play a critical role in asthma pathogenesis and has also main function in immune response to parasites such as helminths. In this research, we aimed to assess total serum IgE level and associated factors among asthmatic patients at the University of Gondar Hospital, Gondar, Northwest Ethiopia.

**Methods:** A comparative cross-sectional study was conducted from June to August 2019 at the University of Gondar Hospital among asthmatic patients. A structured questionnaire was used to collect socio-demographic characteristics of patients. Venous blood was collected from asthmatic patients to determine total IgE and cholesterol levels. A stool examination was also done among the patients. Stored serum sample from blood donors was used as control. Data was analyzed using SPSS version 20. ANOVA, Kruskal Wallis test, spearman's correlation, chi-square, and binary logistic regressions were used in data analysis. P-value  $\leq 0.05$  was considered statistically significant.

**Results:** A total of 88 study subjects were included. The geometric mean of total IgE level was  $366.6 \pm 5.4$  IU/ml and  $52.2 \pm 3.6$  IU/ml for patients and controls respectively ( $p < 0.001$ ). The geometric mean total IgE levels of patients with positive and negative helminth infection were  $1282.9 \pm 3.6$  IU/ml and  $294.4 \pm 5.6$  IU/ml respectively ( $p = 0.237$ ). The geometric mean total IgE level for moderate-severe groups of asthmatics was  $367.4 \pm 5.6$  IU/ml and intermittent-mild groups were  $321.2 \pm 5.4$  IU/ml ( $p = 0.803$ ). The association of cholesterol level and total IgE level among patients was found to be negative and non-significant (with an odds ratio of 0.995 and 95% confidence interval (CI) of 0.982-1.009) ( $p = 0.507$ ).

**Conclusion:** This study showed significantly higher total IgE levels in asthmatics than controls. Hence, assessment of total IgE level in asthmatics is a direct measurement of airway inflammation and estimation of total IgE level should be included in routine practice. Non-significant differences and associations were found between total IgE levels and associated factors among patients.

**Keywords:** Total serum IgE; Asthma; Helminth infection; Asthma severity; Cholesterol level

### \*Corresponding author:

Ayenew Assefa

✉ ayenassef@gmail.com

Tel: +251936379857

Department of Immunology and Molecular Biology, School of Biomedical and Laboratory Sciences, University of Gondar, Gondar, Ethiopia

**Citation:** Assefa A, Geremew D, Wondmagegn T (2021) Assessment of Total Serum IgE Level and Associated Factors among Asthmatic Patients at University of Gondar Hospital, Gondar, Northwest Ethiopia. Health Sci J. 15 No. 6: 853.

Received with Revision May 29, 2021, Accepted: June 13, 2021, Published: June 19, 2021

### Introduction

Asthma is a common chronic disease of airway inflammation [1] characterized by three major features: I) intermittent and reversible airway obstruction leading to recurrent episodes of symptoms such as wheezing, breathlessness, chest tightness and cough ii) bronchohyper responsiveness (BHR) defined as increased sensitivity to broncho constrictors such as histamine and cholinergic agonists and iii) airway inflammation [2].

Asthma has been seen as the hallmark TH2 disorder of the lungs [3] and begins when dendritic cells, a subset of antigen-presenting cells (APCs) found in the lung tissue; processes inhaled antigens and present them to T lymphocytes through the interaction of the receptor molecule CD28 on T cells and its ligand CD80 (B7-1) on dendritic cells. The interaction results in T lymphocyte development down the T helper 2 (TH2) pathway [4]. TH2 lymphocytes are characterized by the release of a family

of proinflammatory cytokines, including interleukin-3 (IL-3), IL-4, IL-5, IL-13, and others that promote development, activation, and survival of eosinophils. Besides, these cytokines and tumor necrosis- $\alpha$  (TNF- $\alpha$ ) activate endothelial cell adhesion proteins, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), which assist inflammatory cell movement from blood vessels into the airway. Moreover, IL4 and IL-13 are key stimuli of B cells for antigen-specific IgE production, which initiate the allergic cascade [5].

Immunoglobulin E antibodies are known for their role in allergy and asthma. Increased concentrations of circulating IgE antibodies are often associated with asthma and genetic analyses of families have shown that BHR and IgE values are linked. Mast cells are thought to be the main link between IgE and BHR. Cross-linking of IgE bound to mast cells by Fc $\epsilon$ R1 triggers the degranulation and release of preformed vasoactive mediators [6] like histamine, prostaglandin (PG) D<sub>2</sub>, and leukotriene (LT) C<sub>4</sub>, which are capable of inducing bronchoconstriction, mucus secretion, and mucosal edema [7]. IgE antibodies also bound to Fc $\epsilon$ R1 receptors on basophils, dendritic cells, airway smooth muscle cells, epithelial cells, endothelial cells, and eosinophils to play a key role in the pathogenesis of asthma [8]. Both specific and total IgE antibodies are the strongest associates and important predictors of asthma [9]. Apart from allergic diseases and asthma increased IgE levels are also seen in other disorders, including parasitic infections (e.g., strongyloidiasis, ascariasis, and schistosomiasis), non-parasitic infections, inflammatory diseases, and primary immunodeficiency diseases [10,11].

Asthma varies considerably in its severity; some patients have extremely severe disease, whereas others have minimal symptoms [12]. Helminth infection, cholesterolemia, and smoking are the main factors affecting asthma development and risk. Soil-transmitted helminths, or geohelminths, cause abnormal natural immune development; causing the immune response to shifting to Th2 type (22). In addition, elevated serum cholesterol has become a health problem of growing concern in many industrialized countries and developing nations. Several reports over the years have suggested an important and perhaps even unique role for cholesterol in pulmonary physiology [13]. Smoking is also one of the environmental factors to trigger asthma and increase asthma-related morbidity, disease severity, and reduced lung function [14]. Hence, this study attempts to assess the level of total serum IgE antibody and associated factors in asthmatic patients attending at inpatient clinic of the University of Gondar hospital, Gondar Ethiopia.

## Methods

### Study area

The study was conducted at the University of Gondar Hospital, Amhara region, northwestern Ethiopia. Gondar is 747 km far away from Addis Ababa and has a total population of 206,987 according to the 2007 Ethiopian Central Statistical Agency (CSA) office report [15]. The Hospital is a 400-bed University Hospital and serves a population of four million across the region. The chronic unit clinic of the hospital serves about 3500 chronic patients annually. It includes patients with diabetes mellitus,

heart failure, rheumatoid arthritis, hypertension, chronic liver disease, renal disease, asthmatics, and others admitted from medical, emergency, surgical, and other wards.

### Study design and period

A comparative cross-sectional study was conducted from June 27 to August 5, 2019. Patients were classified as intermittent, mild persistent, moderate persistent, and severe persistent asthmatics and those co-infected with other chronic infections were not recruited. Stored serum sample of blood donors was used as control.

### Study population

All asthma confirmed patients who have follow up at the chronic unit clinic of Gondar University Hospital during the study period was involved.

### Sample size and sampling technique

The sample size was determined using the statistical formula

$$n = \frac{(z_{1-\alpha/2})^2 \times P(1-P)}{d^2}.$$

We consider the prevalence of asthma to be 2.00% from the study done in Ethiopia by world health survey [16], the p-value of asthma prevalence (5%) = 0.05, 3% margin of error, and 95% confidence interval. Based on this assumption, 88 study subjects were selected. Serum from blood donors in the hospital during the study period was used as the control.

### Data collection

Structured questionnaire including local language (Amharic) was used to collect socio-demographic data and some of the associated factors such as smoking, physical activity, family history, exacerbation, and hospital admission. Blood and stool sample collection was done by laboratory technologists and technicians. Laboratory investigation for the clinical factors, helminth infection and serum cholesterol level, and the outcome variable serum IgE level measurement was done by the investigator and laboratory technologists.

### Laboratory methods

Four ml of the blood sample was drawn from the study subjects and serum was collected from each sample. The serum sample was left at -20°C until the end of data collection and taken to Amhara Public Health Institute (APHI). Then, the serum sample was tested for total IgE level using maglumi 800 IgE analyzer. The maglumi 800 analyzer is based on the principle of chemiluminescence immunoassay that uses an anti-IgE monoclonal antibody to label ABEI, and use another monoclonal antibody to label FITC. Pre-diluted Sample, Calibrator, Control, ABEI Label, FITC Label, and magnetic microbeads coated with anti-FITC are mixed thoroughly and incubated at 37°C, forming a sandwich. After sediment in a magnetic field, decant the supernatant, then cycle washing for 1 time. Subsequently, the starter reagents are added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as RLU (relative luminescence units) within 3 seconds and is proportional to the concentration of IgE present in controls or samples [17].

The remaining serum sample was tested for cholesterol using BT 2000 analyzer. BT 2000 analyzer is based on that the cholesterol present in the sample originates a colored complex after the addition of chemicals and a series of reactions. The intensity of the color formed is proportional to the cholesterol concentration in the sample. Stool samples were examined by direct method and formol-ether concentration technique for helminth infection. Formol-ether concentration technique is based on that parasite sediment by gravity or centrifugal force with minimum damage to their morphology, while the direct method is done after preservation, and two slides were prepared for each sample to increase the sensitivity. All procedures were per national and international guidelines.

### Quality control

Pre-tested questioners, standard reagents, and materials were used, and proper sample collection, regular supervision, and follow-up were performed. In the analytical phase, standard operating procedure (SOP) was followed; quality control was run to assure the performance of instruments (maglumi 800 analyzer and BT 2000 analyzer). In the post-analytical phase, all the transactional measures were checked, and the results were interpreted, accurately recorded, documented, and reported.

### Data analysis and interpretation

Data was entered and analyzed by IBM SPSS statistics version 20. Descriptive statistics were used to summarise the characteristics of the study population. The non-parametric Kruskal Wallis test, Mann Whitney test, and spearman's correlation was used for analysis. For normally distributed variables we used the ANOVA and for categorical data chi-square and logistic regression analysis were used. A p-value of less than 0.05 was considered statistically significant.

### Ethical consideration

The Ethical Review Committee of the school of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences approved the Protocol for the study. Written Informed consent was obtained from all subjects before data collection.

## Results

### Socio-demographic characteristics

A total of 88 subjects; 66 patients (71.2% females) and 22 controls (54.5% females); were included in the study. The mean age of patients was 53.4 years, ranging from 20–84 years, and of controls was 22.8 years, ranging from 19 to 30 years. The majority (72.7%) of the patients were urban residents. The majority of the patients (72.7%) were in the age group 40-70 years while all controls were in the age group 18-40 years (Table 1).

### Total serum IgE levels in controls and patients

The geometric mean total serum IgE level for the patients was  $336.6 \pm 5.4$  IU/ml with a median of 456.9 IU/ml. The values ranged from 1.0 to 3200 IU/ml. The 25<sup>th</sup> percentile was 105.4 IU/ml and the 75th percentile was 1410 IU/ml. The interquartile range was 1304.57 IU/ml. Similarly, the geometric mean total serum IgE level for the controls was  $52.2 \pm 3.5$  IU/ml with a median of 63.07 IU/ml. The values ranged from 3.09 to 811.1 IU/ml. The 25th percentile was 23.7 IU/ml and the 75th percentile was 106.6 IU/ml. The interquartile range was 82.9 IU/ml. There were significantly higher levels of total IgE in the patients as compared to the controls ( $p < 0.001$ ).

Among patients, females had lower IgE levels with a geometric mean of  $287.8 \pm 4.9$  IU/ml versus  $495.8 \pm 6.7$  IU/ml for males ( $p=0.131$ ), and among controls, males had lower levels with a geometric mean of  $41.6 \pm 3.8$  IU/ml versus  $63 \pm 3.4$  IU/ml for females ( $p=0.742$ ). Median values were higher for males than females in both patients and controls. There was no statistical correlation identified between age and levels of IgE in patients ( $p=0.911$ ) and in controls ( $p=0.918$ ). The geometric mean total IgE levels were  $177.3 \pm 9.3$  IU/ml,  $434.6 \pm 4.4$  IU/ml, and  $156.9 \pm 6.3$  IU/ml in the 18-40, 40-70, and 70+ age groups of patients respectively ( $p=0.263$ ). The median total IgE level peaked at 509.3 IU/ml in the 40 to 70 year age group, 200.2 IU/ml in the 18-40 age groups, and decreased reaching to 127.3 IU/ml in the group above 70 years. The geometric mean total IgE levels for rural resident patients was  $337.7 \pm 6.9$  IU/ml and  $336.2 \pm 5.1$  IU/ml for urban resident patients ( $p=0.852$ ).

**Table 1** Sociodemographic characteristics of study subjects at the university of Gondar hospital, North West Ethiopia, 2019.

Patients	N	Percent (%)	Controls	N	Percent (%)
<b>Age</b>					
18-40	12	18.2	18-40	22	100
40-70	48	72.7	40-70	-	-
70+	6	9.1	70+	-	-
<b>Gender</b>					
Male	19	28.8	Male	10	45.5
Female	47	71.2	Female	12	54.5
Residence			Total		
Urban	48	72.7	--	--	--
Rural	18	27.3	--	--	--
Total	66	100	--	--	--

N=Number

Serum total IgE levels varied considerably in the asthmatic patients (coefficient of variation 86.9%). Total IgE levels >100 IU/ml were considered high and <100 IU/ml were considered low IgE levels in the study (18) and among 66 patients in our study, 50 (75.8%) patients had serum IgE levels >100 IU/ml while only 5 (22.7%) of controls had serum IgE levels >100 IU/ml (Table 2).

### Relationship of total serum IgE levels with associated factors

**Helminth infection:** Of the 66 patients in the study only 43 patients were screened for helminth infection due to reasons of no or insufficient sample from whom 2 (4.7%) of patients were positive, one for *S. mansoni* and the other for Tania species, and 41 (95.3%) were negative. Total IgE was > 500 IU/ml for the helminth infected which were 514.3 IU/ml and 3200 IU/ml for *S. mansoni* and Tania positive patients respectively. The geometric mean total IgE levels of patients with positive and negative helminth infection were  $1282.9 \pm 3.6$  IU/ml and  $294.4 \pm 5.6$  IU/ml respectively. There was no significant difference in total serum IgE levels between helminth infected and non-infected, although the highest geometric mean total serum IgE level was found in helminth infected patients ( $p=0.237$ ) (Table 3).

**Cholesterol level:** The mean cholesterol level was 188.7 mg/dl for patients, which was significantly higher than controls who

had a mean cholesterol level of 166.4 mg/dl ( $p=0.039$ ). Non-parametric correlation between total IgE levels and cholesterol levels in patients showed a negative weak correlation with a spearman's rho of -0.057. The correlation in controls showed a positive weak correlation with spearman's rho of 0.185. The correlations were non-significant with ( $p=0.648$ ) and ( $p=0.411$ ) in patients and controls respectively. Besides, the association of total IgE level with cholesterol level in patients was analyzed. The mean cholesterol level is higher in low IgE groups and smaller in the high IgE groups of patients which was negatively associated with IgE levels (with an odds ratio of 0.995 and 95% CI of 0.982-1.009). However, the association was not significant ( $p=0.507$ ) (Table 4).

**Asthma severity:** As the severity of asthma was classified into intermittent, mild, moderate, and severe persistent; the intermittent group accounted for 8 (12.1%) while 35 (53%), 11 (16.7%), and 12 (18.2%) accounted for the mild, moderate and severe persistent groups respectively. The geometric mean total IgE for intermittent, mild, moderate, and severe persistent asthmatics was  $399.7 \pm 14.9$  IU/ml,  $305.6 \pm 4.2$  IU/ml,  $567.1 \pm 5.9$  IU/ml, and  $246.8 \pm 5.2$  IU/ml respectively. There was no significant difference in the distribution of total IgE levels across severity groups ( $p=0.324$ ). However, the median levels tended to be higher in intermittent and moderate persistent

**Table 2** Total IgE levels in the study subjects concerning sociodemographic characteristics and associated factors at the University of Gondar hospital, Northwest Ethiopia, 2019.

Patient characteristics	N	Total IgE (IU/ml)			P-value
		Min	G. mean	Max	
Overall	66	1.0	$336.6 \pm 5.4$	3200	
<b>Age (y)</b>					
18-40	12	1.0	$177.3 \pm 9.3$	2079.8	0.263
40-70	48	13.34	$434.6 \pm 4.4$	3200	
70+	6	30.67	$156.9 \pm 6.3$	2907	
<b>Gender</b>					
Male	19	13.34	$495.8 \pm 6.7$	3200	0.131
Female	47	1.0	$287.8 \pm 4.9$	3200	
<b>Residence</b>					
Urban	48	1.0	$336.2 \pm 5.1$	3200	0.852
Rural	18	13.34	$337.7 \pm 6.9$	3200	
<b>Severity</b>					
Intermittent	8	1.0	$399.7 \pm 14.9$	2590.6	0.324
Persistent mild	35	21.46	$305.6 \pm 4.2$	3200	
Persistent moderate	11	15.99	$567.1 \pm 5.9$	3200	
Persistent severe	12	13.34	$246.8 \pm 5.2$	2595.7	
<b>Smoking</b>					
Non-smoker	62	1.0	$338.7 \pm 5.5$	3200	0.936
Ex-smoker	4	40.31	$305.4 \pm 6.6$	3200	
<b>Family history</b>					
Yes	11	31.35	$164.4 \pm 3.3$	978	0.74
No	54	1.0	$374.3 \pm 5.7$	3200	
<b>Controls</b>					
Overall	22	3.09	$52.2 \pm 3.5$	811.1	--
Male/female	10/12	3.09/15.72	41.6/63	201.8/811.1	0.742
Patient/control	66/22	1/3.09	336.6/52.2	3200/811.1	<0.001

N=Number; Min=Minimum; Max=Maximum; G. Mean=Geometric Mean

**Table 3** Total IgE levels among helminth infected and non-infected asthmatics at the University of Gondar hospital, Northwest Ethiopia, 2019.

Factor	N	TlgE level	G. mean TlgE level	P-value
Helminth infection				
Positive	2		1282.9 ± 3.6	0.237
S. mansoni	1		514.3	
Taenia species	1		3200	
Negative	41		294.4 ± 5.6	

N=Number; TlgE=Total IgE; G. Mean=Geometric Mean

**Table 4** Relationship of cholesterol level and total IgE groups at the University of Gondar hospital, Northwest Ethiopia, 2019.

Cholesterol level*(M)	Factors			P-value
	Low IgE group	High IgE group	Total (M)	
Patients	194.5	186.9	188.7	0.507
Controls	165	171	166.4	0.808

\*Cholesterol Level in mg/dl; Low ≤ 100 IU/ml, High ≥ 100 IU/ml; M=Mean

groups. When patients were grouped into intermittent-mild and moderate-severe asthma groups, the moderate-severe groups had geometric mean total IgE levels of 367.4 ± 5.6 IU/ml which was higher than the intermittent-mild group who had values of 321.2 ± 5.4 IU/ml. However, the difference was not significant (p=0.803). In addition, 36.0% of those with high IgE levels had moderate-to-severe asthma compared to 31.2% of those with low IgE.

**Smoking status:** Based on the self-reported questionnaires regarding their smoking status, 4 (6.1%) patients were ex-smokers, who were smoking but stopped, and the others were non-smokers. The geometric mean of total IgE levels in ex-smokers (305.4 ± 6.6 IU/ml) was lower compared to non-smokers (338.7 ± 5.5 IU/ml) and was not significant (p=0.936).

### Other associated factors according to high and low IgE levels

Patients with and without a family history of asthma had a geometric mean total IgE level of 164.4 ± 3.3 IU/ml and 374.3 ± 5.7 IU/ml respectively (p=0.074). In addition, 14.3% of patients with high IgE had family history compared with 25.0% of patients with low IgE (odds ratio, 0.5; 95% CI 0.125-1.999). Similarly, patients with hospital admission had a geometric mean total IgE level of 292.1 ± 5.6 IU/ml and 491 ± 5.0 IU/ml for patients with no hospital admission (p=0.216). In addition, 72.0% of patients with high IgE had been previously hospitalized, compared with 75.0% of patients with low IgE (odds ratio, 0.857; 95% CI, 0.236-3.111). The difference between IgE levels in the remaining factors such as exacerbation, BMI, and physical activity was not statistically significant.

## Discussion

The result of this study revealed that the geometric mean total IgE levels in asthmatics (336.6 ± 5.4 IU/ml) were significantly higher than controls (52.2 ± 3.5 IU/ml) indicating the central role of total IgE levels in asthma pathogenesis and prognosis. It also confirmed that higher total IgE levels are an important predictor and strongly associated with the disease. The finding was in line with previous studies in India [19], Nepal [20], and Iraq [21].

Almost all studies reviewed found a significant difference in total IgE levels between patients and controls with the highest levels in patients. The high levels of total serum IgE observed in the patients could be explained by that asthmatics produce more IgE as a result of the inflammatory process in their airways [22].

The highest total IgE level recorded in this study was 3200 IU/ml. None of the controls had IgE levels at or above 1000 IU/ml. If we presume the upper limit of IgE level as 300 IU/ml there was only one control subject with levels ≥ 300 IU/ml. Thus, the result indicates a cut point of 300 IU/ml could be a suggestive value for asthma diagnosis and prognosis. This finding was in disagreement with a study in Nepal [20] that reported the highest total IgE level of 3300 IU/ml, found two controls having total IgE level at or above 1000 IU/ml and 19 controls having ≥ 300 IU/ml. The possible reason for the differences might be race, greater sample size, and a wider age range of controls used in the previous study.

In this study, there was no significant correlation of total IgE level with age both in asthma and control groups. However, the lowest median total IgE level was recorded in the 70+ age groups of patients. The probable reason for a decreased median total IgE levels observed could be due to the progressive decline of an immune function called immunosenescence in aging that results in reduced antibody production [23]. The result was in disagreement with a study done in Germany that showed a significant decrease in total IgE levels with age [24]. On the other hand, a study in Italy concluded an increase in total IgE levels with increasing age [23]. The contradictions could be due to variations of sample size and age range, presence of other underline allergic diseases, patient selection, and age of onset of the disease in each study. In this study, geometric mean total IgE levels of patients were higher in males as compared to females, and of controls, geometric mean total IgE levels were higher in females than males. But the differences were not significant in both groups. The possible reason for the variation of total IgE level in genders could be that sex hormone; such as testosterone; could play a role by regulating mast cell activation and Th2 immune responses [25]. Similar to this study, a study in Mexico and the USA found no significant difference in total IgE between genders [18]. In contrast, a study done in Spain [26] and Nepal

[20] found significantly higher IgE levels in males than females. The variations between the studies could be mainly due to differences in the percentage of male and female study subjects.

In the present study, the low rate of positive stool examination was not sufficient to detect the association of helminth infection with total IgE levels. However, based on the available data the study found higher geometric mean total IgE levels in helminth infected patients ( $1282.9 \pm 3.6$ ) than non-infected ( $294.4 \pm 5.6$ ) with a non-significant difference. Even though non-significant the higher total serum IgE levels in helminth infected patients may be due to helminth infection induces non-specific polyclonal IgE and anti-parasite specific IgE production [27]. The non-significant association observed could be mainly because of low prevalence of helminth infection in this study. A number of previous studies showed increased total IgE levels in helminth infected asthmatic patients [28,29]. Furthermore, a study done in Indonesia [30], in Bangladesh [31] in Latin America [32], and in the Philippines [33] showed an association of total IgE levels with helminth infection.

This study disclosed a non-significant association between serum total IgE level and cholesterol level from which the study concluded cholesterol level had no association with total IgE level. Contrary to this result, a study in Japan reported a significant positive association between serum cholesterol levels and total IgE levels [34]. It is well established that cholesterol promotes Th2 immunity and allergic inflammation in rodents [35] supporting the above study. Another mice model study also states that hypercholesterolemia modulates the Th2 switch of immune response and markedly increased IgE antibody titers [36]. On the other hand, a study done in Finland reported that subjects with elevated IgE had low cholesterol levels [37]. These contradicting results may be explained by various factors like different age groups and ethnicity studied as well as inherent methodological limitations in the study design.

Our analysis of the relationship between total IgE levels and asthma severity found a non-significant difference which is in concurrence with a study in Spain [26] and India [38]. However, a study in the USA and Mexico [18], and in Croatia [39] reported an association of IgE levels with asthma severity. On average higher IgE level was associated with moderate to severe asthma in this study indicating the role of total IgE levels in the pathogenesis of asthma severity. These differences could be mainly due to variation in age groups studied, gender, ethnicity, number of patients in each severity group, and asthma severity classification methods.

The association of smoking with total IgE levels was not ascertained, because of the absence of current smokers and small prevalence of ex-smokers. Hence, we didn't get the necessary statistical power to demonstrate an association. But, with the existing analysis, the geometric mean total IgE levels in ex-smokers ( $305.4 \pm 6.6$ ) were lower than non-smokers ( $338.7 \pm 5.5$ ) with a non-significance difference. A study done in Belgium [40] reported that the total IgE level was not increased because of exposure to cigarette smoke. On the contrary, a study done in Korea [41] reported an association between smoking and elevated total IgE levels. Also, a study done in Korea [42] found

enhanced OVA-specific IgE levels with cigarette smoke. When we explored other factors associated with IgE levels a trend towards higher levels was observed in patients without a family history, with no hospital admission, with exacerbation, with no physical activity, and with underweight groups. However, none of these variables remained significant. This could be possibly due to recall bias, length of follow-up, and drugs taken by patients.

## Limitations

The cross-sectional nature of the study design might not implicate casual relationships between total IgE levels and associated factors. During recruitment, a higher number of female patients enrolled as compared to males and an equal number of patients was not present in each severity group which would bias the comparison. The age distribution was not fully matched between patients and controls.

## Conclusion

Serum total IgE level was significantly higher in asthmatic patients than apparently healthy controls. It was found that over three-fourths of patients had high total IgE levels implicating that the assessment of total IgE level could be a direct measurement of airway inflammation in asthmatics and should be included in a day to day practice. In addition, further study on specific IgE levels with total IgE levels must be performed. We did not find a significant difference and association in total IgE levels with helminth infection (though low positive rate), cholesterol level, disease severity, smoking status, sociodemographic, and other clinical characteristics. However, the total IgE level was tended to be higher in helminth infected asthmatics, moderate to severe asthma groups, and non-smokers. Higher cholesterol level was found in the low IgE groups of patients and future research is required in a larger population to determine cholesterol association with IgE and its clinical implications.

## Authors' Contributions

Ayenev Assefa; Conceived the study, run the lab work, analyzed and interpreted the data, drafted, and wrote the paper. Tadelo and Demeke; designed the study, supervised and reviewed the manuscript thoroughly for its scientific content. All authors contributed to the writing of the paper and approved the submitted version of the paper.

## Ethics Approval and Consent to Participate

The Ethical Review Committee of the school of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences approved the Protocol for this study. Written Informed consent was obtained from all subjects before data collection.

## Standards of Research

All procedures performed were per the ethical standards of the 1964 declaration of Helsinki and subsequent amendments.

## Competing Interests

The authors declare that they have no competing interest.

## Data Availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

## Funding

This work was granted by the University of Gondar.

## Acknowledgments

The authors have deep gratitude to the University of Gondar. We also would like to thank the Amhara Public Health Institute (APHI).

## References

- McCormack MC, Enright PL (2008) Making the diagnosis of asthma. *Respir Care* 53: 583-592.
- Mehta AA, Mahajan S (2006) Role of cytokines in pathophysiology of asthma. *Iran J Pharmacol Ther* 5: 1-0.
- Lambrecht BN, Hammad H (2015) The immunology of asthma. *Nature Immunology* 16: 45.
- Smits HH, Everts B, Hartgers FC, Yazdanbakhsh M (2010) Chronic helminth infections protect against allergic diseases by active regulatory processes. *Curr Allergy Asthma Rep* 10: 3-12.
- Cardoso LS, Costa DM, Almeida MCF, Souza RP, Carvalho EM, et al. (2012) Risk factors for asthma in a helminth endemic area in Bahia, Brazil. *J Parasitol Res* 2012: 796820.
- Yu M, Eckart MR, Morgan AA, Mukai K, Butte AJ, et al. (2011) Identification of an IFN- $\gamma$ /mast cell axis in a mouse model of chronic asthma. *J Clin Invest* 121: 3133-3143.
- Heger K, Fierens K, Vahl JC, Aszodi A, Peschke K, et al. (2014) A20-deficient mast cells exacerbate inflammatory responses in vivo. *PLoS Biology* 12: e1001762.
- Matucci A, Vultaggio A, Maggi E, Kasujee I (2018) Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? *Respir Res* 19: 113.
- Sonntag HJ, Filippi S, Pipis S, Custovic A (2019) Blood biomarkers of sensitization and asthma. *Front Pediatr* 7: 251.
- Adkinson Jr NF, Bochner BS, Burks AW, Busse WW, Holgate ST, et al. (2013) *Middleton's Allergy E-Book: Principles and Practice*: Elsevier Health Sciences, UK.
- Pien GC, Orange JS (2008) Evaluation and clinical interpretation of hypergammaglobulinemia E: differentiating atopy from immunodeficiency. *Ann Allergy Asthma Immunol* 100: 392-395.
- Kedda MA, Shi J, Duffy D, Phelps S, Yang I, et al. (2004) Characterization of two polymorphisms in the leukotriene C4 synthase gene in an Australian population of subjects with mild, moderate, and severe asthma. *J Allergy Clin Immunol* 113: 889-895.
- Gowdy KM, Fessler MB (2013) Emerging roles for cholesterol and lipoproteins in lung disease. *Pulm Pharmacol Ther* 26: 430-437.
- Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH (2011) Smoking and asthma. *J Am Board Fam Med* 24: 313-322.
- Ethiopia (2008) Summary and statistical report of the 2007 population and housing census: population size by age and sex. Federal Democratic Republic of Ethiopia Population Census Commission, Addis Ababa, Ethiopia. 2008: 1-0.
- To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, et al. (2012) Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 12: 204.
- Homburger HA (1991) The Laboratory Evaluation of Allergic Diseases: Part I: Measurement Methods for IgE Protein. *Laboratory Medicine* 22: 780-782.
- Naqvi M, Choudhry S, Tsai HJ, Thyne S, Navarro D, et al. (2007) Association between IgE levels and asthma severity among African American, Mexican, and Puerto Rican patients with asthma. *J Allergy Clin Immunol* 120: 137-143.
- Sandeep T, Roopakala MS, Silvia CRWD, Chandrashekara S, Rao M (2010) Evaluation of serum immunoglobulin E levels in bronchial asthma. *Lung India* 27: 138-140.
- Shrestha S, Drews A, Sharma L, Pant S, Shrestha S, et al. (2018) Relationship between total serum immunoglobulin E levels, fractional exhaled breath nitric oxide levels and absolute blood eosinophil counts in atopic and non-atopic asthma: a controlled comparative study. *J Breath Res* 12: 026009.
- Al-Hilali HA, Atta MM (2016) Measurements of Some Asthma Markers (IgE, IFN $\gamma$ , IL-4 IL) by ELISA Technique and FOXP3 and IL-10 Expression in Asthmatic Patients. *Int J Curr Microbiol App Sci* 5: 903-909.
- Sherrill DL, Stein R, Halonen M, Holberg CJ, Wright A, et al. (1999) Total serum IgE and its association with asthma symptoms and allergic sensitization among children. *J Allergy Clin Immunol* 104: 28-36.
- De Amici M, Ciprandi G (2013) The age impact on serum total and allergen-specific IgE. *Allergy Asthma Immunol Res* 5: 170-174.
- Mediaty A, Neuber K (2005) Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. *Immun Ageing* 2: 9.
- Lokaj-Berisha V, Gacaferri-Lumezi B, Bejtullahu GM, Latifi-Pupovci H, Gjurgjeala NK, et al. (2014) Gender differences in Total Immunoglobulin E levels among allergic patients. *Open Access Maced J Med Sci* 3: 69-74.
- Davila I, Valero A, Entrenas L, Valveny N, Herráez L (2015) Relationship between serum total IgE and disease severity in patients with allergic asthma in Spain. *J Investig Allergol Clin Immunol* 25: 120-127.
- Sorensen RU, Sakali P (2006) Does parasitic infection protect against allergy? *Jornal de pediatria* 82: 241-242.
- Lynch NR, Palenque M, Hagel I, Diprisco MC (1997) Clinical improvement of asthma after anthelmintic treatment in a tropical situation. *Am J Respir Crit Care Med* 156: 50-54.
- Medeiros D, Silva AR, Rizzo JA, Motta ME, Oliveira FHBd, Sarinho ESC (2006) Total IgE level in respiratory allergy: study of patients at high risk for helminthic infection. *J Pediatr (Rio J)* 82: 255-259.

- 30 Wijaya H, Irsa L, Supriatmo S, Loebis S, Evalina R (2014) Total serum IgE levels in soil-transmitted helminth infected children with atopy symptoms. *Paediatrica Indonesiana* 54: 149-154.
- 31 Hawlader MD, Ma E, Noguchi E, Itoh M, Arifeen SE, et al. (2014) *Ascaris lumbricoides* infection as a risk factor for asthma and atopy in rural Bangladeshi children. *Trop Med Health* 42: 77-85.
- 32 Neves NMA, Britto GdSG, Veiga RV, Figueiredo CAV, Fiaccone RL, et al. (2014) Effects of helminth co-infections on atopy, asthma and cytokine production in children living in a poor urban area in Latin America. *BMC Res Notes* 7: 817.
- 33 Magbojos CR, Chua SO, Alegria CR, Macalalad FC, Malayba A, et al. (2016) Determination of geohelminthiasis and its association with allergic sensitization among selected children in Batangas, Philippines. *Glob J Health Sci* 9: 33-42.
- 34 Kusunoki T, Morimoto T, Sakuma M, Mukaida K, Yasumi T, et al. (2011) Total and low-density lipoprotein cholesterol levels are associated with atopy in schoolchildren. *J Pediatr* 158: 334-336.
- 35 Fessler MB, Jaramillo R, Crockett PW, Zeldin DC (2010) Relationship of serum cholesterol levels to atopy in the US population. *Allergy* 65: 859-864.
- 36 Robertson AK, Zhou X, Strandvik B, Hansson G (2004) Severe hypercholesterolaemia leads to strong Th2 responses to an exogenous antigen. *Scandinavian Journal of Immunology* 59: 285-293.
- 37 Fessler MB (2015) Regulation of adaptive immunity in health and disease by cholesterol metabolism. *Curr Allergy Asthma Rep* 15: 48.
- 38 Kumar RM, Pajanivel R, Koteeswaran G, Menon SK, Charles PM (2017) Correlation of total serum immunoglobulin E level, sputum, and peripheral eosinophil count in assessing the clinical severity in bronchial asthma. *Lung India* 34: 256.
- 39 Kovač K, Dodig S, Tješić-Drinković D, Raos M (2007) Correlation between asthma severity and serum IgE in asthmatic children sensitized to *Dermatophagoides pteronyssinus*. *Arch Med Res* 38: 99-105.
- 40 Moerloose KB, Pauwels RA, Joos GF (2005) Short-term cigarette smoke exposure enhances allergic airway inflammation in mice. *Am J Respir Crit Care Med* 172: 168-172.
- 41 Kim YS, Kim HY, Ahn HS, Sohn TS, Song JY, et al. (2017) The Association between Tobacco Smoke and Serum Immunoglobulin E Levels in Korean Adults. *Intern Med* 56: 2571-2577.
- 42 Kim DY, Kwon EY, Hong GU, Lee YS, Lee SH, et al. (2011) Cigarette smoke exacerbates mouse allergic asthma through Smad proteins expressed in mast cells. *Respiratory Res* 12: 49.