JABET
Journal of Advanced Biotechnology and Experimental Therapeutics

ORIGINAL ARTICLE

J Adv Biotechnol Exp Ther. 2025 Jan; 8(1): 116-124
eISSN: 2616-4760, https://doi.org/10.5455/jabet.2025.10
Published by www.bsmiab.org

Investigation on the effectiveness of progranulin as a novel predictive biomarker for allergic disorders

Nisreen W. Mustafa[1], *, Zaid N. Elia[2], Abeer M. Abdel Rasool[3], Sanaria F. Jarjes[2], Salam F. Nawara[4], Shakhawan H. Hamid[5]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Iraq
[2]Department of Medical Laboratory Technology, Erbil Technical Health and Medical College, Erbil Polytechnic University, Erbil, Iraq
[3]Pharmaceutical Department, Pharmacy College, Ninevah University, Iraq
[4]Department of Medicine, College of Medicine, University of Mosul, Iraq
[5]Erbil Dermatologic Teaching Center, Iraq

***Corresponding author**
Nisreen W. Mustafa
Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Iraq
Email: nisrenw@yahoo.com

Academic editor
Md Jamal Uddin, PhD
ABEx Bio-Research Center
Dhaka, Bangladesh

Article info
Received: 29 June 2024
Accepted: 16 November 2024
Published: 22 December 2024

Keywords
Biomarkers, Progranulin, Respiratory allergy, Skin allergy

ABSTRACT

Progranulin (PGRN) has been implicated in the emergence of several inflammatory conditions. However, the function of PGRN in allergy-related conditions has not been clearly elucidated. Thus, the current study aimed to investigate the effectiveness of PGRN as a biomarker in allergic disorders. A total of 124 participants (84 with allergic disorders and 40 healthy individuals) were included in this study. Patients were divided into two groups, 38 were classified as having allergies related to the respiratory system and 46 with allergies related to the skin, based on their clinical diagnosis. This categorization was confirmed by serological diagnosis by estimating the levels of immunoglobulin E (IgE). Additionally, C-reactive protein (CRP) levels were measured for the detection of inflammation. Serum PGRN level was estimated by the enzyme-linked immunosorbent assay (ELISA) technique, while interleukin-6 (IL-6) concentration was determined by the fluorescent immunoassay technique. Serum PGRN levels were significantly increased ($p>0.05$) in all patient groups as compared with controls. Adult patients recorded a significant elevation in PGRN level ($p<0.05$) compared to the children, while no significant difference ($p>0.05$) was recorded in terms of disease type (respiratory tract and skin allergies) or gender. Additionally, the results of Spearman's correlation test revealed that there was no significant correlation between PGRN and each of IgE, CRP, and IL-6. Thus, the current study concluded that PGRN had efficacy as a predictive biomarker for various allergic disorders.

INTRODUCTION

Allergy-related diseases are one of the most prevalent chronic conditions worldwide, affecting people of all ages, from infancy to old age, and they have emerged as one of the 21st century's epidemics [1]. An allergic reaction involves a misguided immune response to harmless dietary and environmental antigens called allergens [2].

Allergens differ in source and nature, causing mild to severe cutaneous and systemic symptoms based on the exposure mechanism and route of sensitization. These can come into contact with the skin, be breathed in, or be ingested [3]. Numerous immune system components are crucial in mediating allergic disorders; however, immunoglobulin E (IgE) is considered one of the main drivers [4]. Following exposure to the allergen, allergen-specific IgE binds to the allergen, activating mast cells that then rapidly release histamine and other mediators, resulting in symptoms [5]. Aeroallergen inhalation results in allergic asthma and allergic rhinitis, whereas contact with allergens causes cutaneous allergies [3].

On the other hand, biomarkers are known as either quantitative or qualitative indicators of a biological state or condition that are related to the occurrence, severity,

pathogenesis, progression, and treatment response of a certain disease [6]. Thus, the evaluation of biomarkers could be a useful tool for establishing accurate diagnosis, selecting the most effective treatment, and reducing future adverse clinical outcomes [7]. Several biomarkers have been investigated in allergic disorders, but the most thoroughly available for clinical use is the blood IgE level. Importantly, the elevated IgE levels typically signify allergic disorders [8].

Furthermore, progranulin (PGRN) is a protein having anti-inflammatory and immunomodulatory characteristics that is mainly produced by immunological and epithelial cells [9]. Increased levels of PGRN in the serum are thought to be a useful nonspecific inflammatory marker for both acute and chronic inflammations, and they have recently been linked to diseases caused by a variety of etiologies [10]. Thus, the present study aimed to investigate the efficacy of PGRN as a novel biomarker in different allergic disorders and to find out whether it is specific to a particular type of allergy or not.

MATERIALS AND METHODS

Study design and participants

During the period from February to August 2023, a total of 84 patients (40 females and 44 males, aged 4-73 years) who were clinically diagnosed as having allergic disorders were included in this study. Further, the patients were split into two groups: 38 with respiratory allergies and 46 with skin allergies. Another 40 healthy individuals without any evidence of allergic diseases were also enrolled as a control group.

Ethical approval

The study methodology was confirmed by the medical ethics committee of Erbil Polytechnic University, Iraq (permission no.: 24/0016HRE in 2023/4/8). Additionally, all participants provided verbal consent.

Sample collection and laboratory assays

Blood samples were collected from all participants by vein puncture and allowed to clot. The sera were separated using centrifugation at 4000 rpm for 15 minutes, and they were kept at -20 °C until they were utilized in subsequent assays. To confirm the clinical diagnosis of allergic cases, total serum IgE levels were measured using the ichroma™ II (Boditech, Korea), which calculates and displays the result automatically in terms of IU/mL.

Furthermore, latex immunoassay using Architect Abbot c4000 (Abbott, USA) was employed to estimate the levels of CRP. 10 µL of serum was added to the glycine buffer. Then, anti-human CRP rabbit serum was added and mixed. After that, the mixture was determined by measuring the decrease of transmitted light at a wavelength of 572 nm.

Serum PGRN levels were estimated by the sandwich enzyme-linked immunosorbent assay (ELISA) technique utilizing the Human PGRN ELISA Kit (MyBiosource/USA). Anti-PRGN antibody was pre-coated onto the micro-ELISA plates. The biotin-conjugated anti-PRGN antibody was utilized as a detecting antibody. The standards and test samples were added to the wells, incubated for 60 minutes, and then rinsed with wash buffer. Biotin-conjugated detection antibody was added and incubated, and the unbound conjugates were removed using a wash buffer. Finally, horseradish

peroxidase (HRP)-Streptavidin was added, followed by an acidic stop solution. The results were read using a Thermo Scientific microplate reader (Multiskan FC-USA) at an absorbance of 450 nm.

Serum concentrations of IL-6 were determined with an automatic biochemical analyzer (Cobas® 6000; Roche, Germany), in which serum samples were incubated with biotinylated monoclonal IL-6-specific antibody and detected by fluorescent immunoassay technique. Every assay was carried out in accordance with the guidelines provided by the manufacturers.

Statistical analysis

GraphPad Prism Software Version 8 was used to analyze the data. The independent t-test, Mann-Whitney U test, and Spearman's correlation were used to estimate the differences between the variant groups. A p value of less than 0.05 ($p < 0.05$) was considered statistically significant, and all data are presented as mean ± standard deviation (SD).

RESULTS

Serological characteristics of allergic patients

During the study period, 84 patients clinically diagnosed with allergic disorders were recruited into this research, and they were categorized into respiratory and skin allergic groups. Levels of serum IgE as a common biomarker were estimated to approve the diagnosis. The result revealed higher serum IgE levels (> 100 IU/ml) in patients with skin allergies. However, no significant differences ($p > 0.05$) regarding allergy type and gender were found between different groups in the serum IgE levels (IU/ml), while the differences were significant regarding age (Table 1).

Table 1. Differences in serum IgE levels among patient groups.

Groups	IgE (IU/ml)		p-value
	Mean ± SD	Range	
Respiratory allergy (n=38)	385.9±291.1	102-1000	0.051^{ns}
Skin allergy (n=46)	520.9±343.0	126-1070	
Children (n=16)	736.2±388.3	145-1070	0.040*
Adult (n=68)	416.5±299.1	102-1030	
Male (n=44)	593.0±397.4	102-1070	0.079 ^{ns}
Female (n=40)	342.7±176.3	131-737	

p-value > 0.05 is not significant (^{ns}); p-value ≤ 0.05 is significant*. The values are presented as mean ± standard deviation (SD); *p-value: significant regarding the age; IgE: Immunoglobulin E.

Serum levels of CRP in allergic patients

CRP had been measured in the serum of patients with allergic disease. It is used to determine whether allergic symptoms are related to an inflammatory or non-inflammatory condition. Results that are 10 mg/L or more were considered positive. It was found that the mean serum CRP levels were positive for all patient groups, while no statistically significant differences were found between various patient groups according to allergy type, age, and gender (Table 2).

Table 2. Differences in serum CRP levels among patient groups.

Groups	CRP (mg/L)		p-value
	Mean ± SD	Range	
Respiratory allergy (n=38)	15.75±16.44	2.5-55	
Skin allergy (n=46)	14.80±11.26	2-27	0.639 ^{ns}
Children (n=16)	11.67±12.01	2-27	
Adult (n=68)	16.33±15.45	2-55	0.523 ^{ns}
Male (n=44)	11.79±11.35	2-30	
Female (n=40)	12.94±10.37	2-55	0.593 ^{ns}

p-value > 0.05 is not significant (^{ns}). The values are presented as mean ± standard deviation (SD); p-value: non-significant between various patient groups according to allergy type, age, and gender; CRP: C-reactive protein.

Serum levels of PRGN and IL-6 in allergic patients

As shown in Figure 1, serum PGRN levels in the patient groups, respiratory and skin allergic disorders, were significantly elevated as compared with healthy controls (10.43±4.042 ng/ml and 9.924±4.303 ng/ml, respectively *vs* 1.422±0.374 ng/ml; $p < 0.05$). Additionally, when serum PGRN levels were evaluated in patients with normal CRP and those with elevated CRP in comparison with the control group, they both displayed significantly greater values than controls (Figure 1).

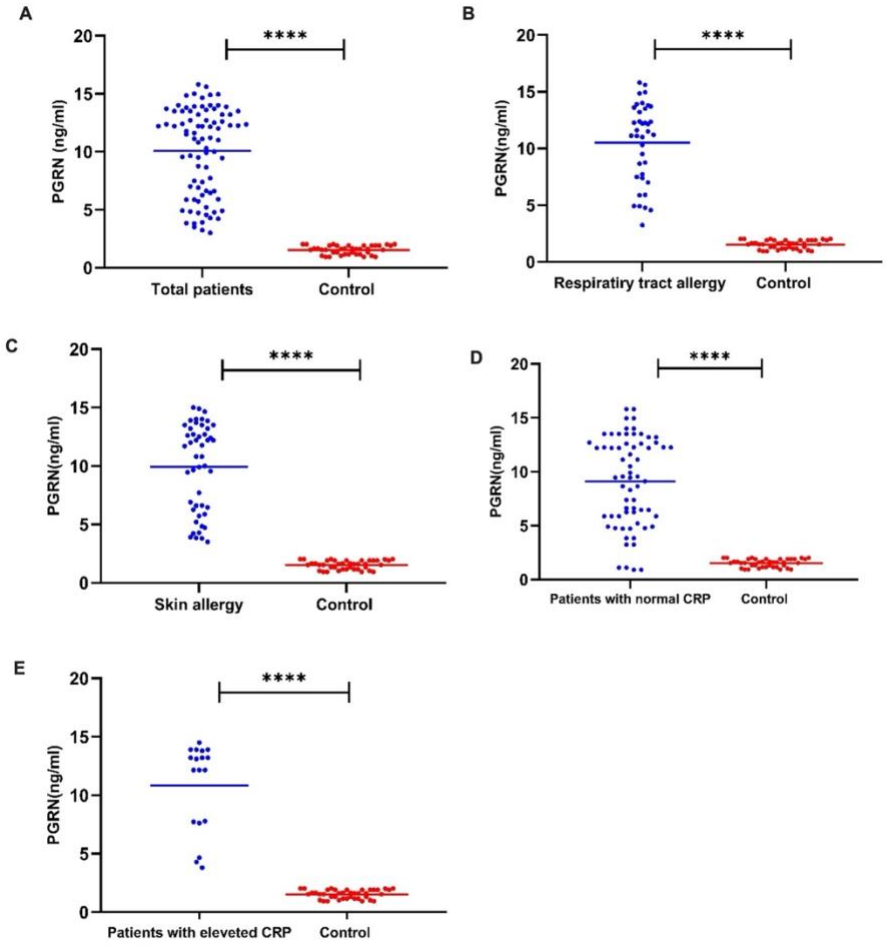

Figure 1. Comparison of serum PGRN levels (ng/ml) among patient groups and control. Serum PGRN levels were significantly elevated (****p-value ≤ 0.0001) in patients with allergies compared with controls. (A) total patients. (B) Patients with respiratory allergic conditions. (C) Patients with skin allergic conditions. (D) Patients with normal CRP levels. (E) Patients with elevated CRP levels. PGRN, progranulin; CRP, C-reactive protein.

Moreover, Table 3 shows comparisons in serum PRGN levels among patient groups. With respect to allergy type, gender, and CRP level, there were no statistically significant variations. Interestingly, there was a significant difference between adults and children in serum PRGN levels (11.04±3.773 *vs* 6.267±3.75 ng/ml, respectively; $p < 0.05$).

On the other hand, serum IL-6 levels were also determined in patients with allergies. Considerably high serum IL-6 levels (> 5 pg/ml) in patients with allergies were detected. Regarding allergy type, the differences in the IL-6 levels between patients with respiratory allergy and skin allergy were statistically significant (8.013±1.942 and 6.687±1.467, respectively; $p > 0.05$) (Table 4). However, there were no significant differences in mean serum IL-6 levels regarding gender and age (Table 4).

Table 3. Differences in mean serum PGRN levels among patient groups.

Groups	PGRN (ng/ml)		p-value
	Mean ± SD	Range	
Respiratory allergy (n=38)	10.43±4.042	3.266-15.8	0.523 ^{ns}
Skin allergy (n=46)	9.924±4.303	3.505-15.09	
Children (n=16)	6.267±3.75	3.526-13.8	0.025*
Adult (n=68)	11.04±3.773	3.241-16.02	
Male (n=44)	8.890±4.442	2.983-15.8	0.546 ^{ns}
Female (n=40)	10.17±3.326	4.388-13.9	
Patients with normal CRP (n=66)	9.116±4.281	1.15-15.8	0.127 ^{ns}
Patients with elevated CRP (n=18)	10.84±3.713	3.266-15.09	

p-value > 0.05 is not significant (^{ns}), and p-value ≤ 0.05 is significant *. The values are presented as mean ± standard deviation (SD); *p-value: significant regarding the age; PGRN: Progranulin.

Table 4. Differences in mean serum IL-6 levels among patient groups.

Groups	IL-6 (pg/ml)		p-value
	Mean ± SD	Range	
Respiratory allergy (n=38)	8.013±1.942	5.23-11.3	0.001**
Skin allergy (n=46)	6.687±1.467	5.12-8.93	
Children (n=16)	7.383±0.8873	6.2-8.23	0.370 ^{ns}
Adult (n=68)	7.719±2.103	5.12-11.3	
Male (n=44)	6.941±1.304	5.12-9.14	0.101 ^{ns}
Female (n=40)	7.711±2.141	5.22-11.3	

p-value > 0.05 is not significant (^{ns}) and P-value ≤ 0.05 is significant **. The values are presented as mean ± standard deviation (SD); **p-value: significant regarding the allergy type; IL-6: Interleukin-6.

Correlation between PGRN levels and the other biomarkers in allergic patients

According to the results, PGRN levels exhibited no considerable correlations with IgE levels ($r = 0.09374$; $p < 0.586$), CRP levels ($r = -0.2281$; $p < 0.472$), and IL-6 levels ($r = 0.2437$; $p < 0.300$) in patients with allergic disorders (Figure 2).

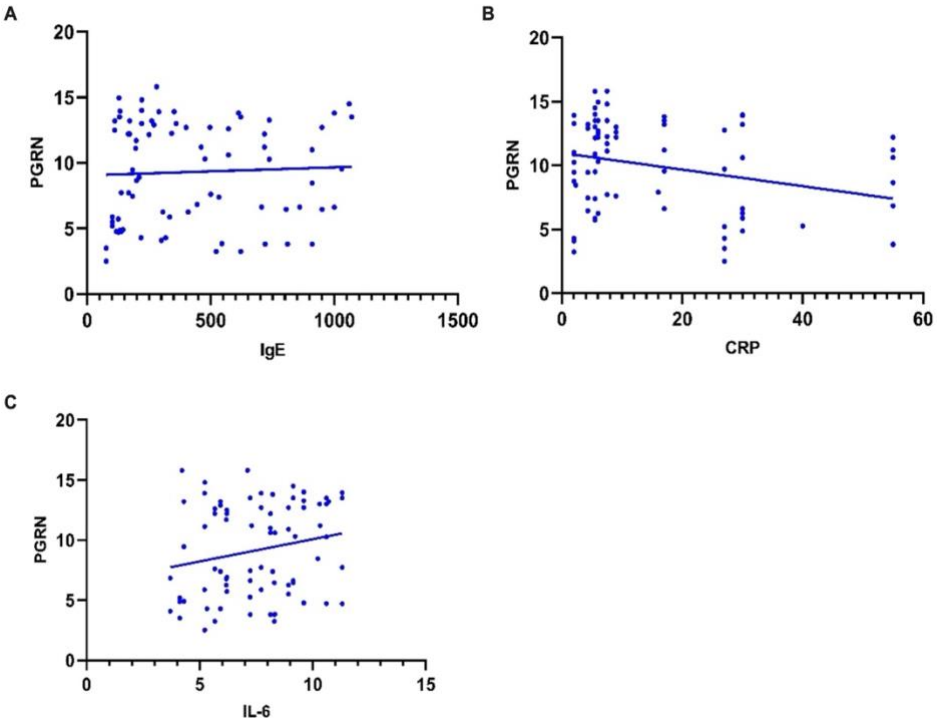

Figure 2. Correlation between PGRN levels and biomarkers of allergies and inflammations. PGRN levels exhibited no correlations with A) IgE levels ($r = 0.09374$; $p < 0.586$), B) CRP levels ($r = -0.2281$; $p < 0.472$), and C) IL-6 levels ($r = 0.2437$; $p < 0.300$) in patients with allergic disorders. PGRN: Progranulin, IgE: Immunoglobulin E, CRP: C-Reactive protein, IL-6: Interleukin-6.

DISCUSSION

The constantly rising incidence rates and significant recurrence rates of allergic disorders are recently garnering more attention [1]. Therefore, it is becoming increasingly important to develop diagnostic tools for allergic disorders, and the purpose of this study was to investigate the effectiveness of PGRN as a novel biomarker in allergic disorders and ascertain whether it is specific to a certain type of allergy or not. Consequently, this study has covered airway and skin allergies. Biomarkers have always been an essential part of more recent and advanced therapeutic approaches for the diagnosis, prognosis, and treatment of diverse diseases [7].

In this study, IgE levels were elevated in all patient groups; this result emphasized the presence of allergic reactions in all patients. Kostova et al. reported that one of the main indicators of allergic disorders is elevated IgE [8]. Patients with symptoms of asthma, allergic rhinitis, and atopic dermatitis can be identified as allergic by measuring their total IgE [11, 12]. Moreover, CRP is a benchmark for physicians to detect or rule out inflammation and infection [13, 14]. Hence, in this study, CRP was measured to detect the inflammation status in allergic patients. There were no significant differences in the levels of CRP between groups according to allergy type, age, and gender despite the elevating mean levels of CRP that have been recorded in allergic patients. Similar results were obtained from previous studies that concluded increasing serum CRP concentrations in patients with allergic diseases compared to controls [15, 16]. Additionally, chronic allergies, particularly those that contribute to asthma or eczema, can cause a continuous low-grade inflammatory state, and this persistent inflammation might lead to a mild to moderate increase in CRP levels over time [17].

PGRN is a crucial modulator of inflammation and immunity [18]. Numerous studies have demonstrated the critical role that PGRN plays in the human body, including its involvement in angiogenesis, wound healing, cell formation, neoplasia, cell cycle regulation, embryogenesis, and the modulation of autoimmune responses [10, 19-23]. Despite that, little data has been published regarding PGRN in relation to allergic disorders, particularly skin allergies.

In this study, patients with allergic diseases had considerably higher serum PGRN levels than healthy controls. To our knowledge, this is the first study to reveal that patients with allergies, especially those with skin allergies, had considerably higher levels of PGRN in their sera. However, in line with this finding, Choi and colleagues investigated the role of PGRN in the etiology of allergic asthma in mice and showed that, upon exposure to allergens, macrophage-derived PGRN stimulated the production of type 2 cytokines in natural killer (NK) T cells and epithelial cells during the initial sensitization phase [24]. In contrast, Park et al., found that the asthma group had considerably lower blood PGRN levels than the healthy group and they suggested that serum PGRN could be an indication of severe asthma [25]. In this study also, PGRN levels of the respiratory allergy group were comparable to those in skin allergy; the differences between them were found to be non-significant. According to the findings of a prior study conducted by Mustafa et al., this could be connected to the non-specific function of PGRN that affects various inflammatory conditions in a similar way [10]. Likewise, considering the serum levels of CRP, the differences in PGRN levels between these groups were also non-significant. In a prior study, PGRN levels were linked to pulmonary cell damage caused by the inflammatory process and corresponded with activity markers like CRP [26]. On the other hand, it is important to note that serum PRGN was independent of the patient's gender [27]. In the current study, there was no statistical difference in serum PGRN levels between males and females. Furthermore, the mean serum PGRN levels were higher in adults than in children, supporting the previous reports that PGRN levels increased with age [28, 29]. However, Gunes et al. showed no correlations between PGRN serum levels and age [30]. Moreover, the current study has shown that individuals with respiratory allergic conditions have statistically significant elevations in serum IL-6 levels compared to those with skin allergies. This could be due to the localized nature of skin allergic reactions compared to the more systemic nature of respiratory allergies. Similarly, Gubernatorova and colleagues reported that allergic asthma is characterized by an elevation in IL-6 levels, which is similar to other pro-inflammatory cytokines and is important in the pathogenesis of this disease [31]. On the other hand, even though all patient groups in the current study had elevated serum levels of IgE, CRP, and IL-6, PGRN levels did not show significant relationships with any of them. This could be due to the different functions and mechanisms these biomarkers play in the inflammatory process. In the last few decades, several studies have shown that IgE, IL-6, CRP, and recently the PGRN are components of an immunological and inflammatory response network that interact in allergic disorders [32]. PGRN may influence IL-6 levels by modulating immunological responses and inflammation. IL-6 enhances the inflammatory response and accelerates Th2 cell differentiation by stimulating CD4 T cells to produce more IL-4, which promotes IgE production. CRP is induced by IL-6, and increased IL-6 can raise CRP levels, which are indicators of systemic inflammation [14, 18, 33, 34].

The relatively small sample size and the restricted previous data were realized as potential limitations of this investigation. Therefore, large and in-depth studies are required to confirm the findings of the current study and to fully understand the role of PGRN in allergic conditions, particularly in skin allergies.

CONCLUSIONS

In summary, this study has shown that PGRN levels are raised in individuals with both respiratory and skin allergic disorders and suggests that PGRN has the efficiency to be a novel, non-specific, and useful biomarker of various allergies. Furthermore, there is no correlation found between the PGRN and increasing IgE, CRP, and IL-6 within these patient populations.

ACKNOWLEDGEMENT

None.

AUTHOR CONTRIBUTIONS

NWM and ZNE participated in the study's design. SFN and SHH performed the patients' clinical examination. The laboratory testing was done by AMA and ZNE. NWM conducted the statistical analysis for this study. SFJ wrote this article and assumed charge of the manuscript's revision. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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