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ORIGINAL ARTICLE

CORRELATION BETWEEN GLUCOCORTICOID RECEPTOR GENE VARIATION AND RESPONSIVITY IN PATIENTS WITH CHRONIC BRONCHITIS TAKING ORAL PREDNISOLONE

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Summary

Chronic bronchitis is increasingly reported as a healthcare challenge in clinical settings partially due to the disease's bad prognosis and unresponsiveness to therapy, including the ineffectiveness of glucocorticoids. The ineffectiveness could have a link with genetic polymorphism of receptor genes resulting in inappropriate glucocorticoid pharmacodynamics. We sought to identify the role of gene polymorphism in the response of patients with chronic bronchitis to prednisolone therapy. To do so, a total of 60 newly diagnosed chronic bronchitis patients enrolled in the present study. Prednisolone at a dose of 30mg/day for two weeks was given and respiratory parameters [forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC were measured before and after therapy. Blood samples were withdrawn for genetic profiling of genes involved in glucocorticoids pharmacodynamics, including BCII (rs41423247), N363S (rs56149945), and ER22/23EK (rs6189/rs6190) measured for their homozygous versus heterozygous gene splice variants.

Results: Gene splice variants for BCII (rs41423247), N363S (rs56149945), and ER22/23EK (rs6189/rs6190) homozygous (73.3%, 98.7%, and 95%) represented a higher percentage than heterozygous (26.7%, 1.7%, and 5%). The respiratory parameters FEV1, FVC, and FEV1/FVC have shown significantly ($p<0.05$) better values at baseline in homozygous versus heterozygous, correspondingly, the responsiveness to therapy has shown significantly ($p<0.05$) better values in homozygous versus heterozygous.

Conclusion: The study has provided a good template for genetic behaviour toward individualised medicine in our locality providing that these genes could be a cornerstone for discovering issues related to the pharmacodynamics profiling of drugs in clinical settings.

Key words: Corticosteroid responsivity; Gene polymorphism; Splice variants; Chronic bronchitis

Introduction

Chronic bronchitis is clinically as a chronic productive cough for at least 3 months in each of two consecutive years in a patient in whom other causes have been excluded (1). The disease is often caused by long-term exposure

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to irritants such as cigarette smoke, air pollution, and dust (2). Chronic bronchitis is a type of chronic obstructive pulmonary disease (COPD), which causes the airways to become narrowed and makes it difficult to breathe (1). Symptoms of chronic bronchitis include coughing, wheezing, shortness of breath, and chest tightness (1, 2). These symptoms can be severe and persistent, with exacerbations that can last for weeks or months (2). Chronic bronchitis can also lead to other health problems, such as respiratory infections, lung cancer, and heart disease (3). Treatment for chronic bronchitis may involve medications, such as bronchodilators and steroids, as well as lifestyle changes, such as quitting smoking and avoiding exposure to irritants. In severe cases, oxygen therapy or surgery may be required (2-4).

One of the biggest challenges in treating chronic bronchitis is managing the persistent cough and excessive mucus production that are characteristic of the condition. Medications such as bronchodilators and inhaled corticosteroids can help to reduce inflammation and open up the airways, making it easier to breathe. However, these medications may not be effective for everyone, and they can have side effects such as nausea, headaches, and insomnia (2, 4).

The treatment choices are limited, only focusing on bronchodilators and corticosteroids, patients who don't responds to these therapy may precipitate attack of the disease. Both are subjective to unresponsiveness, bronchodilators due to receptor down regulation and corticosteroids due to genetic polymorphism, therefore, addressing the potential of unresponsiveness of either therapy is equally important in terms of therapy and reducing adverse effect profile (5-9). The present study aimed at investigating genetic polymorphism and potentially relating that to corticosteroid-responsiveness quality of therapy.

Patients and methods

Patients: A total of 60 newly diagnosed chronic bronchitis patients were enrolled in the present study, with an age range of (40-65 years old) . Respiratory parameters were conducted at a respiratory unit in Al-Sader Teaching Hospital by specialized technical staff using a spirometer, the recorded results were collected for further analysis according to these records, the patients were diagnosed with chronic bronchitis. Immediately prednisolone therapy started (30mg/day for 14 days). At the end of 14 days, the pulmonary function tests [forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC] were done again and results gather with the baseline records for comparisons. According to their response to prednisolone therapy, the patients were sub-classified into 35 patients responsive to therapy and 25 patients unresponsive to prednisolone therapy.

Inclusion criteria:

1- Newly diagnosed patients with chronic bronchitis who are aged 40-65 years of either sex are accepted to participate in the study with mild, moderate, and severe chronic obstructive pulmonary diseases.
2- Patients with a post-bronchodilator FEV1/FVC ratio of <70%.

Exclusion criteria:

1- Patients with contraindications to steroids.
2- Patients with other respiratory diseases such as asthma, emphysema, exacerbations of COPD and very severe chronic obstructive pulmonary diseases.
3- Patients with nephropathies.
4- Patients have various tumours of respiratory tract tissues.
5- Pregnant and lactating women.

Response prediction: Callahan, *et al* (1991) defined steroid responders as patients with a response to prednisolone of >20% of baseline forced expiratory volume in 1 second. The American Thoracic Society (ATS) defines responders as those with a response of >12% baseline of forced vital capacity. These were termed by Callahan, *et al* (1991) and ATS criteria, respectively, and were used to determine differences between steroid responders and non-responders. Accordingly, patients in our study were subclassified as responders or non-responder based on measured spirometer parameters (10).

Blood samples (2ml) were withdrawn from patients and placed in an EDTA tube with continuous shaking for 5 minutes by Roller mixer (VM-370, Gemmy) genetic profiling was conducted for gene polymorphism analysis according to manufacturer instructions as summarized below:

DNA extraction: Briefly, isolating genomic DNA from a blood sample using the ReliaPrep™ Blood gDNA Miniprep System (Promega). The process involves mixing the blood sample with Proteinase K solution and Cell Lysis Buffer, incubating it in a water bath, and transferring the mixture to a binding column. The column is washed with Column Wash Solution and Nuclease-Free Water, and the resulting eluate is saved. The Quantus Fluorometer was utilized to measure the concentration of DNA extracted from samples. The concentration of DNA was determined by mixing 1 µl of DNA with 200µl of diluted Quantifluor Dye and then detecting the concentration values after a 5-minute incubation at room temperature. This was done to determine the quality of the DNA for downstream applications.

Primers design: Preparation of primers supplied by Macrogen Company. The primers were in a lyophilized form and were dissolved in nuclease-free water to obtain a stock solution of 100pmol/µl. A working solution was prepared by adding 10µl of the stock solution to 90µl of nuclease-free water, resulting in a working primer solution of 10pmol/µl.

Table 1. Primer designed for single nucleotide polymorphism analysis.

Primer Name	Sequence 5`-3`	Annealing Temp. (°C)	Product size (bp)
NR3C1-F	ACAAGCTGCCTCTTACTAATC	63	1445
NR3C1-R	GGTTGTCTACCTTTCCTACTTT		
NR3C1-F2	TGTAAAACGACGGCCAGTTGAATACAGCATCCCTTTCTC	60	935
NR3C1-R2	CAGGAAACAGCTATGACGAGAACTTGCAGGAACATTTG		

Primers optimization: The study aimed to determine the optimal annealing temperature of a primer by amplifying a DNA template with the same primer pair at different temperatures using PCR. The PCR amplification was performed with a 20µl volume containing GoTaq Green Master Mix, primer, nuclease-free water, and template DNA. The PCR cycling was performed with a temperature program consisting of denaturation, annealing, and extension steps. The study concluded with a final extension incubation followed by a 10 min incubation to stop the reactions. Reaction Setup and Thermal Cycling Protocol were followed up as per the kit instruction protocol (Figures 1 and 2).

PCR product gel electrophoresis: Agarose gel electrophoresis was used to confirm the presence of PCR amplification. Agarose was prepared by dissolving 1.5 gm of agarose in 100 ml of 1X TAE buffer and adding 1µl of Ethidium Bromide. The solution was poured into a gel tray, allowed to solidify, and loaded with PCR products. The gel was then placed in an electrophoresis tank and visualized using a Gel imaging system.

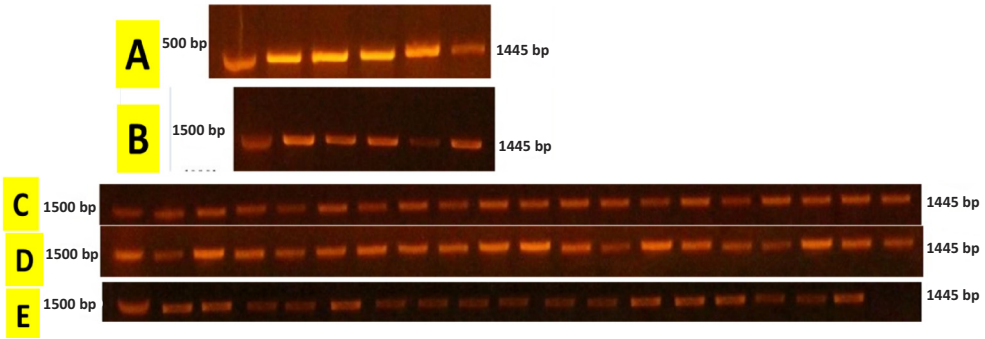

Figure 1. Results of the amplification of *the NR3C1 gene* of human samples were fractionated on 1.5% agarose gel electrophoresis stained with Eth. Br. M: 100bp ladder marker. (A) Results of *NR3C1 primer optimization*. (B) Lanes 1-5 resemble 1445bp PCR products. (C) Lanes 6-24 resemble 1445bp PCR products. (D) Lanes 25-46 resemble 1445bp PCR products. (E)Lanes 47-65 resemble 1445bp PCR products.

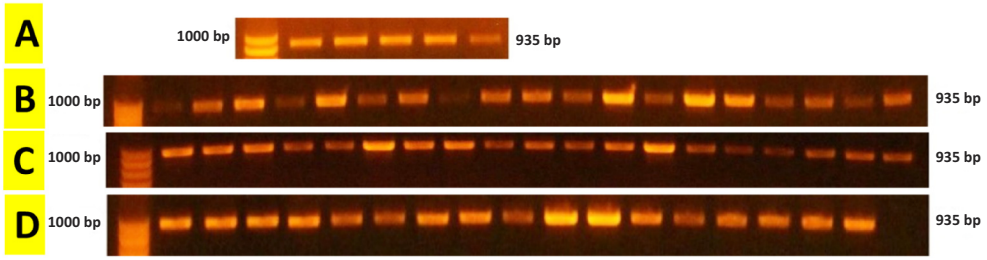

Figure 2. Results of the amplification of *the NR3C1-2 gene* of Human samples were fractionated on 1.5% agarose gel electrophoresis stained with Eth. Br. M: 100bp ladder marker. (A) Results of *NR3C1-2 primer optimization* (B) Lanes 1-19 resemble 935bp PCR products. (C) Lanes 20-40 resemble 935bp PCR products. (D) Lanes 41-60 resemble 935bp PCR products.

Statistical analyses were conducted using IBM SPSS statistics version 28.0.0.0(190) for Windows. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Mean± standard deviation or medians and interquartile range (IQR) were used to present normally and non-normally distributed data, respectively. Independent- samples t-test, Mann-Whitney U test, and Kruskal-Wallis H test were utilized for comparing continuous variables. Frequencies, percentages and mean ± standard deviation were used to describe the data. The response of FEV1, FVC and FEV1/FVC variables. A significance level of 0.05 was used to determine statistical significance.

Results

The demographic characteristics of patients enrolled in the present study are in Table 2. Patients were middle-aged (49.1±7.5 years old). Their body mass index (BMI) (26.2±2.9) was slightly higher than the normal BMI (18.5-24.9) but still acceptable. Most of the participants were males (75%) versus (25%) females. Two-third of the participants were from the town while the rest were from the countryside. Nearly two-thirds were smokers and one-third were represented as smoke-free or ex-smokers.

Table 2. Demographic and clinical characteristics of patients with chronic bronchitis.

Demographic Parameters		
Age (years)		49.1±7.5
BMI(kg/m^2)		26.2±2.9
Sex	Male, N(%)	45 (75.0%)
	Female, N(%)	15 (25.0%)
Residence	Rural, N(%)	20 (33.3%)
	Urban, N(%)	40 (66.7%)
Smoke status	Positive, N(%)	36 (60.0%)
	Negative, N(%)	24 (40.0%)

Table 3. Genetic polymorphisms of GR gene (NR3C1) in 60 chronic bronchitis patients.

Genotyping Variations		**N**	**%**
BCII (rs41423247)	CC	42	70.0
	GG	2	3.3
	CG	16	26.7
N363S (rs56149945)	AA	58	96.7
	GG	1	1.7
	AG	1	1.7
ER22/23EK (rs6189/rs6190)	GG	57	95.0
	GA	3	5.0

Analysis of genetic parameters responsible for responsiveness to corticosteroids GR gene (NR3C1) has revealed that the BCII (rs41423247), N363S (rs56149945), and ER22/23EK (rs6189/rs6190) gene variants presented at a higher percentage as a CC, AA, GG-homozygote, respectively than that of heterozygotes percentage (Table 3).

The spirometer data analysis comparing responder versus non-responder has revealed that the baseline results of the measured parameters (FEV1, FVC, and FEV1/FVC) before administration of prednisolone have shown a non-significant difference (P>0.5) compared to each other using median and IQR as a measured outcome. However, comparing the same parameters after administration of prednisolone has shown significant (P<0.5) differences between non-responders versus responders. In responders, the median values of these parameters have reduced and their IQR were closer to the median values compared to that of the non-responders. However, comparing pre versus post values for all parameters has shown a highly significant (p<0.001) higher levels in post-prednisolone administration values (Table 4).

Table 4. Relationship between spirometric analysis and responsivity in chronic bronchitis patients.

	Responsivity						P. Value [a]
	Responders(n=35)			Non-responders(n=25)			
	Median	IQR		Median	IQR		
pre (FEV1(L))	3.0	2.4	3.1	3.0	2.8	3.1	**0.816[NS]**
post (FEV1(L))	3.6	3.1	3.8	3.1	2.9	3.2	**<0.001****
P. Value [b]	**< 0.001****			**< 0.001****			
pre (FVC)	4.4	3.6	4.6	4.4	4.1	4.8	**0.373 [NS]**
post (FVC)	5.0	4.4	5.4	4.5	4.3	4.9	**0.013***
P. Value [b]	**< 0.001****			**< 0.001****			
(pre (FEV1/FVC)	68.0	66.9	68.8	68.1	64.8	69.2	**0.697 [NS]**
post (FEV1/FVC)	70.2	69.2	71.5	68.5	65.9	70.3	**0.003***
P. Value [b]	**< 0.001****			**< 0.001****			

Data presented as median & interquartile range,
[a] Mann–Whitney U-test used to test statistical differences between responsivity groups),
[b] Wilcoxon signed-rank test used for comparison between (pre & post) in the same group,
[NS] No significant changes (p≥0.05),
* Significant changes (p<0.05),
** Highly significant changes (p<0.01).

Regarding BCII (rs41423247) variants, the spirometer data analysis comparing homozygotic and heterozygotic gene variants in responder versus non-responder has revealed that the baseline results of the measured parameters (FEV1, FVC, and FEV1/FVC) before administration of prednisolone were dissimilar. At baseline, FEV1, FVC, and FEV1/FVC in CC-homozygote and CG heterozygotes were significantly higher than GG homozygotes. Correspondingly, significantly (p<0.05) better responses were obtained after administration of prednisolone in CC-homozygote and CG heterozygote compared to GG homozygotes (Table 5).

Regarding N363S (rs56149945) variants, the spirometer data analysis comparing homozygotic and heterozygotic gene variants in responder versus non-responder has revealed that the baseline results of the measured parameters (FEV1, FVC, and FEV1/FVC) before administration of prednisolone were dissimilar.

At baseline, FEV1, FVC, and FEV1/FVC in homozygotes (AA or GG) and heterozygotes (AG) were non-significantly different.

Correspondingly, non-significantly (p<0.05) different responses were obtained after the administration of prednisolone in homozygotes (AA or GG) and heterozygotes (AG). Nevertheless, a significantly higher response was achieved in AA homozygotes after administration of prednisolone (Table 6).

Table 5. Relationship of BCII (rs41423247) genetic variation and spirometric analysis in chronic bronchitis patients.

	BCII (rs41423247)									P. Value [a]
	CC			GG			CG			
	Median	IQR		Median	IQR		Median	IQR		
pre (FEV1(L))	3.0	2.9	3.2	2.0	2.0	2.1	2.8	2.2	3.1	**0.040***
post (FEV1(L))	3.4	3.1	3.7	2.7	2.6	2.9	3.4	2.9	3.8	**0.223** [NS]
P. Value [b]	**< 0.001****			**0.180** [NS]			**< 0.001****			
pre (FVC)	4.5	4.2	4.7	2.9	2.9	3.0	4.1	3.3	4.6	**0.046***
post (FVC)	4.9	4.4	5.2	3.8	3.7	4.0	4.8	4.2	5.5	**0.186** [NS]
P. Value [b]	**< 0.001****			**0.180** [NS]			**< 0.001****			
pre (FEV1/FVC)	68.4	66.7	69.3	68.4	68.0	68.7	67.1	65.1	68.0	**0.041***
post (FEV1/FVC)	69.8	68.1	70.7	71.1	70.2	71.9	69.9	68.4	71.1	**0.475** [NS]
P. Value [b]	**< 0.001****			**0.180** [NS]			**< 0.001****			

Data presented as median & interquartile range,
[a] Kruskal-Wallis H test used to test statistical differences between BCII (rs41423247) groups,
[b] Wilcoxon signed-rank test used for comparison between (pre &post).
[NS] No significant changes (p≥0.05),
* Significant changes(p<0.05),
** Highly significant changes (p<0.01).

Table 6. Relationship of N363S (rs56149945) genetic variation and spirometric analysis in chronic bronchitis patients.

	N363S (rs56149945)									P. Value [a]
	AA			GG			AG			
	Median	IQR		Median	IQR		Median	IQR		
pre (FEV1(L))	3.0	2.5	3.1	2.7	2.7	2.7	2.8	2.8	2.8	**0.550** [NS]
post (FEV1(L))	3.3	3.0	3.7	3.5	3.5	3.5	3.5	3.5	3.5	**0.815** [NS]
P. Value [b]	**< 0.001****			**NA**			**NA**			
pre (FVC)	4.4	4.0	4.7	3.9	3.9	3.9	4.2	4.2	4.2	**0.581** [NS]
post (FVC)	4.8	4.3	5.2	4.8	4.8	4.8	5.2	5.2	5.2	**0.704** [NS]
P. Value [b]	**< 0.001****			**NA**			**NA**			
pre (FEV1/FVC)	68.0	66.5	69.1	68.3	68.3	68.3	65.9	65.9	65.9	**0.590** [NS]
post (FEV1/FVC)	69.9	68.4	70.7	71.2	71.2	71.2	68.5	68.5	68.5	**0.449** [NS]
P. Value [b]	**< 0.001****			**NA**			**NA**			

Data presented as median & interquartile range,
[a] Kruskal-Wallis H test used to test statistical differences between N363S (rs56149945) groups,
[b] Wilcoxon signed-rank test used for comparison between (pre &post).
[NS] No significant changes (p≥0.05),
** Highly significant changes (p<0.01), NA : not applicable.

Regarding ER22/23EK (rs6189/rs6190) variants, the spirometer data analysis comparing homozygotic and heterozygotic gene variants in responder versus non-responder has revealed that the baseline results of the measured parameters (FEV1, FVC, and FEV1/FVC) before administration of prednisolone were dissimilar.

At baseline, FEV1, FVC, and FEV1/FVC in homozygotes (GG) and heterozygotes (AG) were non-significantly different.

Correspondingly, non-significantly ($p<0.05$) different responses were obtained after administration of prednisolone in homozygotes (GG) and heterozygotes (AG). Nevertheless, a significant higher response was achieved in GG homozygotes after administration of prednisolone versus non-significant differences in heterozygotes after administration of prednisolone in heterozygotic variants (GA) (Table 7).

Table 7. Relationship of ER22/23EK(rs6189/rs6190) genetic variation and spirometric analysis in chronic bronchitis patients.

	ER22/23EK (rs6189/rs6190)						P. Value [a]
	GG			GA			
	Median	IQR		Median	IQR		
pre (FEV1(L))	3.0	2.5	3.1	3.0	2.9	3.1	**0.973** NS
post (FEV1(L))	3.4	3.0	3.7	3.1	2.9	3.1	**0.263** NS
P. Value [b]	**< 0.001****			**0.109** NS			
pre (FVC)	4.4	3.9	4.6	4.3	4.1	4.8	**0.932** NS
post (FVC)	4.9	4.3	5.2	4.5	4.2	4.8	**0.360** NS
P. Value [b]	**< 0.001****			**0.102** NS			
pre (FEV1/FVC)	68.0	66.5	68.8	69.2	64.8	69.3	**0.623** NS
post (FEV1/FVC)	70.1	68.4	71.0	69.4	64.9	69.9	**0.285** NS
P. Value [b]	**< 0.001****			**0.109** NS			

Data presented as median & interquartile range,
[a] Mann–Whitney U-test used to test statistical differences between ER22/23EK (rs6189/rs6190 groups,
[b] Wilcoxon signed-rank test used for comparison between (pre & post) in the same group,
NS No significant changes ($p\geq0.05$),
** Highly significant changes ($p<0.01$).

Discussion

The present study investigated the variation of response of newly diagnosed chronic bronchitis patients to prednisolone therapy. The outcome confirmed that gene polymorphism greatly impacted the response to prednisolone with better responses being on the side of homozygotes than that of heterozygotes.

The studied samples were composed mostly of males and this might be related to the higher distribution of respiratory diseases in males than females (1-3). More enrolled subjects were from the urban (within the town) than from rural (surrounding villages) and this might be due to the close access of patients living in the town to these healthcare providers than those living in villages, therefore, the findings of this study disagree with internationally published studies (1, 2, 4) which do confirm a higher prevalence of bronchitis in rural than urban areas due to easy access of rural area to healthcare providers and presence of more mature healthcare system in the developed countries compared to other localities. Being the sample with a higher percentage of males, the smoker's percentage was higher than non-smokers which agrees with previously published results (1, 2, 4).

The percentage of splice variants [BCII (rs41423247), N363S (rs56149945), and ER22/23EK (rs6189/rs6190)] were represented mostly as homozygous [CC, AA, and GG] and to less extent as a heterozygous, this is typically could be responsible about variation in the response to glucocorticoids. It seems that the encoding gene for glucocorticoid responsiveness is a recessive gene, hence, homozygous were responsive while heterozygous ceased response to glucocorticoid therapy. Most genes usually appear to be prevalent in the form of homozygous and to less extent as heterozygous in the general population so the balance is always toward homozygous (5, 6). Correspondingly, glucocorticoid receptors were more prevalent than heterozygous resulting in variation in responsiveness even with other non-respiratory diseases (7, 8). A case study of Infertile women with Chrousos syndrome was heterozygous for glucocorticoid receptors resulting in unresponsiveness (9).

Measurements of FEV1, FVC, and FEV1/FVC have confirmed that the baseline of these parameters was significantly higher in homozygous compared to heterozygous patients. In harmony with these findings, it has been reported that asthmatic children with moderate to severe bronchitis exacerbations have shown better responses to glucocorticoid therapy for those children with homozygous genes compared to heterozygous gene profiles (11). Moreover, the heterozygous genetic presentation could be linked to the aetiology of these respiratory diseases due to variations in the baseline characterization of respiratory function tests (FEV1, FVC, and FEV1/FVC). A pilot study conducted by Pietras *et al*. (2011) reported that asthmatic exacerbation has been linked to single nucleotide polymorphism resulting in unresponsiveness to glucocorticoid therapy (12).

In addition, the measurement of FEV1, FVC, and FEV1/FVC after therapy has confirmed that these parameters obtained better values in homozygous versus heterozygous polymorphic gene expression. Several studies have confirmed that glucocorticoid resistance is associated with diseases, such as asthma (4-10%), rheumatoid arthritis (30%), sepsis (100%), and chronic obstructive pulmonary diseases(100%) (13-15). In congruent with our results, the genotype has been found to be involved in glucocorticoid responsiveness in asthmatic patients, where the respiratory parameters showed betterment in the homozygous genotype compared to the heterozygous (16).

Four essential steps in GC dysfunction, which are reduced GR expression, defective steroid binding to the receptor, reduced ability of the receptor to bind to DNA, and increased expression and antagonism from proinflammatory transcription factors. Additionally, other mechanisms, such as increased GRβ expression, defective histone acetylation, and involvement of immune cells, have also been demonstrated. The severity of asthma and the effectiveness of corticosteroid treatment can be influenced by genetic variability. The GR gene (NR3C1) and IL17 gene polymorphisms may contribute to glucocorticoid resistance in asthmatic patients(17).

The text explains that Single nucleotide polymorphisms (SNPs) are common variations in the genome which can cause differences in traits among individuals. Polymorphisms can affect the structure or function of proteins and even gene transcription. The text also mentions that many SNPs have been identified in the IL17 gene, specifically in the IL17A and IL17F genes. These genes are located closely together and can form a heterodimer (18-23).

The SNPs rs9382084, rs763780, and rs2397084 have been linked to cancer, ulcerative colitis, rheumatoid arthritis, and reduced IL-17F levels in asthmatic patients. The IL17A gene has 3 exons and encodes a 155 amino acid protein. SNPs such as rs3819024, rs2275913, rs8193037, and rs3819025 have been associated with different diseases, including atherosclerosis, Graves' disease, cervical cancer, and oral squamous cell cancer. Some SNPs have been positively or negatively associated with asthma development, but their impact on glucocorticoid response is still unclear (24, 25).

Pro-inflammatory interleukins, such as IL-2, IL-4, and IL-13, can reduce the affinity of CR in inflammatory cells, leading to steroid resistance in patients with glucocorticoid-resistant asthma (26-28). The activation of p38 MAP kinase by IL-2 and IL-4 can reduce corticosteroid binding affinity and steroid-induced nuclear translocation of CR, resulting in glucocorticoid insensitivity. However, p38 MAPK inhibitors may reverse glucocorticoid insensitivity. Corticosteroids increase macrophage secretion of IL-10, contributing to their anti-inflammatory actions, but there is a reduction in T-lymphocyte secretion of IL-10 in patients with glucocorticoid-resistant asthma, which may contribute to the reduced responsiveness to the anti-inflammatory actions of corticosteroids (29, 30). Eventually, the surrounding inflammation and localized oxygen tension of the alveolar tissue will decide the fate of the response-boosting or diminishing the output response to steroids- due to released plethora of trophic factors contributing to the response (31, 32).

Conclusion

The study aimed to investigate the possible correlation between genetic variations in the glucocorticoid receptor (GR) gene and the responsiveness to prednisolone. The findings suggest that there is a significant difference in the frequency of different polymorphic GR gene variants between patients, indicating that these genetic variations play a significant role in the development of glucocorticoid hyporesponsiveness. Overall, this study provides valuable insights into the role of genetic variations in the development of glucocorticoid ineffectiveness and highlights the need for further research to better understand the complex interplay between genetics and glucocorticoid receptors.

While these findings may not have immediate practical implications for patient management, they represent an important step towards a more comprehensive understanding of the underlying mechanisms of glucocorticoid pharmacodynamics.

Conflict of interest

The authors declare no conflict of interest concerned in the present study.

Adherence to Ethical Standards

The study was approved by the Research Ethical Committee in the College of Pharmacy/ Al-Mustansiriyah University, with approval number (60) on 23.05.2023.

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