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Identifying the Association of Advanced Glycation End – Product with Asthma in the Iraqi Kurdish Population

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Abstract

Asthma is a chronic inflammatory disease of the lungs that could strike people of any age. Wheezing, coughing, chest tightness, and shortness of breath are all common side effects. Smooth muscle contractions across the airways cause chronic inflammation and occlusion, narrowing the airway and plugging it with thick mucus.Advanced glycation end products (AGEs) are formed when aldoses interact with proteins, causing molecular rearrangements of the covalently related sugars, resulting in a large community of yellow-brown fluorescent compounds.Seventy asthmatic patients who were already diagnosed previously by physicians and were considered to be suffering fromasthma and 20 healthy controlling were included. In patients and controllinggroup, laboratory examination was conductedfor IgE and C-reactive protein (CRP) by using Cobas Integra analyser. While serum AGEs and IL-4 level were measured using ELISA kit. Serum CRP levels (Mean±SE= 15.21±0.92) in patients with asthma were greater when comparison toset ofcontrolling(Mean±SE= 2.3570 ± 0.38936 mg/dl), with highly significant difference (P-valueless than 0.01). The serum level of IL-4 in asthmatic patients and (Mean±SE=8.8171 ± 0.26306 pg/ml)wasgreater than the controllingset (Mean±SE=0.0586 ± 0.00231 pg/ml) withhighly significant differences between them (P-value less than0.05). The (mean ± SE) of IgE in the sera of asthma was (508.6343± 70.02653 ng/ml) while the (mean ± SE) of controllingsets was (170.2688 ± 58.49945 ng/ml) with highly significant differences (P-valueless than 0.01). The (mean ± SE) of AGEs in the sera of patients with asthma was (5610.5714 ± 139.28093 ng/dl) while (the mean ± SE) AGEs in the sera of controllingsets was (463.3000 ± 52.95609 ng/dl) with highly significant difference (P-valueless than 0.01). There is ahighly significant correlation found between AGEs and IL-4, CRP among Asthmatic patients (P-valueless than 0.01),wherethere was no correlation found between AGE and IgE (P-value greater than 0.05). The existing investigation revealed a great serum level of AGEs in asthmatic patients compared to the healthy controlling set and a significant correlation found between CRP, IL-4, IgE with Asthma and that the AGEs could be a causative agent for asthma.

Keywords: Asthma, advanced glycation end products,IL-4.

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Introduction

A chronic inflammatory condition of the airways refersto Asthma that could affect people of all ages. It causes coughing, chest tightness, wheezing, and shortness of breath. Smooth muscle contractions around airways cause persistent inflammation and obstruction, shrinking the airway and plugging it with thick mucus (Mahdi et al. 2018).

Asthma is a widespread and potentially life-threatening disease that affects an estimated 3 hundred million people of any age worldwide, accounting for 1–18% of the people in various countries. Itis the most prevalent in economically developed countries, but it is also increasing in low- and middle-income countries (Nunes et al. 2017). Patients, their families and neighbourhoods, in addition to health economies, are all affected.(Holgate and Thomas 2017).

It is a complicated disease with several genes and molecular mechanisms; disease susceptibility comesfrom genetic factors, but environmental exposures and interactions between these components modulate disease manifestation (Meng and Rosenwasser, 2010).For example, Immunoglobulin E (IgE) antibodies, eosinophils and Th-2-derived cytokines, are all known to contribute in the progression of chronic respiratory disease, which could be seen amild disease in patients (Pelaia et al. 2018).

Inflammation of the airways is a key factor in the progress of bronchial asthma. That linked to increased airway sensitivity to a variety of triggers, including aeroallergens, could cause bronchoconstriction in atopic patients with asthma, and may work in tandem with other triggers including viruses and pollutants. (D'Amato *et al.*,2016).

The pathogenesis of allergic asthma is complicated by IgE levels of common environmental allergens whichare elevated in the bloodstream.IgE antibodies also induce chronic bronchial inflammation by activating effector cells including basophils and mast cells stimulatedby low-affinity (FcRII) IgE receptors or great-affinity (FcRI). (Froidure *et al.*, 2016).

Th2 lymphocytes, mast cells, and eosinophils infiltrate the region, causing inflammation. Furthermore, Th2 lymphocytes produce cytokines that are crucial in orchestrating inflammatory responses. (Davoine and Lacy 2014). Furthermore, Th17 lymphocytes were linked to the pathogenesis of asthma.(Murdaca *et al.*, 2011).

AGEs are created by interacting aldoses with subsequent molecular rearrangements of the covalently linked sugars and proteins, resulting in a diverse collection of yellow-brown fluorescent compounds(Radhakrishnan, 2021). The heterogeneous kind of lipids or non-enzymatically glycated proteins is discovered in the accumulates and plasma in the tissues even normally and vessel wall (Senatus and

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Schmidt, 2017) . AGEs are indeed a heterogeneous andcomplex group of compounds that are primarily produced by the Maillard reaction. When reducing sugar,interacts non-enzymatically with amino acids in DNA, proteins or lipids the Maillard reaction occurs. (Luevano-Contreras and Chapman-Novakofski., 2010).

One of the significant pathways suggested for the pathogenesis is AGEsthrough Non-Enzymatic Glycation (Singh, 2014). Non-enzymatic glycation (NEG) is how reducing sugars are included in irreversibly modifying free amino sets of proteins by several events, which ultimatelycause the formation of a Schiff base resulting in Amadori products andculminating into AGEs (Parwani and Mandal, 2017). The synthesis of accumulation in the body and AGEs is a natural processes throughout aging (Roorda, 2017).

Aim

The aim of the study isto evaluate the serum grade of AGE in the patient of asthmatic whencomparedto the controlling subject.Furthermore,measurements of Immunoglobulin-E (IgE), Interleukin-4 (IL-4), C-reactive protein (CRP) levels in asthmatic patients are compared to controlling subjects.

Material and Methods

The existing investigation participants consisted of 70 patients (29 males and 41 females) who were already diagnosed with asthma, and all attended the respiratory centre inRezgari Teaching Hospital in Erbil city. The age ofall participators was between (15-75) years. All patients subjected to personal interviews were through a specially designed questionnaire form. Verbal consent was taken from all participants before participation, and the questionnaire form was filled up by a direct interview with the patients, which included a complete medical history. Patients with other types of autoimmune disease like ankylosing spondylitis and psoriatic arthritis were excluded. While the controllingset consisted of 20 individuals (6 males and 15 females), their ages ranged between (15 – 65) years. The controllingset wasselected after confirming they had not any clinical signs of asthma. After precise inspection, each of the controlling subjects was selected with nohistory of clinical evidence for any acute or chronic disease and inflammatory or autoimmune diseases. All procedures were per the established ethical standards.

Specimen Collection

Venous blood specimens (8 ml) were collectedby using a disposable syringe from all the subjects following standard procedure. Five ml of the collected blood specimenweretransferred into a vacuum gel tube and serum was obtained after 30 minutes at room temperature and 15 minutes centrifugation at 3000 rpm. The sera were

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dispensed into four labelledsterile Eppendorf tubes and stored at -80ºC to perform IgE, IL-4, CRP, and AGEs concentration tests.

Methods

Sera were prepared to estimate human AGEskit of ELISA (Catalog No: CEB353Ge), an in vitro assay used forAGEs in human serum are measured quantitatively. The Diaclone Human IL-4 kit of ELISA is a solid-phase sandwich ELISA (Catalog No: 950.020.096)is aquantitative determination of IL-4 and in-vitro qualitative in supernatants in serum. While, for Quantitative determination (IgE and CRP), Cobas E411 and Cobas Integra immunoassay analyserisin accordance with the manufacturer's recommendations determining levels of serum (IgE, CRP) turbidimetrically by used commercial kits from the company (Roche Diagnostics, GmbH). The normal range of each test in the existing investigation according to (Roche Diagnostics, GmbH) company was thatIgE≤ 200 ng/ml, CRP ≤ 5 mg/dL, and IL-4 ≤ 0.7 pg/ml.

Ethical consideration

The investigationprotocol was submitted to the ethics committee of the Health Technical College of Erbil Polytechnic University, and official acceptance was obtained from Erbil Directorate of Health and Rezgari Teaching Hospital in Erbil city. Throughout the interview of the participants, details of the investigation, its importance, and keeping the anonymity of respondents wereexplained verbally to the participants and the information kept by the researchers and no names mentioned and only codes used. All the participants were given the right to participate in the investigation and possibly consult others before giving verbal consent.

Statistical analysis

Findings demonstratedin this investigation are in the form of means and standard error. The Graph Pad Prism software was used to conduct the statistical analysis. If the values were (p less than 0.05) and weresignificantly important, the differences were considered statistically highly significant when (p-value less than 0.01).

Results

The finding of the existing investigation revealed thatthere were no significant differences (P-valuegreater than 0.05) in the age (mean ± SE) years between asthmatic patients and controllingset. While,an incidence of asthma inwomen, in both sets (asthmatic and controllingsets),was greaterthan that in male with significant differences (P-valueless than 0.05). Furthermore, the greatest percentage of asthmatic patients and the controllingset were from the centre (the city) with non-significant differences (P valuegreater than 0.05). When it comes to family history, asthmatic patients have a

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greater ratio of positive relatives than non-asthmatics, with a highly significant difference. (P-valueless than0.01) (Table 1).

Table (1) Baseline characteristics among asthmatic patients and controlling

Characteristics	Asthmatic patients No. 70	Controlling No. 20	P value
Age /years(mean±SE)	34.4±2.99	32.5±3.81	0.61
Gender No.(%) Male Female	 29 (41.4%) 41 (58.6%)	 6 (30%) 14 (70%)	0.02*
Residency No(%) Centre Surrounding	 51(72.9%) 19 (27.1%)	 15 (75%) 5 (25%)	0.6
Family history No(%) Yes No	 41(58.57%) 29(41.43%)	 4(20%) 16(80%)	0.001**
P value greater than 0.05: Non-significant, * Pvalue less than0.05 : Significant, ** P value less than0.01: Highly Significant			

Comparison of immunological factors between asthmatic patients and controllingsets:

Table (2) comparison of immunological factors between the asthmatic patients and controlling sets.

Factors	Number	Mean	Std.Error Mean	P -value
CRP controlling	20	2.3570	.38936	0.00008 **
CRP patients	70	8.3171	.26306	
IL4controlling	20	.0586	.00231	0.00007 **
IL4patients	70	8.8171	.26306	
IgEcontrolling	20	170.2688	58.49945	0.009 **
IgE patients	70	508.6343	70.02653	
Glycation of	20	463.3000	52.95609	

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controlling				0.0001**
Glycation of patients	70	5610.5714	139.28093	
P valuegreater than 0.05: Non-significant, * P less than 0.05: Significant, ** P less than 0.01: Highly Significant				

Table (2) shows certain immunological factors linked to asthma pathogenesis.

Thefindings shows that the two sets were comparable (asthmatic and controllingsets), C-reactive protein (CRP mg/dl), Immunoglobulin E (IgE ng/ml) and Interleukin-4 (IL-4 pg/ml). Furthermore,levels of AGEs ng/dl were greater in asthmatic patients than non-asthmatic ones. The findings of this investigation indicated significantly greater serum CRP concentration in patients with asthma in which the (mean± SE)of CRP was (8.3171± 0.26306 mg/dl) and greater than healthy controllingin which its (mean ± SE) was (2.3570 ± 0.38936 mg/dl) with highly significant difference (P-valueless than 0.01). Statistical analysis showsthat greater serum IL4 pg/mlconcentration in patients with asthma in which the (mean ± SE)was (8.8171 ± 0.26306 pg/ml) while the (mean ± SE)of healthy controlling was (0.0586 ± 0.00231pg/ml) with highly significance difference (P. valueless than 0.01). In addition, there are highly significant differences in the (mean ± SE) in the concentration of (IgE ng/ml) between asthmatic patients when compared to controllingsets (P. valueless than 0.01). The (mean ± SE) ofIgE in the sera of patients who haveasthma was (508.6343± 70.02653 ng/ml) while the (mean ± SE) of controllingsets was (170.2688 ± 58.49945 ng/ml). The finding of statistical analysisdemonstrates that there are highly significant differences in the (mean ± SE) in the concentration of (AGEs ng/dl) between Asthmatic patients compared to controlling sets (p-valueless than 0.01). The (mean ± SE) of AGEs in the sera of patients with asthma was (5610.5714 ± 139.28093 ng/dl) while (the mean ± SE) AGEs in the sera of controllingsets was (463.3000 ± 52.95609 ng/dl).

Correlation between AGEs level and other parameters among asthmatic patients

Figures 1 and 2 interpret the Pearson correlation between AGEs and IL-4, CRP among Asthmatic patients. There is a highly significant correlation found between them (P-valueless than 0.01), whereas in Fig3,there is no correlation found between AGE and IgE with no significant difference (P-valuegreater than 0.05).

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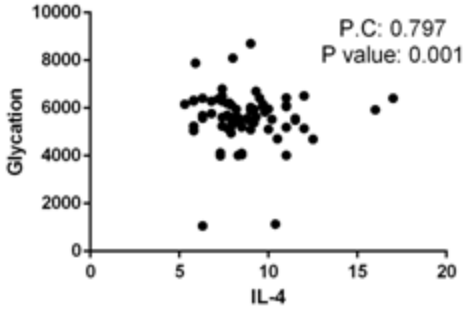

Fig. 1: Correlation between AGEs & IL-4

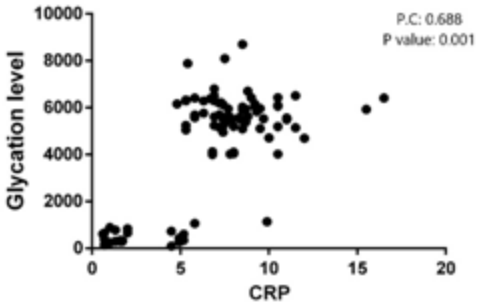

Fig. 2: Correlation between AGEs & CRP

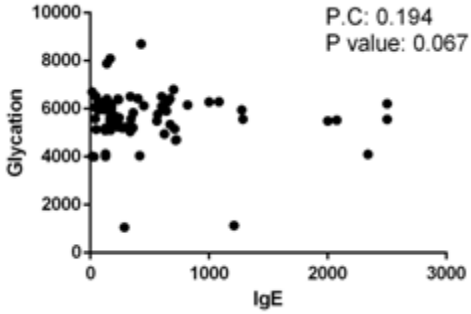

Fig. 3: Correlation betweenAGEs&IgE

Discussion

Hippocrates, an old Greek physician, was the first to describe asthma, which is derived from the Greek word asthma, which means gasping or panting. (Kaufman, 2011). Asthma is a severe public health problem throughout the world, affecting people of all ages,when losing controlling, asthma could severely limit daily life and is sometimes fatal (Li et al. 2018).

Asthma results from a dynamic relationship between a patient's immune system, the environment, and their underlying genetics, it is becoming increasingly clear. (Ayakannu *et al.*, 2019).

In the existing investigation, the mean age of patients was (34.4±2.9)years with no significant differences with thecontrollingset(P-value less than 0.05). Within adult population of asthma, the age of onset of asthma may have an effect on clinical and inflammatory variables. (Chaudhuri et al. 2016).Similar to investigation done by (Abdullah 2020) found that the (36.5 ± 1.8) and another investigation show mean±SE of the age of the patients with asthma were(36.7±2.5) years (Mediaty and Neuber, 2005) while, another investigation done by (Little et al. 2000) (mean ± SE) age of asthmatic patients was (48.6 ± 12.2) years which greater than this finding.Childhood asthma have been identified a variety of risk factors, in addition to a broad range of contributing factors for the development of adult-onset asthma (Lajunen et al. 2013). Genetic

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influences, occupational exposure to wheat flour and cleaning materials, air pollution, and cigarette smoke exposure are all examples. (Polosa et al. 2008). Respiratory infections, Nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity (Wöhrl 2018), female sex hormones, stress and obesity (Rod et al. 2012). Within the general adult asthma population, the age of onset of asthma may have an effect on clinical and inflammatory variables (Chaudhuri et al. 2016).

Concerning gender, the incidence of asthma seems to be more common in female than male. Accordingto many reports, adult-onset asthma is extra prevalent in females and associated with additional persistent a poorer prognosis and airflow obstruction. In asthma,itis more common in boys than girls, but more common in women than men. In recent decades, adolescent gender transitions have become more common, and asthma has become more common in people of all ages. It is linked to Western lifestyles, and as societies follow these lifestyles and become more urbanized, its prevalence rises(de Nijs et al. 2013).

The greatest percentage of asthmatic patients were from thecentre (the city), and this was in agreement withtheinvestigation done by (Abdullah 2020), who revealed the same finding. Thisfinding may be explained by exposure to contaminants in the environment(Busse, 2000andVon Ehrenstein *et al*., 2000)especially when increasing exposure to domestic allergens such as house dust mites, livestock, plants, and chemical agents in the domestic climate, in addition to changes in lifestyle and construction. This may clarify how particular microbial exposure, either by ingestion or inhalation, could alter immune development in a non-atopic manner (Hulin et al. 2012).

The familyhistory will assist doctors in distinguishing between infants whose wheezing is the product of a viral infection and infants whose wheezing is indicative of the development of chronic asthma in the future. Inthis investigation, the greater percentage of the asthmatic patient gave positive family history of asthma as a finding, to help minimize great-risk infants' sensitivity to asthma-triggering environmental causes.The impact of heredity on the risk of developing asthma decreased with age,but remained substantial even at older ages, and the impact of heredity increased over time when both parents had asthma, suggesting strong gene-environment interactions (Davoodi et al. 2015).

This investigation found that serum CRP in Asthma patients is greater than in normal controlling, which is consistent with a previous investigation, serum CRP measurement could help predict asthma controlling and treatment response(Monadi et al. 2016). C-reactive protein (CRP) is a highly responsive marker of infection, inflammation, and tissue damage , which activates complement pathways to aid in the host's defence against infection(Sproston and Ashworth 2018).

The existing investigation revealsa great level of IL-4 and IgE in asthmatic patients in comparison to thecontrollingset. The extreme rise of (IgE) induced by (IL-4)

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was identified as one of the pathogenesis of asthma, implying that (IL-4) may indirectly cause asthma(Munitz et al. 2008). The pathogenesis of asthma has piqued researchers' interest in recent years, and it is widely recognized, which a cytokine network imbalance has a significant function in the disease (Movahedi et al. 2008). A potent activator of inflammatory responses is Interleukin-4 (IL-4), which considered like the central T-Helper-2 (Th2) cytokine of the immune system and has a significant functiona major role in fibrosis throughout (Th2) inflammation (Luzina et al. 2012). Furthermore, itwasdemonstratedthat (Th2) in asthma patients is overactive, resulting in an increase inimmunoglobulin E (IgE) and (IL-4), which stimulates the activation and proliferation of eosinophilic granulocytesfollowed by the secretion of various inflammatory mediators, causing a bronchial chronic inflammation and asthma. (Murdoch and Lloyd 2010).

AGEs have long beenseen as potentially toxic molecules that facilitate hostcelldeath and cause human organ damage(Byun et al. 2017).The existing investigationdemonstrates increases in the serum concentration of AGEs of asthmatic patients when compared to a controllingset, and this is in agreement with theinvestigation done by(Brandt and Lewkowich 2019) who found that RAGE was implicated in lung development and in the pathogenesis of chronic lung diseases ranging from cystic fibrosis to asthma T lymphocytes, B lymphocytes, and macrophages have all been demonstratedto express elevated levels of the receptor of glycation end products (RAGE), which was related to immune cell activity in addition to inflammatory responses.(Ramasamy et al. 2008). Since (RAGE) activation by its ligands wasdemonstrated to participate in the early events that finally initiate T-helper 1 (Th1) differentiation. (RAGE) expressed on T cells is associated with this cell type differentiation. (RAGE) expressed on T cells has a significant function in the antigen-activated proliferative response.(Chen et al. 2008). Findings done by(Zhou *et al.*,2012)in asthmatic patients, there were positive associations between (RAGE) levels and the number of neutrophils.Advanced glycation end products (AGEs) are a heterogeneous kind of compounds reported to play a pathogenic role in developing and progressing chronic diseases (Perkins et al. 2020).

C-reactive protein reduces endothelial nitric oxide synthase (eNOS) expression and activity by increasing the expression of cell adhesion molecules (CAMs), chemokines, endothelin-1, and the receptor for advanced glycation end products (RAGE). (Abe et al. 2006).Findings doneby(Mahajan *et al.*, 2010) demonstrated thereceptor for advanced glycation end products (RAGE) might play an essential role in inflammatory processes and endothelial activation.The role of C-reactive protein (CRP) as a mediator in inflammation and atherosclerosis is the subject of recent investigations worldwide. The increased expression of (RAGE) in the presence of (CRP) supports the theory that (RAGE) is included in one of the mechanisms that could explain its function in a variety

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of diseases characterized by underlying inflammation. According to a single investigationby(Zhong *et al.*, 2006).

A similar investigation wasdone by (Milutinovic et al. 2012)to the existing investigation that found a non -significant relation between RAGE and IgE in asthmatic patients. However, another investigation done by (Liska et al. 2016)found that AGEs cause increased oxidative stress and an increased probability of allergy and asthma in a child´s future and therefore proposed that such children should be followed to lower AGEs and IgE throughout life.

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