Sumer Journal for Pure Science (ISSN: 2790-7031)
SJPS 2026 (June), Vol. 5, No. 1, p.p.: 203-209

Evaluation of Serum Levels of Beta-2 Adrenergic Receptor Gene ADRB2 in Asthmatic Patients

Athraa Khalil [*1] and Intisar Hussein Ahmed[2]

[1, 2] *Department of Biology, College of Education for Pure Science, University of Wasit –Iraq*

Std.2024205.a.mutshar@uowasit.edu.iq

07726528290

Abstract

Asthma is a chronic inflammatory airway disease characterized by reversible airflow obstruction, bronchial hyperresponsiveness, and variable respiratory symptoms. The current study aims to evaluate serum levels of Beta-2 adrenergic receptor gene ADRB2 in asthmatic patients. This case–control study was conducted in Wasit Province, Iraq, with participants recruited from several private clinics across different areas of Kut Governorate, Wasit Province, Iraq. A total of 80 individuals were included, comprising 45 asthmatic patients and 35 apparently healthy controls. The mean age of patients was (38.44 ± 11.02) years, while controls had a mean age of (36.71 ± 10.15) years, with a balanced distribution of males and females in both groups. The results showed that serum ADRB2 levels were significantly lower in asthmatic patients (1.172 ± 0.060 ng/ml) compared to controls (1.483 ± 0.093 ng/ml) (P = 0.005). This reduction was not genotype-dependent but was more pronounced in male patients (P = 0.004), while no significant difference was observed in females (P = 0.151). In conclusion, the greater reduction of serum ADRB2 in male patients implies that gender-specific physiological or hormonal factors can modulate receptor expression and may contribute to differential disease manifestations.

Keywords: Asthma, ADRB2 gene, β2-adrenergic receptor, ELISA, Pharmacogenetics.

تقييم مستويات مستقبل الأدرينالين بيتا−2 (ADRB2) في مصل الدم لدى مرضى الربو

عذراء خليل[*1] ، انتصار حسين احمد [2]

[2،1] قسم علوم الحياة, كلية التربية للعلوم الصرفة , جامعة واسط, واسط, العراق

الخلاصة

الربو هو مرض التهابي مزمن في مجرى الهواء يتميز بوجود انسداد عكوس في تدفق الهواء، وفرط استجابة القصبات الهوائية، وتنوع في الأعراض التنفسية.تهدف الدراسة الحالية إلى تقييم مستويات مستقبل بيتا-2 الأدرينالي (ADRB2) في مصل المرضى المصابين بالربو.أُجريت هذه الدراسة من نوع حالات–شواهد (Case–Control)في محافظة واسط، العراق، حيث تم تجنيد المشاركين من عدة عيادات خاصة في مناطق مختلفة من قضاء الكوت، محافظة واسط، العراق. شملت الدراسة ما مجموعه 80فردًا، منهم 45مريضًا بالربو و 35فردًا سليمًا ظاهريًا مجموعة سيطرة .بلغ متوسط عمر المرضى (38.44 ± 11.02) سنة، بينما بلغ متوسط عمر مجموعة السيطرة (36.71 ± 10.15) سنة، مع توزيع متوازن للذكور والإناث في كلا المجموعتين.أظهرت النتائج أن مستويات مستقبل ADRB2 في المصل كانت أقل بشكل معنوي لدى مرضى الربو (1.172 ± 0.060 نانوغرام/مل) مقارنةً بمجموعة السيطرة (1.483 ± 0.093 نانوغرام/مل = P) (.(0.005ولم تكن هذه الانخفاضات معتمدة على النمط الجيني، إلا أنها كانت أوضح لدى الذكور = P) (0.004، في حين لم يُلاحظ فرق معنوي لدى الإناث(P = 0.151) .في الختام، يشير الانخفاض الأكبر في مستويات ADRB2 لدى المرضى الذكور إلى أن العوامل الفسيولوجية أو الهرمونية المرتبطة بالجنس قد تلعب دورًا في تنظيم تعبير المستقبل، وقد تسهم في اختلافات في مظاهر المرض بين الجنسين.

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by reversible airflow obstruction, bronchial hyperresponsiveness, and variable respiratory symptoms. It remains a major global health burden affecting millions of individuals across all age groups [1]. This variability in drug response has been increasingly attributed to genetic factors, highlighting the importance of pharmacogenomics in asthma management. Among the most extensively studied candidate genes is the β2-adrenergic receptor gene (ADRB2), which is located on chromosome 5q31-q32 and plays a critical role in regulating airway smooth muscle relaxation through cyclic adenosine monophosphate (cAMP)-mediated signaling pathways. Genetic polymorphisms within this gene can alter receptor expression, desensitization, and downstream signaling, thereby influencing the clinical response to bronchodilator therapy. One of the most clinically relevant variants is the single nucleotide polymorphism rs1042713 (Arg16Gly), which results in an amino acid substitution at position 16 of the receptor. This substitution has been associated with altered receptor downregulation and variable responsiveness to β2-agonists in asthma patients. Several studies have reported that individuals carrying the Gly16 variant may exhibit enhanced receptor desensitization and reduced bronchodilator responsiveness compared to Arg16 carriers, although findings remain inconsistent across different populations [2]. A number of genetic markers have been well investigated in asthma pharmacogenomics: *ADRB2* (β2-adrenergic receptor gene): Genetic variants (Arg16Gly and Gln27Glu) influence the bronchodilator efficacy of β2-agonists. This can result in increased or decreased response to short- and/or long-acting β2-agonists, CRHR1 (Corticotropin-Releasing Hormone Receptor 1): Polymorphisms in this gene can affect responses to inhaled corticosteroids, impacting on improvements in peak flow and asthma symptoms [3] and ALOX5 (Arachidonate 5-Lipoxygenase): Variants in the promoter region influence the leukotriene pathway and thus response to leukotriene inhibitors like montelukast [4].

β2-adrenergic receptors (β2-ARs) are encoded by the *ADRB2* gene and are expressed in several different cell types that play a role in asthma, such as airway smooth muscle (ASM) cells and immune cells [5]. Functional studies have shown a number of effects of the Arg16Gly SNP: Receptor Down regulation: Carriers of Gly16 may have faster loss in receptors following multiple β2-agonist exposures, leaving a less number of receptors for bronchodilation. Desensitization: Arg16 homozygotes may have a later onset of desensitization but still exhibit variation based on environmental exposures, drug exposures, asthmatic status and inflammation level [6]. Impaired Signalling: both alleles affect the cAMP signalling pathway, affecting airway smooth muscle relaxation and inflammation [7] [8].

The aim of this study is to evaluate serum levels of ADRB2 in asthmatic patients.

2. Materials and Methods

This case–control study was conducted in Wasit Province, Iraq, with participants recruited from several private clinics across different areas of Kut Governorate, Wasit

Province, Iraq. A total of 80 individuals were included, comprising 45 asthmatic patients and 35 apparently healthy controls. The mean age of patients was (38.44 ± 11.02) years, while controls had a mean age of (36.71 ± 10.15) years, with a balanced distribution of males and females in both groups.

From each participant, 5 mL of blood was collected via venipuncture. The blood was placed in a tube without anticoagulant. Serum was separated by centrifugation at 2000 × g for 10 minutes, aliquoted into 2 mL Eppendorf tubes, and stored in a deep freezer until analysis of serum *ADRB2* levels by ELISA (BT LAB Bioassay Technology Laboratory).

The mean ± SE of serum *ADRB2* was compared using Student's t-test or One-way Analysis of Variance (ANOVA).

3. Results and Discussion

The mean serum level of ADRB2 in healthy controls was 1.483 ± 0.093 ng/ml, whereas asthmatic patients showed a lower mean level of 1.172 ± 0.060 ng/ml. The difference between the two groups was statistically significant (P = 0.005, significant), indicating a potential association between reduced ADRB2 expression and asthma Table 1.

Table 1- Serum ADRB2 concentration in asthmatic patients versus healthy controls (Mean ± SE, P-value)

Group/Parameter	**ng/ml** **Mean ±SE**
Control	1.483±0.093
Patients	1.172±0.060
P-value	0.005
Significance level	**Sig.

SE = standard error; ng/mL = Nano gram per milliliter; P = P-value; **Sig P < 0.01 = Highly significant

3.1 Gender-specific comparison of serum ADRB2 *levels in asthmatic patients and healthy controls*

Serum ADRB2 levels were assessed in male and female participants to explore potential gender-specific effects Table 2. Among healthy controls, males exhibited slightly higher mean levels (1.576 ± 0.113 ng/ml) compared to females (1.394 ± 0.148 ng/ml), this difference was not statistically significant (P = 0.338). In asthmatic patients, males had a mean serum level of 1.208 ± 0.060 ng/ml, while females showed a slightly lower mean of 1.141 ± 0.101 ng/ml (P = 0.589), with non-significant difference.

When comparing patients to controls, a clear reduction in ADRB2 was observed in male patients relative to male controls (P = 0.004, significant), highlighting a pronounced gender-specific decrease. In contrast, the difference between female patients and female controls was smaller and non-significant (P = 0.151, Ns).

These findings suggest that asthma is associated with a more substantial decline in serum ADRB2 levels in males, pointing toward a potential gender-specific modulation of ADRB2 expression in the pathophysiology of asthma.

Table 2- Serum ADRB2 concentrations in male and female asthmatic patients and healthy controls (Mean ± SE, P-value)

Group/Parameter	**ng/ml Mean ±S E**			
	Male	Female	P-value	Significance level
Control	1.576±0.113	1.394±0.148	0.338	Ns.
Patients	1.208±0.060	1.141±0.101	0.589	Ns.
P-value	0.004	0.151		
Significance	**Sig.	Ns.		

SE = standard error; ng/mL = Nano gram per milliliter; P = P-value; Sig = significant; Ns = not significant ($P \geq 0.05$); **Sig $P < 0.01$ = Highly significant

Asthma is a multifactorial inflammatory disease characterized by complex immunological mechanisms. Evidence from local studies within the same population group suggests an association between asthma and altered levels of interleukins, particularly interleukin-17 ,indicating its potential role in the pathogenesis and modulation of airway inflammation. Jiad and Ahmed, 2022 indicated that cf-mt DNA down regulated significantly in Iraqi asthmatic patients [9]. A potential association is between lower ORMDL3 levels and asthma [10]. There is evidence that single nucleotide polymorphism rs730012 in leukotriene C4 synthase is associated with asthma in an Iraqi population and that this effect is comparable in males and females.

Regarding age, the present study demonstrated that the mean age of asthmatic patients (38.44 ± 11.02 years) was slightly higher than that of the control group (36.71 ± 10.15 years), with a corresponding increase in median age (40 vs. 35 years). This slight but significant difference is likely due to the chronic nature of asthma disease, where the risk of being diagnosed, persistence of disease or cumulative exposure to environmental risk factors increases with age. This finding is in agreement with global evidence that asthma can occur at any age, but persistent asthma that starts in adulthood is often linked to environmental and immunological factors [11]. From a regional prospective, while the limited published Iraqi studies that specifically address age distribution in asthma are scarce, the few reports indicate similar age distributions between cases and controls with a slight inclination to older ages among patients. This is in line with the current study and suggests that the sample in the study is representative of the local population. With regard to gender distribution, the study groups had a rather equal distribution, with a slight female preponderance. This also agrees with the literature, which suggests that the prevalence of asthma in adults is greater in females than males. This may be related to various factors including hormonal effects, airway hyper-responsiveness and immune

dysfunction [12]. It has also been found that the gender distribution pattern of asthma changes with age; where asthma is more prevalent in males during childhood and it starts increasing in females once the person reaches adulthood.

Large meta analyses of genetic association studies of *ADRB2*. A meta-analysis of 17 case–control studies found no significant association between the Arg16Gly polymorphism and asthma susceptibility in adults and none of the genetic models exhibited increased asthma risk due to the Gly16 allele/genotype. Similarly another large meta-analysis of *ADRB2* gene polymorphisms including Arg16Gly showed no single nucleotide polymorphism or composite single nucleotide polymorphism score was significantly associated with asthma risk in the overall population or in any subpopulation, regardless of how it was stratified by ethnicity [13]. These comprehensive meta analyses clearly demonstrate that the Arg16Gly polymorphism is unlikely to play a major role in asthma susceptibility.

These population meta analyses are in agreement with individual studies that have shown mixed results. For instance, a study of South Indian asthmatics found no overall effect of the Arg16Gly on asthma status, but the variant was found to influence disease severity and broncodilator response in subpopulations of asthmatics. Likewise, analysis in multi ethnic European populations have shown effects of the *ADRB2* genotypes on a range of asthma phenotypes (such as lung function decline or response to therapy) but not on presence of disease. These observations reflect that *ADRB2* effects are potentially context specific, with greater impact on disease features and pharmacogenetics, rather than disease susceptibility.

Asthmatic males had lower serum *ADRB2* levels compared to normal subjects; the difference in females was non-significant. This observation suggests that reduced *ADRB2* expression might be a contributing mechanism in the development of asthma, and that sex-specific differences (hormonal and immunological factors) might modulate *ADRB2* expression. While levels were reduced in females, this was not statistically significant, and underscores the need for sex-specific analyses in assessing the regulation of receptors and disease outcomes in asthma.

4. Conclusion

The greater reduction of serum ADRB2 in male patients implies that gender-specific physiological or hormonal factors can modulate receptor expression and may contribute to differential disease manifestations.

References

[1] P. J. Barnes, "The cytokine network in asthma and chronic obstructive pulmonary disease," *Journal of Clinical Investigation*, vol. 118, no. 11, pp. 3546–3556, 2008. https://doi.org/10.1172/jci36130

[2] Y. Zhao, J. Wang, Z. Liu, and Q. Xu, "Association between ADRB2 gene polymorphisms and bronchodilator responsiveness in asthma patients," *Molecular Medicine Reports*, vol. 20, no. 3, pp. 2453–2462, 2019.

[3] S. Lake, E. S. Silverman, L. J. Palmer, R. Lazarus, E. K. Silverman, S. B. Liggett, E. W. Gelfand, L. J. Rosenwasser, B. Richter, E. Israel, M. Wechsler, S. Gabriel, D. Altshuler, E. Lander, J. Drazen, and S. T. Weiss. K. G. Tantisira, "Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids," *Human Molecular Genetics*, vol. 13, no. 13, pp. 1353–1359, 2004. DOI: 10.1093/hmg/ddh149

[4] C. N. Yandava, L. Dubé, N. Szczerback, R. Hippensteel, A. Pillari, E. Israel, N. Schork, E. S. Silverman, D. A. Katz, and J. Drajesk. J. M. Drazen, "Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment," *Nature Genetics*, vol. 22, pp. 168-170, 1999. https://doi.org/10.1038/9680

[5] M. Johnson, "Beta2-adrenoceptors: mechanisms of action of beta2-agonists," *Paediatric Respiratory Reviews*, vol. 2, no. 1, pp. 57-62, 2001. https://doi.org/10.1053/prrv.2000.0102

[6] D. S. Postma, R. M. Lawrance, D. A. Meyers, H. J. Ambrose, and M. Goldman. E. R. Bleecker, "Effect of ADRB2 polymorphisms on response to longacting β2-agonist therapy: a pharmacogenetic analysis of two randomised studies," *The Lancet*, vol. 370, no. 9605, pp. 2118-2125, 2007. https://doi.org/10.1016/S0140-6736(07)61906-0

[7] S. A. Green, J. Turki, I. P. Hall, and S. B. Liggett, "Implications of Genetic Variability of Human β2-adrenergic Receptor Structure," *Pulmonary Pharmacology*, vol. 8, no. 1, pp. 1-10, 1995. https://doi.org/10.1006/pulp.1995.1001

[8] F. D. Martinez, P. E. Graves, M. Baldini, S. Solomon, and R. Erickson, "Association Between Genetic Polymorphisms of the Beta2-Adrenoceptor and Response to Albuterol in Children with and without a History of Wheezing," *Journal of Clinical Investigation*, vol. 100, no. 12, pp. 3184-3188, 1997. doi: 10.1172/JCI119874

[9] L. A. Jiad and I. H. Ahmed, "Investigation of The Molecular Role of Cell-Free Nuclear DNA and Cell-Free Mitochondrial DNA in Asthmatic Patients," *Natural Volatiles & Essential Oils*, vol. 9, no. 1, pp. 450-455, 2022.

[10] Z. M. Abdul Redha and I. H. Ahmed, "Polymorphism Of Orosomucoid-Like 3 ORMDL3 Rs4795405 C>T In Iraqi Patients with Asthma," *South Eastern European Journal of Public Health*, vol. XXIV, no. 1, pp. 858–865, 2024. DOI:10.70135/seejph.vi.1609

[11] S. C. Dharmage, J. L. Perret, and A. Custovic, "Epidemiology of asthma in children and adults," *Frontiers in Pediatrics*, vol. 7, no. 249, pp. 1-15, 2019. https://doi.org/10.3389/fped.2019.00246

[12] J. G. Zein and S. C. Erzurum, "Asthma is Different in Women," *Current Allergy and Asthma Reports*, vol. 15, p. 28, 2015. https://doi.org/10.1007/s11882-015-0528-y

[13] S. Q. Liang et al., "Beta-2 adrenergic receptor (ADRB2) gene polymorphisms and the risk of asthma: a meta-analysis of case-control studies," *PLoS One*, vol. 9, no. 8, p. e104488, 2014.

doi: 10.1371/journal.pone.0104488