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Association of Arginase-1 Gene and Immunoglobulin E Levels with Asthma Severity in Erbil City Patients

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ABSTRACT

Background and Objectives: Asthma is a chronic respiratory disease that affects the airways and is a major health issue worldwide. We aimed to examine some of these factors.

Methods: The arginase-1 gene detected in 50 healthy individuals and 50 in the patients group. Then the level of arginase-1 enzyme examined by using Enzyme-linked immunosorbent assay (ELISA) and immunoglobulin E (IgE) by Cobas e 411.

Results: This study found substantial differences in arginase-1 and IgE means between controls and asthmatics. The severe group had the highest mean AGR1 2.35±0.45, whereas the control group had the lowest 0.52±0.27. The severe group had the greatest mean IgE 1285±518.6, whereas the control group had the lowest 53.27±30.45. The arginase gene was found in all participants, but BMI did not affect asthma severity.

Conclusions: ARG1 gene found in both patients and healthy people. ARG1 enzyme and IgE significantly associated with the severity of asthma in Erbil city.

Keyword: Asthma, arginase-1 gene, IgE, FEV1

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INTRODUCTION

Asthma is a chronic respiratory disease. It is a major worldwide health issue that affects individuals across all age groups.[1] There are approximately 300 million people all over the world who are impacted by this condition, and by 2025, an additional 100 million individuals may be affected.[2] There are several factors that influence the development of asthma. These factors include environmental elements, hereditary factors and immune factors.[3] The inflammation and narrowing of the airways recur frequently, resulting in excessive mucus production, wheezing, shortness of breath, and coughing.[4] The development of asthmatic symptoms is strongly correlated with allergen exposure. The major asthma risk factor is atopy, which is a predisposition to generate too much IgE antibodies upon contact with allergens.[5] A major factor in asthma pathophysiology is the interaction of several immunological components, including immunoglobulin E (IgE) and the enzyme arginase.1.[6] Immunoglobulin E is a type of antibody that is generated by B cells in reaction to allergens.[7] Which is encoded by genes situated on chromosome 12, particularly in the 12q23.2 locus.[8] It is usually linked with allergic reactions.[9] On mast cells and basophils, IgE attaches to high-affinity receptors (FcεRI), resulting in the production of inflammatory mediators including histamine, leukotrienes, and cytokines. Apart from causing bronchoconstriction, this rapid hypersensitive response worsens persistent airway inflammation.[10]

Arginase-1 is encoded by the ARG1 gene on chromosome 6 (6q23) in humans.11 with a molecular weight of approximately 37 kDa.[12] Its active site comprises a manganese ion, essential for its enzymatic function.[13] ARG1 expression is upregulated in response to Th2 cytokines, which play an important role in allergic responses and asthma.[14] It is often linked to M2 macrophage polarization, which is associated with tissue repair.[15] ARG1 enzyme plays an important role in the urea cycle. It is responsible for the conversion of arginine into ornithine and urea.[16] In addition, arginine is an essential substrate for the production of nitric oxide (NO) which is an essential component for the relaxation of the airways.18 Imbalances between both pathways are a contributing factor in asthma sufferers experiencing airway hyperresponsiveness (AHR).[17] Reduced NO generation and elevated airway responsiveness are linked to this overexpression of ARG1.[19]

There is a possibility that the interaction between IgE and arginase could suggest an important connection in the pathogenesis of asthma.[6]

This study aims to investigate the molecular association between the arginase 1 (ARG1) gene and Immunoglobulin E (IgE) levels in asthmatic patients, while assessing the expression levels of the ARG1 enzyme in asthmatics compared to healthy controls, and highlighting its correlation with IgE levels.

METHODS

Participants: This study comprised 50 asthma patients from the Department of Medicine at Rizgary Hospital, from 1st September, 2024, to 1st January, 2025. All patients diagnosed with asthma which confirmed by a pulmonary function test. Additionally, it comprised fifty age-matched healthy adults without respiratory complications, a family history of asthma, allergies, or any other conditions who were randomly recruited outside of a hospital.

All the participants' ages varied from 20 to over 60 years, which classified into five subgroups: 20 to 30, 31 to 40, 41 to 50, 51 to 60, and over 60. On the other hand, patients further classified into groups based on severity using spirometry under the Global Initiative for Chronic Obstructive Lung Disease.20 follows; those with Force Expiratory Volume in One Second (FEV1) ≥80% predicted designated as mild persistent; those with FEV1 between 60% and 79% predicted as moderate persistent; and those with FEV1< 60% predicted as severe persistent.

Sample collection: 10ml of blood collected from each participant, which divided into two 5ml portions. One portion is collected in a gel tube and the other one in an EDTA tube. The 5 ml of blood which collected in an EDTA tube used for DNA extraction of the ARG1 gene. And the 5 ml of blood which collected in a gel tube after centrifugation had serum separated from each patient and control group that used for measuring IgE by Cobas E 411 and examining the level of the ARG1 enzyme by Enzyme-Linked Immunosorbent Assay (ELISA).

DNA extraction and amplification by PCR: Genomic DNA extracted from peripheral blood leukocytes using the ADD BIO DNA Extraction Kit

(ADD BIO Inc., South Korea) according to the manufacturer's protocol. DNA purity and concentration assessed using a NanoDrop 1000 spectrophotometer (Thermo Scientific, UK), with acceptable A260/A280 absorbance ratios ranging between 1.7 and 2.0. An Applied Biosystems thermal cycler in a medical research center used to perform PCR. The reaction mixture (25 µL) contained 12 µL master mix, 3 µL of genomic DNA, 1 µL primer (forward), 1 µL primer (reverse), and 8 µL nuclease-free water. Thermal cycling conditions included: initial denaturation at 95°C for 4 minutes, 35 cycles of denaturation at 94°C for 45 seconds, annealing at 59.45°C for 45 seconds and extension at 72°C for 45 seconds, and final extension at 72°C for 7minutes. Forward primer: 5 TCAGGGGCATAGAGGTTGAC -3 and reverse primer: 5 TAC-CATGTGTCCGATGCAGT-3 used. The PCR product visualized on 2% agarose, and the gel stained with ethidium bromide dye.

Enzyme-linked immunosorbent assay (ELISA): ELISA (ELx800-BioTeK80, U.S.A.) conducted at the medical research center for all subjects to investigate the correlation between ARGI and bronchial asthma. 100 blood samples collected from people with and without asthma. Serum of the samples isolated for the purpose of conducting ELISA via the Human Arginase Assay Kit (ARG ELISA kit, SUNLONG, China). The standard diluted using tiny tubes, beginning with a concentration of 3.6 ng/ml and decreasing to 0.3 ng/ml. Subsequently, 50 µl from each tube pipetted into microplate wells, utilizing two wells per tube, resulting in a total of ten wells in the micro-ELISA strip plate, as well as a designated a blank control. 40 µL of sample dilution buffer and 10 µL of sample are added into the sample wells and next incubated for 30 minutes at 37 degrees Celsius. After washing five times, 50 µL of HRP-conjugate reagent applied to each well, excluding the blank, followed by incubation and another wash. We added 50 µL of chromogen solution A and 50 µL of chromogen solution B into each well for coloration, incubating at 37°C for 15 minutes, followed by the addition of 50 µL of stop solution to each well to terminate the reaction. Eventually, the absorbance optical density measured at 450 nm using a microtiter plate reader. Serum IgE: The human serum IgE tests conducted for 100 participants, which 50 patients and 50 controls, by the (Cobas® e 411 analyzers, Roche Switzerland) through the standard kit (Elecsys IgE II, REF 07027516190, USA) via the electrochemiluminescence (ECL) technology.

Exclusion criteria: This study excluded patients lacking certain information in their records, those with any kind of allergy, including eczema, and those with any type of chronic disease, such as diabetes or hypertension, as well as those with other infectious diseases and those vaccinated against coronavirus.

Questionnaire: Patients' demographic and clinical data collected using a two-part questionnaire based on related studies. The first portion asked patients about their age, gender, disease duration, and body mass index (BMI). The questionnaire's second section covered historical medical and clinical characteristics, smoking and family history. Ethical consideration: The Research Ethics Committee of Hawler Medical University College of Dentistry approved the study protocol (Reference number: HMUD/2425181, Date of Approval: 5/1/2025). Statistical analysis: IBM SPSS Statistics version 26 used for data analyses. the Kolmogorov–Smirnov test used for normality distribution. One-way ANOVA done for the comparison of group means of IgE and Arginase 1 enzyme, with the consideration of a p-value of ≤ 0.05 as statistically significant. Eventually, depending of the levinsin test the Bonferroni test used for ARG1 and IgE done for performing multiple comparisons test The chi-square test of association used to find the correlation between smoking states and the severity of asthma, and Fisher's exact test employed when the predicted count of more than 20% of the cells was fewer than 5.

RESULTS

Out of one hundred participants, which separated into two groups, fifty participants assigned to the control group, whereas fifty allocated to the asthma group.

The patient's group categorized into subgroups based on severity using lung function tests: mild, moderate and severe. As it is shown in the table 1

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Table 1. General information of the participants

Group	Control	Severity of Asthma		
		Mild	Moderate	Severe
Total No.	50 (100)	17 (34)	14 (28)	19 (38)
Gender Male / Female	19 (38) / 31(62)	6(12)/11(22)	4(8)/10(20)	9(18)/10(20)
Age:				
20 – 30	10	0	4	6
31 – 40	10	3	5	2
41 – 50	10	5	2	3
51- 60	10	6	1	3
> 60	10	3	2	5
Duration of disease;				
1 – 5	0.0	7	13	9
6 – 10	0.0	5	0.0	3
>10	0.0	5	1	7
Family history				
Yes	0.0	7	11	11
no	50	10	3	8
BMI mean / SD	30± 7.2	27.44±6.1	33.3 ± 7.4	28.2 ± 6.1

Among controls, female is higher than male. Also, between the asthmatic patients, the number of females, which was 31 individuals, affected by the disease was higher than males, distributed as follows: 11 was in the mild group, 10 was in the moderate group, and 10 was also in the severe group, and the number of male patients was 19 individuals, which distributed as follows: 9 was in the severe, followed by 6 in the mild and 4 in the moderate. As it is shown in the table (1).

All participants classified into 5 subgroups, 20-30 and over 60, as it is shown in table (1). For all the control groups, the number of participants was equal, which was 10, while in the asthmatic patients, it varied. The lowest number recorded for mild patients in the age of 20-30, which was 0, while the highest number of patient participants recorded in the age of 20-30 for severe groups and 51-60 for mild categories, which was 6.

Regarding the duration of the disease, many of the patients had the disease for up to 5 years. And only 8 patients had the disease for 6-10 years. As it is shown in the table (1).

According to the family history of the disease, all the control groups did not have any history of the disease. On the other hand, 29 (58%) of the patients have a family history with the disease. As it is seen in the table (1).

In terms of BMI, the means of the control and patients' groups were close to each other. The table (1) illustrates this clearly.

Table 2. The arginase-1 gene, serum arginase and IgE in asthma patients regarding the severity of asthma

Group	Control	Severity of asthma			P Value
		Mild	moderate	severe	
Arginase mean /SD	0.52± 0.27a	1.21±0.3 b	1.55±0.3c	2.35±0.45d	0.001
IgE mean / SD	53.27±30.45ab	62.2±28.6ba	325.1±143.2c	1285±518.6d	0.001
The mean difference is significant at the 0.05 level (2-tailed) Combined letter: Means no-significant differences between groups					

The mean level of arginase 1 enzyme of the control and asthmatic patients' groups were significantly different from each other (p = 0.001). By increasing the severity of asthma, the mean of the arginase enzyme increased, as is shown in table (2). The highest mean of *AGR1* observed in the severe group, which was 2.35±0.45, while the lowest *AGR1* observed in the control group, which was 0.52±0.27.

A notable disparity detected in mean IgE levels between asthmatic individuals and controls. As the severity of asthma rises, the mean IgE levels correspondingly increase as demonstrated in table (2). Although there were statistically significant differences between all the groups (p = 0.001), but depending on the post hoc test, there is not significant differences only between the control and mild groups. The highest mean of IgE observed in the severe group which had the highest mean IgE of 1285±518.6, whereas the control group displayed the lowest IgE level at 53.27±30.45. As seen in table (2).

Table 3. severity of asthma regarding smoker habits

Group	Control	Asthma		
		Mild	Moderate	Severe
Current Smoker	15(30)	3(6)	2(4)	2(4)
Former smoker	3(6)	1(2)	3(6)	5(10)
Non smoker	32(64)	13(26)	9(18)	12(24)
P value				0.59

In this study of the smoking status among controls and patients, it has been found out that there is not a significant correlation between smoking status and severity of asthma. As it is shown in the table (3). Most of the control group were not smokers (n=32), and 34(68) patients were also non-smokers.

According to Fig.1 and table. 4, in each group of asthma (severe, moderate and mild) all patients selected with 50 healthy individuals, PCR (polymerase chain reaction) At a voltage of 99 volts for forty-five minutes, DNA samples electrophoresed on a 2% agarose gel that stained with ethidium bromide. All the samples scored as positive for arginase-1 that correspond to the fragment size that predicted to be 223 base pairs.

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Table 4. ARG1 gene detection among all participants

Group	Control	Severity of asthma		
		Mild	moderate	severe
ARG1 detection	50 (100%)	17 (100%)	14 (100%)	19 (100%)

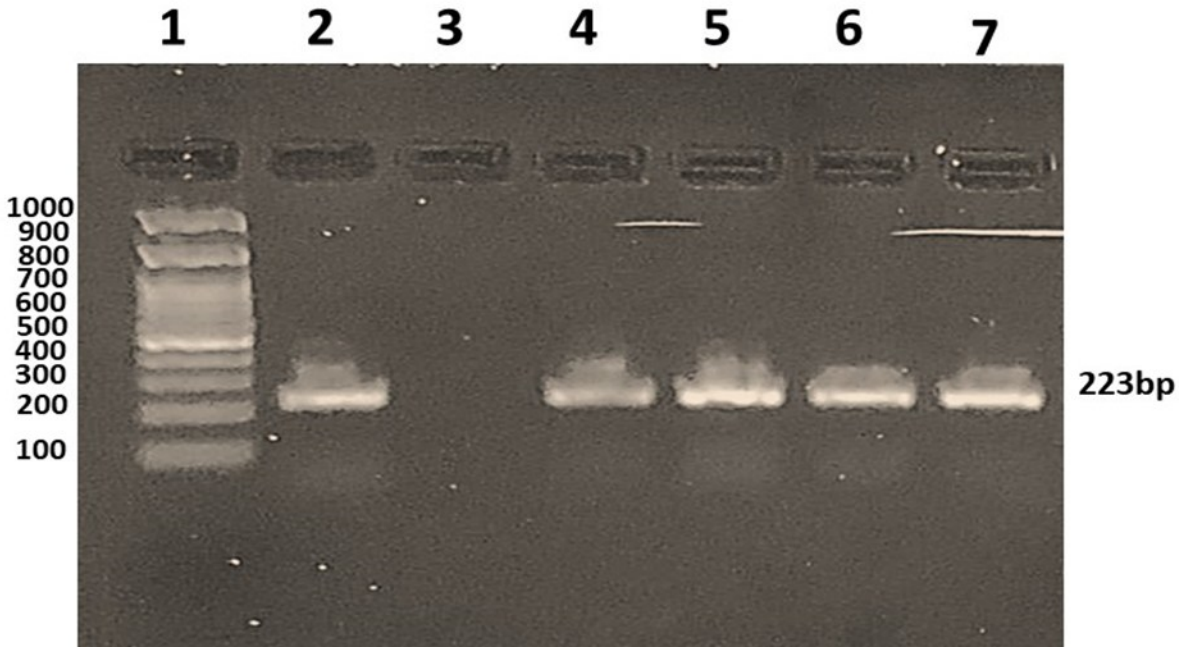

Figure 1. PCR amplification of the arginase-1 gene in asthma patients

DISCUSSION

Blood samples obtained from 50 asthma patients and 50 normal persons. The asthmatic patients classified into three subgroups depending on FEV1: severe, moderate and mild. In addition, it is further classified based on age into 5 groups. The ARG 1 gene detected by PCR, and the level of serum arginase 1 enzyme examined by using ELISA and IgE by Cobas e 411. On the other hand, a questionnaire form filled out by all participants, in which any type of chronic disease or allergy excluded.

In this study, the participants ranged in age from 20 to over 60 years; the age group of 31-50 had the highest patient number, which closed to the study of Anupama et al [21], in which the highest patient number was 46 % for 31-45.

The patients subgrouped based on severity using a lung function test(spirometry) according to the GINA guidelines. Those having FEV1 ≥80% labelled as mild, 60-79 as moderate and <60 as severe, which was similar to the study by donthi et al.[22] In this study 19 patients were severe, 14 were moderate and 17 were mild , while in the Anupama et al,[21] 52 patients were severe, 44 patients were moderate and 36 were mild. This difference is largely due to the sample size, because the sample size of this study is 50 patients, but the sample size of the Anupama et al study [21] is 132 patients.

The current study shows a higher incidence of bronchial asthma in females compared to males, consistent with the results of kole et al study, senna et al and Hansen et al study.[23-25] This higher frequency and severity of asthma in females are multifaceted, including some specific female hormones which demonstrated in the studies of cephus et al which conducted at 2017 and han et al

conducted at 2020,[26, 27] Testosterone hormone can suppress the activity of group 2 innate lymphoid cells (ILC2s), which associated with airway inflammation. This suppression may lead to a reduction in asthma symptoms among men as demonstrated in another study of cephus et al which conducted at 2017.[28] In addition, based on anatomy, they have smaller lungs and tighter airways than men, which can lead to more asthma symptoms and more airway resistance as presented in both mokra et al investigation at 2023 as well as in dominelli et al at 2018.[29, 30] On the other hands, environmental and socioeconomic factors have important role in increasing asthma symptoms among women, because women may be more exposed to indoor allergens like dust mites and bleach such is investigated by the chittleborough et al study.[31]

Regarding the duration of disease of this study, only 29(58%) patients had bronchial asthma for 1-5 year, 8(16%) patients for 6-10 years and 13 (26%) patients for more than 10 years, but in Anupama study which conducted at 2006,[21] 39 (29.5%) patients had it for 1-5 years, followed by 26 (19.6%) and 64(48%) respectively.

Among 50 asthma patients in our study, 29(58%) have a familial history of the condition, surpassing those without such a history. Conversely, in the study of mohammad et al,[32] 61% of patients lack a familial history, exceeding those with a familial history.

Numerous studies indicate that the BMI correlates with increased severity of asthma , diminished control, and reduced quality of life as demonstrated in the study of maalej et al,[33] but in this current study the mean BMI of the controls and patients' group closed to each other and did correlate with the severity of asthma.

This study assessed the serum arginase 1 enzyme levels utilizing ELISA, as conducted in the investigation by Mohammad et al.,[3] while Lara et al.,[34] tested arginase levels via radiometric assay. The IgE levels in this investigation were quantified using the cobas E 411, analogous to the methodology employed by Torres et al.,[35] in contrast, the studies conducted by (al-Saimary and mezban),[36, 37] utilized ELISA for serum IgE measurement.

Individuals with asthma in this study demonstrated markedly elevated arginase enzyme activity and IgE levels relative to healthy controls. Individuals afflicted with severe chronic asthma exhibited the highest arginase activity and IgE level, suggesting a significant correlation between arginase activity and IgE with disease severity, such as the study of donthi et al which conducted at 2018.[38] On the other hand, in the donthi et al study, some elevation of IgE level in the control group is observed which may due to a parasite or other type of infection. But in our investigation, all healthy individuals with diseases or any type of allergies removed. Consequently, these findings indicate that healthy individuals exhibit low IgE levels. In addition, people with more severe asthma have higher elevated level of arginase-1, while those without any disease had normal level of ARG1. In this study 100 samples of arginase genes detected and although SNP analysis for the ARG1 gene did not conduct in this study, it is recommended as a potential direction for future research to help understand the genetic factors that influence arginase activity levels in asthma as in the study of Donthi et al.[22] Because Studies have identified single nucleotide polymorphisms (SNPs) in the ARG1 gene that may be associated with asthma susceptibility and severity. Specific changes are linked to increased arginase activity, which related with asthma phenotypes characterized by airway inflammation and hyperresponsiveness.[39] This study revealed that there is no significant association between smoking status and asthma severity among the control and patient groups, which was similar to ali study.[40]

Many potentially confusing factors were taken into account when choosing participants, such as excluding viral infection, long-term illness, allergies, or COVID-19 vaccination. However, unmeasured factors like environmental allergens or medication use may have altered the results. Because each group had 50 persons, the results may not be very statistically strong. The cross-sectional design also makes it harder to draw conclusions about causes. To validate and expand these findings, longitudinal studies involving larger and more diverse populations are necessary.

CONCLUSIONS

Asthma is a chronic bronchitis disease that affects all age groups. In this study, the level of arginase-1 and IgE were significantly associated with the severity of asthma. The highest mean of both markers observed in the severe group, and the lowest observed in the control group. And all samples of the arginase-1 gene were detected by using PCR. Regarding the duration of the disease, the

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majority of the patients had the disease for up to 5 years. Moreover, the BMI did not have an association with asthmatic severity in Erbil city.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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Legend to table (1): General information of the participants. The table displays demographic information (gender and age), disease duration, family history, and Body Mass Index (BMI) in control subjects and asthma patients, classified as having mild, moderate, or severe asthma according to pulmonary function tests (FEV1). The data for BMI are presented as mean ± standard deviation (SD). Age is classified into five categories: 20–30, 31–40, 41–50, 51–60, and over 60 years, while disease duration is indicated in years after the diagnosis of asthma.This study included 50 asthma patients and 50 control subjects.

Legend to table (2): The arginase-1gene, serum arginase-1 and IgE in asthma patients regarding the severity of asthma. This table compares the mean serum levels of arginase-1 and IgE ± SEM among patients with mild intermittent, moderate persistent, and severe persistent asthma. A notable elevation in arginase-1 and IgE levels was detected in severe persistent groups relative to the mild and moderate group. The Combined letter Means no-significant differences between groups (abcd), and the Statistical significance is denoted as follows: $p < 0.05$.

Legend to able (3): Severity of asthma regarding smoker habits. This table compares the mean serum smoking status ± SEM between the control group and patients with mild, moderate, and severe chronic asthma. No significant association was discovered between the control group and the patient group. Statistical significance is denoted as follows: $p < 0.59$.

Legend to table (4): ARG1 gene detection among all participants. This table displays gene detection rates among patients (mild , moderate, severe) asthma and control groups.

Legend to figure (1): PCR amplification of the arginase-1 gene in asthma patients. DNA samples were electrophoresed on a 2% agarose gel, stained with ethidium bromide, at 99 V for 45 minutes. Lane 1 displays the DNA ladder ranging from 100 to 1000 base pair displays molecular size reference; lane 2 is positive control lane which has a known DNA template and shows a clear band at 223bp; lane 3 displays negative control lanes which contain a sample that is not produce a band, it is PCR reaction mix contain water instead template DNA. Lanes 4 and 5 denote healthy individuals with clear amplification bands at 223bp, while lanes 6 and 7 correspond to asthma patients DNA samples analyzed for the presence of the arginase gene. The detected bands match with the anticipated fragment size of 223 bp.

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