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Study of Bcl-1 Single Nucleotide Polymorphism of Glucocorticoid Receptor Gene in Patients with Bronchial Asthma Thesis

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Abstract: **Objective:** Fluid infusion, the most critical step in the resuscitation of patients with septic shock, needs preferably continuous invasive hemodynamic monitoring. The study was planned to evaluate the efficacy of ultrasonographically measured inferior vena cava collapsibility index (IVC CI) in comparison to central venous pressure (CVP) in predicting fluid responsiveness in septic shock. Materials and Methods: Thirty-six patients of septic shock requiring ventilatory support (invasive/noninvasive) were included. Patients with congestive heart failure, raised intra-abdominal pressure, and poor echo window were excluded from the study. They were randomly divided into two groups based on mode of fluid resuscitation – Group I (CVP) and Group II (IVC CI). Primary end-points were mean arterial pressure (MAP) of ≥65 mmHg and CVP >12 mmHg or IVC CI <20% in Groups I and II, respectively. Patients were followed till achievement of end-points or maximum of 6 h. Outcome variables (pulse rate, MAP, urine output, pH, base deficit, and ScvO2) were serially measured till the end of the study. Survival at 2 and 4 weeks was used as secondary end-point. Results: Primary end-point was reached in 31 patients (15 in Group I and 16 in Group II). Fluid infusion, by either method, had increased CVP and decreased IVC CI with resultant negative correlation between them (Pearson correlation coefficient –0.626). There was no significant difference in the amount of fluid infused and time to reach end-point in two groups. Comparison in outcome variables at baseline and end-point showed no significant difference including mortality. Conclusion: CVP and IVC CI are negatively correlated with fluid resuscitation, and both methods can be used for resuscitation, with IVC CI being noninferior to CVP.

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Key Words: Central venous pressure, fluid responsiveness, hypovolemia, septic shock, sonographic inferior vena cava variability.

1. Introduction:

Bronchial asthma (BA) is a chronic inflammatory disease of the airways characterized by bronchial hyper-reactivity and a variable degree of airway obstruction [1]. The worldwide prevalence of BA is estimated to be approximately 4.5% and it may reach to 18% in some countries [1,2]. Moreover, prevalence of BA is anticipated to be increased over time, similar to other allergic disorders [3].

Bronchial asthma represents a dysfunctional interaction between genetic and environmental factors. Several environmental risk factors have been identified such as exposure to air pollution, tobaccos smoke as well as occupational risk factors [4, 5].

The genetic component of BA is determined by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis, with each gene having its own tendency to be influenced by the environment [6, 7].

Gluco-corticosteroids (GCs) constitute the basic group of medications used to control inflammatory conditions in patients with BA [8, 9]. They bind to an intracellular receptor named human glucocorticoid receptor (hGR). So, the sensitivity to these drugs may depend on the receptor number and affinity or on their availability to the receptors [10]. Polymorphisms in the hGR gene (Bcl-1) have been described in different populations and may contribute to the variability in sensitivity to GCs observed in some clinical settings as inflammatory bowel disease and cystic fibrosis. Therefore, it is hypothesized that Bcl-1 gene polymorphism may be related to GCs sensitivity in patients with BA [11].

2. Materials and Methods:

This study was conducted in 100 subjects recruited from the Chest Medicine Department of Ain Shams University hospitals. It included: 80 patients and 20 age and sex matched apparently healthy

controls. Informed consents were obtained from all subjects before enrollment in the study according to the Ethical Committee of Faculty of Medicine, Ain Shams University.

Subjects in this study were classified into eighty adult patients with BA diagnosed according to the Global Initiative for asthma (GINA, 2017) and twenty healthy control subjects with matched age and sex and excluded to have history or symptoms of BA, allergy or atopic dermatitis and no first-degree relatives with BA or atopic disorders. Bronchial asthma patients were subdivided according to the effect of GCs therapy into 2 subgroups; (GCs resistant patients) and (GCs sensitive patients). GCs resistant patients group lack any clinical response to GCs. This subgroup included 44 patients, 21 males and 23 females. Their ages ranged from 23 – 62 years GCs sensitive patients group who responding to GCs treatment. This subgroup included 36 patients (15 males and 21 females) their ages ranged from 30 – 69 years. All individuals in this study will be subjected to full history taking with special emphasis on clinical manifestations of BA, thorough clinical examination with special emphasis on chest examination according to GINA 2017, full history taking for DM as a disease linked to GCs therapy, thorough clinical examination for BMI (weight / height * height in meters) as a tool for diagnosis of obesity and > 30-35 considered obese and detection of Bcl-1 single nucleotide polymorphism using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) technique [Figure 1].

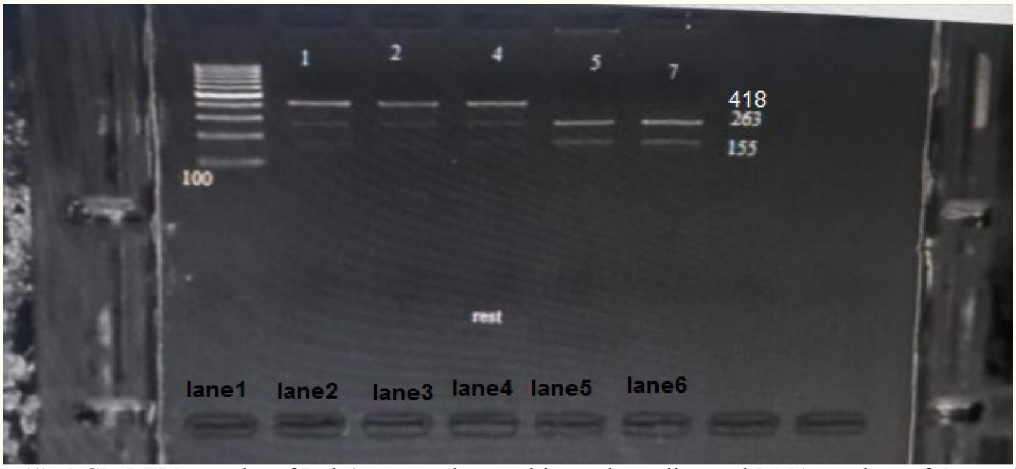

Figure (1): PCR-RFLP results of Bcl-1 gene polymorphisms show digested DNA product of 5 samples.
Lane (1) is 100 bp DNA ladder, Lane (2, 3 and 4) shows heterozygous mutation type GC (155 bp, 263 bp and 418 bp), Lane (5 and 6) show homozygous mutation type GG (155 bp and 263 bp).

Statistical analysis

Categorical variables of the Bcl-1 genotypes regarding qualitative data were presented as percentages and compared by using Chi-square test and/or Fisher exact test only when the expected count in any cell found less than 5. The test is applied to study the association between each 2 variables (Pearson chi-square) or comparison between 2 independent groups as regards the categorial data. The differences of the distributions of alleles and genotypes between cases and controls were analyzed using $\chi 2$ test. Allo-genotype frequencies were checked for Hardy–Weinberg equilibrium through $\chi 2$ test.

3. Results:

The descriptive and comparative statistics of demographic characteristics between bronchial asthma patients and healthy control groups are illustrated in Table (1). Patients and controls are age and sex matched (p>0.05).

Table (1): Descriptive and comparative statistics of demographic data between bronchial asthma patients and healthy controls using Chi-Square test:

Parameters		**Patients** (n =80)	**Controls** (n=20)	**χ2 /t***	**P Value**
		n (%)/X± SD*/			
Age (years)		42.10±15.56*	40.60±16.16*	1.84*	>0.05
Gender	Females ♀ Males ♂	(55.0%)44 36 (45.0%)	(45.0%)9 11 (55.0%)	1.00	>0.05

p-value>0.05: Non-significant.

The descriptive and comparative statistics of demographic characteristics between resistant and sensitive groups of bronchial asthma patients are illustrated in Table (2). Regarding the female gender, the prevalence among resistant group is 52.3% and 58.3% in sensitive group while male gender represents 47.7% in resistant group and 41.7% in sensitive group with no significant statistical difference between resistant and sensitive groups (p>0.05).

Table (2): Descriptive and comparative statistics of demographic data between glucocorticoids-resistant and sensitive patients using Chi-Square test:

Parameters		**GCs resistant Patients** (n=44)	**GCs sensitive Patients** (n=36)	χ^2/ t*	**P value**
		n (%)/X± SD*/			
Age (years)		44.68 ±11.09* 23.0-62.0	48.92 ±16.07* 30.0 –69.0	0.62	>0.05
Gender	Females ♀ Males ♂	23 (52.3%) 21 (47.7%)	21 (58.3%) 15 (41.7%)	0.29	>0.05

P-value >0.05: Non-significant.

The Bcl-1 in the promoter polymorphism within h-GR/NR3C1 gene was genotyped in all subjects using PCR- RFLP; three genetic variations were detected (C/C, C/G and G/G genotypes). The descriptive and comparative statistics of the genotype and allele frequencies of the studied polymorphism between bronchial asthma patients and healthy controls are presented in **Table (3) and Figures (2)**. In bronchial asthma patients, 45% had GG genotype, 55% had CG genotype and 0.0% had CC genotype. On the other hand, 55% of controls were GG genotype, 45 % were CG genotype and 0.0% was CC genotype. As regards Bcl-1allele, ¨G¨allele was present in 72% of patients and in 81.0% of controls; meanwhile, ¨C¨ allele was found in 28% of patients and in 19% of controls. No statistically significant differences were observed regarding Bcl-1polymorphism genotype and allele frequencies between patients and controls (p>0.05).

Table (3): Descriptive and comparative statistics of genotypes frequency of Bcl-1 gene polymorphism and the alleles frequency in bronchial asthma patients and control groups using Chi square test:

Parameters	**Patients** (n =80)	**Controls** (n=20)	χ2	**P Value**
	n (%)			
Genotype **GG** **CG** **CC**	(%45.036 ((%55.044(0 (0.0%)	(%55.0)11 (%45.0)9 0 (0.0%)	0.64	>0.05
Allele **G** **C**	(%72.0)116 44 (28.0%)	(%81.0)31 9 (19.0%)	0.41	>0.05

P-value >0.05: Non-significant.

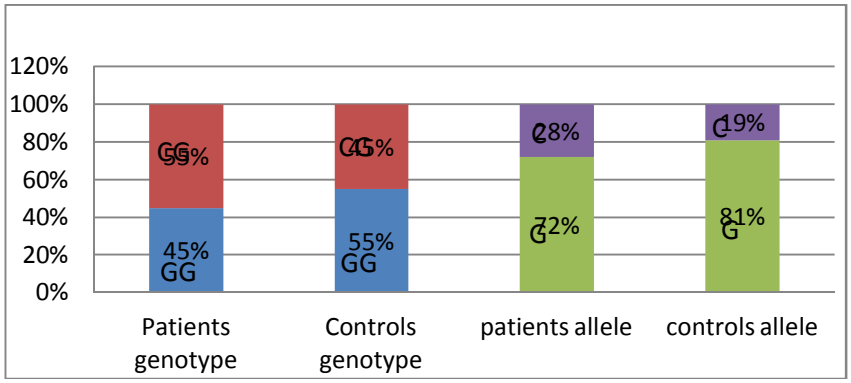

Figure (2): Statistical comparison between patients and controls regarding Bcl-1 polymorphism genotype and alleles frequencies.

Descriptive and comparative statistics of genotype of Bcl-1 gene polymorphism and the allele frequency in bronchial asthma resistant patients and sensitive groups are illustrated in Table (4) and Figure (3). The (GG) genotype homozygous mutant type and the allele frequency (G) showed significantly higher frequencies in resistant group than in sensitive group and statistical significant difference ($p< 0.05$).

Table (4): Descriptive and comparative statistics of genotypes frequency of Bcl-1 gene polymorphism and the alleles frequency in glucocorticoids-resistant and sensitive patients using Chi square test:

Parameters	GCs resistant patients (n = 44) n (%)	GCs sensitive patients (n = 36)	χ^2	P Value
Genotype				
CG	19(43.2%)	27 (75.0%)	8.203	< 0.05
GG	25 (56.8%)	9 (25.0%)		
Allele			4.893	< 0.05
G	69(78.4%)	45 (62.5%)		
C	19 (21.6%)	27 (37.5%)		

Statistically significant at $p < 0.05$.

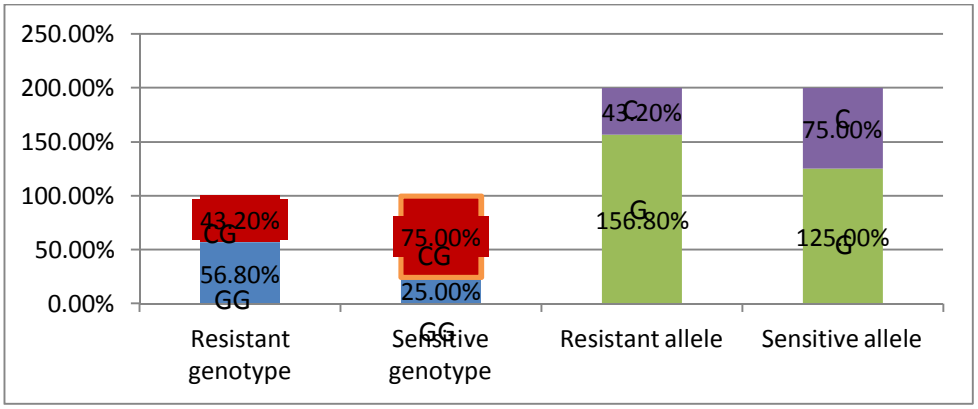

Figure (13): Statistical comparison between BA resistant and sensitive patients regarding Bcl-1 polymorphism genotypes and alleles frequency.

Descriptive and comparative statistics for incidence of DM and obesity linked to glucocorticoid treatment between bronchial asthma patients and healthy control groups are shown in table (5) and Figure (4). The study revealed that 53.8 % of bronchial asthma patients had DM, while only 30% of control group was diabetic. However, there was non-significant statistical difference between the two groups ($p>0.05$). As regards obesity, it was significantly higher among bronchial asthma patients when compared to healthy controls ($p<0.05$) with prevalence 43.8 % among bronchial asthma patients and 10 % among healthy control groups.

Table (5): Comparison between the Patients and Control groups according to Prevalence of DM and obesity using chi square test:

Parameters		Control group (n=20) n (%)	Patients group (n=80)	χ^2	P value
DM	Yes	6 (30%)	43 (53.8%)	3.61	>0.05
	No	14 (70%)	37 (46.2%)		
Obesity	Yes	2 (10%)	35 (43.8%)	7.82	<0.05
	No	18 (90%)	45 (56.2%)		

P >0.05: Non-significant. P<0.05: significant.

The descriptive and comparative statistics between the two groups of bronchial asthma patients (resistant and sensitive) are presented in table (6) and Figure (4) regarding the prevalence of DM and obesity linked to glucocorticoid treatment**.** In the resistant group of patients, 70.5% had DM and 29.5 % were non-diabetic, while in the sensitive group of patients, 33.3% had DM and 66.7 % were non-diabetic, and statistical significant difference was found ($p < 0.05$). On the other hand, the prevalence of obesity was 54.5% among resistant group and 30.5% among sensitive group, while 45.5 % of resistant group were not obese and 69.5 % among the sensitive group were not obese so, statistical significant differences were observed ($p<0.05$)

Table (9): Comparison between the glucocorticoids - resistant and sensitive patients according to Prevalence of DM and obesity using Chi square test:

Parameters		**GCs resistant patients** (n = 44)	**GCs sensitive patients** (n = 36)	χ^2	**P-value**
		n (%)			
DM	Yes	31 (70.5%)	12 (33.3%)	10.97	< 0.05
	No	13 (29.5%)	24 (66.7%)		
Obesity	Yes	24 (54.5%)	11 (30.5%)	9.98	< 0.05
	No	20 (45.5%)	25 (69.5%)		

P-value < 0.05: Significant.

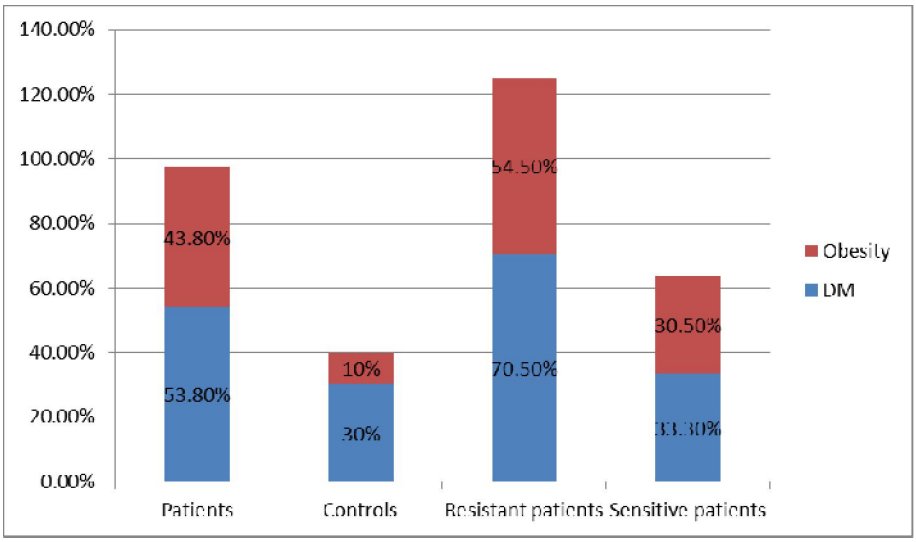

Figure (4): Bar chart showing the statistical comparison between DM and Obesity in all studied population.

4. Discussion

Bronchial asthma is a chronic inflammatory disorder of the airways. It presents clinically with variable airway narrowing (wheezes and dyspnea) and cough. Long-standing asthma induces airway remodeling and permanent alterations in the airway structure leading to intractable asthma [(12).]

Bronchial asthma is by far prevalent worldwide to be estimated approximately 4.5% and it may reach to 18% in some countries [(1).] In Egypt, the prevalence of asthma and allergies is increasing in both Western and developing countries [(13).] ***The Global asthma report 2018,*** mentioned that the highest Asthma prevalence rates are found in the United Kingdom (>15%) and New Zealand (15.1%)**.**

Airway inflammation is a major factor in the pathogenesis and pathophysiology of asthma. The treatment of a patient with BA can be either pharmacological such as β-2 agonists, corticosteroids and antibiotics or non-pharmacological such as avoidance or reduction of exposure to precipitating factors and triggers or in most of patients a combination of both [(14).]

Glucocorticoids are powerful and fast acting anti-inflammatory drugs that have been used as treatment for acute and long-term treatment of BA. GCs exert their effect via the ligand dependent nuclear receptor (Glucocorticoid receptor) [(15)].

Identification of modifier genes that may influence the development and progression of the

disease is an important issue for patients with respiratory diseases. It helps not only for understanding the pathophysiology of progression, but also for identifying patients who may benefit from new therapeutic strategies and adaptation of treatment to their genetic profile. Bcl-1 gene is one of the candidate genes of interest that may influence the inflammatory cascade and response to anti-inflammatory drugs, exogenous and endogenous GCs through glucocorticoid receptors. Consequently, Bcl-1gene polymorphism may cause changes in the receptor expression level and, respectively, affect sensitivity to GCs either increase or decrease it [16].

Therefore, the aim of this study is to study the frequency of the Bcl-1 single nucleotide polymorphism by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in patients with bronchial asthma and to evaluate its association with the response to glucocorticoids therapy.

This study was conducted on eighty patients with BA diagnosed according to GINA guidelines recommendations 2017, and twenty controls with age- and sex- matched to patients group. According to response to glucocorticoids the bronchial asthma patients' group was further subdivided into 2 subgroups; glucocorticoids resistant patients (n=44) and glucocorticoids sensitive patients (n=36).

The results of the present study revealed that there was no significant difference between BA patients and controls regarding age and gender, also no significant difference was found between resistant and sensitive groups of patients.

When the frequency of the different Bcl-1 polymorphism genotypes was compared between patients and controls, our results revealed that in the control group, the most frequent genotype was GG genotype (55%) followed by GC (45%) and lastly CC (0%), while among the patients' group, the most frequent genotype was GC genotype (55%) followed by GG (45%) and lastly CC (0%). Regarding alleles frequency, G allele was more frequent (81.0%) than C allele (19.0%) in controls. And in patients' group, G allele was more frequent also by (72.0%) than C allele (28.0%). Thus, the genotypic and allelic frequencies of Bcl-1 polymorphism of *h-GR/NR3C1* gene were found in higher percentages in patients with BA than controls, yet they didn't show statistically significant association with the presence of BA.

However, ***Kmyta and Prystupa (2015)*** found that Bcl-1 polymorphism of *h-GR/NR3C1* gene distribution in asthmatics is significantly associated with BA with GG homozygous genotype showed a five-fold higher risk of BA than those homozygous for CC regardless of gender. These divergent results can be attributed to genetic heterogeneity and the relative small sample size of our study so, lack the ability to be representative for the whole population. This may also explain why the CC genotype couldn't be detected in our study.

Furthermore, previous studies and meta-analyses on different ethnic populations observed a significant difference in the Bcl-1 genotypes between patients with BA and controls. Accordingly, they linked the Bcl-1 polymorphism to cause BA [16,7].

The divergence of the results of the Bcl-1 gene polymorphism may be attributed not only to different study designs, sample sizes and selection of controls, but also to the distinct patient populations.

These conflicting results stem partially from the differences in several genetic and environmental factors that can lead to allelic variant distribution of Bcl-1 SNPs. [7].

In context of comparison of the genotypes and alleles frequency in the patients' groups according to response to glucocorticoids, our study revealed statistical significant difference between glucocorticoids- resistant and sensitive groups.

The G allele were more frequent in GCs resistant than in GCs sensitive group than GCs sensitive, these results reach statistically significant differences. As regards the heterozygous mutant type (GC), it was more frequently distributed in GCs sensitive than GCs resistant and the C allele was more frequent in GCs resistant group than in GCs sensitive group and that was statistically significant different.

Our results were in concordance to ***Panek et al. (2012)*** who found that Bcl-1 polymorphism of h-GR/NR3C1 gene plays an important role in the development of BA, the development of severe form of the disease and it is associated with an altered sensitivity to glucocorticoids.

In addition, ***Kmyta et al. (2015)*** found that GG genotype of Bcl-1 gene polymorphism of h-GR/NR3C1 gene is associated with BA severity and is more likely to be present in the individuals with severe persistent BA course that matched with our study results.

Moreover, ***Pietras et al. (2010)*** also stated thatBcl-1 polymorphism can play an important role in BA development and severity, and can influence response to corticosteroids. They found out that BA developed more frequently in the carriers of allele G. C allele was associated with a lesser risk of BA, and C allele carriers (CC+CG) had BA less often than G allele carriers. Thus, this study despite the small size of the study groups confirmed that the substitution of G allele for C allele contributed to the development of BA among the polish population.

These results could be attributed to the molecular mechanism of action of GCs which involves binding of the glucocorticoids /glucocorticoid receptor

complex to the sequences of regulator genes encoding the synthesis of anti-inflammatory proteins determining the clinical effects of GCs [17]. Upon binding of the GCs to GR, the HSP dissociates and the GCs/GR complex changes its conformation and travels to the nucleus via nuclear pores to exert its action. HSP regulates ligand binding, as well as cytoplasmic retention of GR by exposing the ligand-binding site and masking the nuclear localization sequences [18]. So, Bcl-1 polymorphisms may inhibit formation of GCs/GR complexes and thereby reducing gene transcription and cause trans-repression of the genes encoding proteins synthesized within the framework of cellular response to GCs [6].

Moreover, in 2011, ***Pietras et al.*** studied the *Bcl-1* single nucleotide polymorphism of the human glucocorticoid receptor gene *h-GR/NR3C1* promoter in patients with BA and found that it is impossible to define precisely the role of single loci regions of the particular genes and individual single nucleotide polymorphisms of the h-GR/NR3C1 gene in the etiopathogenesis of BA and response of the patients to glucocorticoids therapy. The key role is attributed to determination of the gene structure and its allelic variants as well as to assessment of the correlation between the level of expression and biological properties of proteins. Nevertheless, they observed that allele G promotes the development of BA and also, mutation GC within the gene promoter is protective in character and correlates with reduced frequency of the disease.

Data of the present study revealed that there was statistical significance difference between BA patients and control groups as regards obesity. Moreover; the study revealed statistical significance difference between the resistant and sensitive groups of BA patients. Such finding was similar to ***Kmyta et al. (2016) who*** reported an association between Bcl-1 polymorphism of glucocorticoid receptor gene and obesity in patients with BA. It was demonstrated that G/G genotype in the patients with visceral obesity was associated with BA. Moreover, it was found out that genotypes distribution for Bcl-1 polymorphism in patients with BA showed a statistically significant difference between patients with different BMI unlike the control group.

In accordance with our previously demonstrated results, ***Baruwa et al., 2013*** support a link between obesity and asthma in both adult and children, they explained their results as obesity causes a higher oxygen cost of breathing leading to dyspnea because of decreased compliance from excess weight compressing the chest wall, fatty infiltrate of the chest wall, and an increase in blood volume. In addition, obesity causes a decrease in functional residual capacity, and decreases in both forced expiratory volume in (FEV1) and forced vital capacity (FVC), with a normal FEV1/FVC ratio, resulting in rapid shallow breathing.

In contrast with obesity, our study showed absence of statistical significance difference between patients with BA and healthy control groups as regards the incidence of DM linked to glucocorticoid treatment.

On the other hand, ***Srivastava et al, 2011***[19] study who investigated the influence of Bcl-1 Gene polymorphism of glucocorticoid receptor gene (NR3C1, rs41423247) on blood pressure and glucose level in Northern Indians, they found that, the GG genotype may modulate blood pressure, blood glucose and hormonal levels in northern Indians because glucocorticoids and its receptor are known to be involved in the dysregulation of hormone and lipid levels.

Limitations of the study

These divergent results can be attributed to genetic heterogeneity and the relative small sample size of our study so, lack the ability to be representative for the whole population. This may also explain why the CC genotype couldn't be detected in our study.

Conclusion and future work

The current study has introduced an additional evidence for the significant association between GCs resistance development and Bcl-1 SNP. On the other hand, the study failed to prove the presence of an association between Bcl-1 SNP and BA disease. Moreover, there is absence of statistical significance difference between patients with BA and healthy control groups as regard the incidence of DM linked to glucocorticoid treatment. In contrast with obesity, there was statistical significance difference between BA patients and control groups. Moreover; the study revealed statistical significance difference between the resistant and sensitive groups of BA patients.

Well- designed studies with large sample sizes regarding the association of Bcl-1 gene polymorphisms with BA on different ethnic population and wide range of age groups will be needed to verify our study findings in the future. Also, prospective longitudinal studies are recommended to study the association of Bcl-1 gene polymorphisms with BA, to evaluate its contribution in the pathogenesis of the disease, and its association with other diseases as hypertension, IHD, MI, obesity and diabetes mellitus. This will help in developing novel strategies for early screening of individuals at risk of developing these diseases and early management of patients with BA. Also, Evaluation of Bcl-1 gene polymorphisms in BA patients and its associations

with other allergic diseases. Further evaluation of Bcl-1 gene polymorphisms other than h-GR/NR3C1 and their association with BA is also recommended. Presence of large-scale genetic studies based on the haplotyping of different SNPs in order to be more influential than the study of a single SNP.

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Conflicts of interest:
There are no conflicts of interest.

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