Evaluation of the inflammatory predictive efficiency of progranulin as compared with common pro-inflammatory regulators

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ABSTRACT

Progranulin (PGRN), is a multifunctional protein with profound expression in epithelial and immune cells in which plays a crucial role in controlling host-defense signaling pathways during infection and inflammation. The current study was carried out to evaluate the efficiency of PGRN as a predictive inflammatory marker for a group of diseases with different etiologies that cause acute and chronic inflammations. A total of 120 participants with various diseases including rheumatoid arthritis (RA), *Helicobacter pylori* infection, burn wound, hepatitis B and prostate cancer, and 20 healthy people were enrolled in this study. The levels of serum PGRN and interleukin-6 (IL-6) were detected. Elevated serum PGRN levels have been reported in all patient groups when compared with those in healthy controls ($P < 0.05$). Likewise, increased serum hsCRP and IL-6 levels were seen in all patient groups. However, for some patient groups, the differences in hsCRP and IL-6 levels did not reach statistical significance ($P > 0.05$) in comparison with control group. Furthermore, serum PGRN levels exhibited positive correlation with hsCRP in *H. pylori* and RA patient groups. As well as, with IL-6 only in RA patient group, whereas no significant correlations were found with the rest of studied diseases. This study concluded that PGRN is an effective nonspecific inflammatory indicator of acute and chronic inflammations. It had also a higher predictive efficiency than hsCRP and IL-6 which are commonly used as inflammatory predictive markers.

INTRODUCTION

Inflammation is a defense mechanism that involves immune cells, blood vessels, and chemical mediators in the intricate biological reaction of body tissues to deleterious stimuli like pathogens, damaged cells, or irritants [1]. Many diseases, such as cancer, rheumatoid arthritis, infection, burn injury and gastrointestinal disease, all have inflammation as a common etiology [2-5]. Although the specifics of the initial stimulus and its location within the body determine how the inflammatory response processes are carried out, they all share a common mechanism that involves the recognition of harmful stimuli by cell surface pattern receptors, activation of inflammatory pathways, liberation of inflammatory markers, and attraction of inflammatory cells [6].

The immune system performs a number of important tasks, including preventing the invasion of harmful microbes, eliminating mutant somatic cells, and regulating the level of immune response to antigenic stimuli [7]. In connection to physiological and pathological situations, the immune system is inextricably linked to alterations in inflammatory pathways. However, unmanaged inflammatory reactions and persistent immunological responses may cause immune system illnesses such as rheumatoid

arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS) and type 1 diabetes mellitus (T1DM) [8].

PGRN, a secretory glycoprotein with 593 amino acid remnants, has been found to be present in a variety of tissues, including epithelia, cell lines derived from myeloid and lymphoid tissues, bone marrow, and solid organs. It is a critical actor and regulator of numerous system activities [7]. It involved in cancer, tissue repair, embryonic development, and wound healing [9, 10]. PGRN is also crucial for controlling inflammation by directly interacting with the tumor-necrosis-factor receptors (TNFR1, TNFR2 and DR3) and blocking the TNF-mediated inflammatory signaling cascade [11]. Elevated serum PGRN levels are recently linked to systemic lupus erythematosus (SLE) and RA [12]. This finding implied that PGRN played a key role in modulating the inflammatory process and mediating its anti-inflammatory effects, therefore the goal of the present study was to assess the efficiency of PGRN as a predictive inflammatory marker for a group of diseases with various etiologies that lead to acute and chronic inflammations.

MATERIALS AND METHODS

Study participants

Between March 2022 and July 2022, 120 participants with various diseases (20 with RA, 20 with *H. pylori* infection, 20 with burn wound, 30 patients with hepatitis B and 30 patients with prostate cancer) in addition to 20 apparently healthy people, as controls, were enrolled in this study.

The study methodology was confirmed by the ethics committee of Pharmacy College, Basrah University, Iraq, according to the document number (7/40/1011). As well as all participants provided a verbal consent.

Sample collection and laboratory measurements

A blood sample of 5 ml was collected from all participants using venipuncture with aseptic precautions. After centrifugation, sera were separated and stored at −20°C until utilized in subsequent assays. Serum PGRN concentrations were measured by Sandwich ELISA technique using (Hu PGRN ELISA kit, MyBioSource, USA). Likewise, the Double Antibody Sandwich ELISA technique was employed to qualify serum IL-6 concentrations utilizing Hu IL-6 ELISA kit (MyBioSource, USA). PGRN and IL-6 analyses were performed using a Thermo Scientific microplate reader (Multiskan FC-USA) at 450nm.

The hs-CRP concentrations were measured on Abbott's Architect c4000 analyzer by CMIA technique using Abbott's FDA-approved kit (Multiagent CRP Vario). Furthermore, CMIA technique using Architect (Abbott-USA) was utilized for detection of hepatitis B surface antigen (HBsAg), anti-cyclic citrullinated peptide (Anti-CCP), prostate specific antigen (PSA) and procalcitonin concentration. VIDAS® *H. pylori* IgG test (BioMérieux/ France) was used for detection of anti-*Helicobacter pylori* IgG antibodies in patients' sera by enzyme-linked fluorescence assay (ELFA) technique to confirm the infection with *H. pylori*. All tests were carried out in accordance with the manufacturer's instructions.

Statistical analysis

Statistical analysis was carried out using SPSS (Statistical Package of Social Science) software. The independent t test, Mann-Whitney U test, and person's correlation were used to compare the differences between the patient groups and control group. Data are reported as the mean ± standard deviation and a P value of less than 0.05 ($P < 0.05$) was deemed to be statistically significant.

RESULTS

Demographic profile of participants

The distribution of patient groups as well as control group according to gender have been represented in Figure 1. Males were predominating in all patient groups except in RA. Regarding the age of patients, they were ranged between 38-65, 37-62, 47-63, 27-77 and 2-45 years old in patient groups of *H. pylori*, hepatitis B, RA, prostate cancer and burn wound, respectively. While in healthy group, the range of age was 17-55 years old.
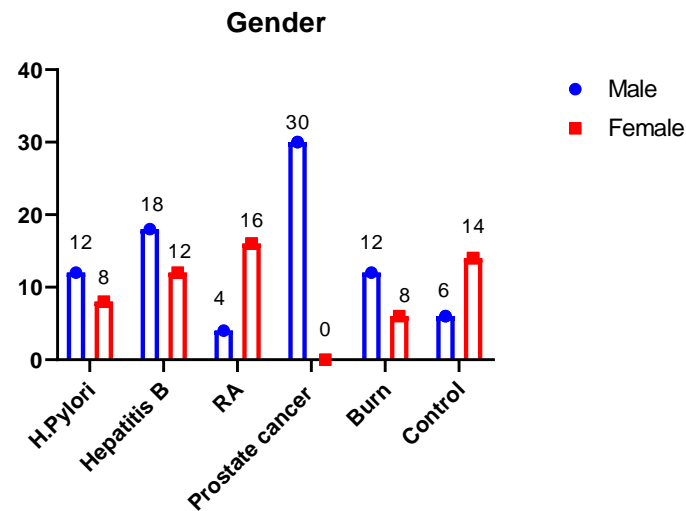
Figure 1. Distribution of different patient groups and the control group according to gender. *H. pylori* infected patients =20; patients with hepatitis B =30; patients with RA= 20; prostate cancer patients =30; patients with burn wounds= 20 and control= 20 healthy people.

Levels of serological parameters in patients

Serological tests that approved to diagnose patients within this study were IgG (IU/ml), HBs-Ag (S/CO), Anti-CCP(IU/ml), PSA (ng/ml) and procalcitonin (ng/ml) for confirming of *H. pylori* infection, hepatitis B, RA, prostate cancer and burn wound, respectively (Table 1).

Table 1. Confirmative laboratory tests in different patient groups.

| Disease	Serological test	Mean	Range	Cut-off value
H. pylori infection	IgG (IU/ml)	3.35	2.29- 4.81	1
Hepatitis B	HBs-Ag (S/CO)	2865.04	612.5-5290.04	1
RA	Anti-CCP (IU/ml)	169.10	134.22-200	0.8
Prostate cancer	PSA (ng/ml)	112.58	8.1-202	4
Burn wound	Procalcitonin (ng/ml)	3.63	0.02- 17.46	0.5

Levels of serum PRGN, hsCRP, and IL-6 in patients

Serum PGRN levels were evidently greater ($P < 0.05$) in patients with *H. pylori*, hepatitis B, RA, prostate cancer and burn wound than in healthy controls (14.96±1.75, 14.22±1.43, 12.60±3.23, 13.19±1.99 and 13.17±1.59, respectively *vs* 1.29±0.36 ng/ml) (Table 2; Figure 2). On the other hand, serum hsCRP levels were also found to be comparable, patients with *H. pylori*, RA, prostate cancer and patients with burn wound had significantly higher ($P < 0.05$) mean hsCRP level than control group (1.61±2.04, 4.462±5.29, 3.33±3.43 and 6.07±3.60 respectively *vs* 0.22±0.15 mg/dl). Whereas statistically non-significant variation ($p = 0.109$) was found in the patient group of hepatitis B in comparison with healthy group (0.96±1.67*vs* 0.22±0.15 mg/dl) (Table 3; Figure 3).

Moreover, serum IL-6 levels were considerably higher ($P < 0.05$) in the patient groups of hepatitis B, RA, prostate cancer and burn wound as compared with healthy controls (13.23±5.51, 17.62±12.49, 14.14±8.09 and 25.52±15.81 respectively *vs* 7.89±1.846 pg/ml). While statistically non-significant variations ($P = 0.890$) were observed between patients infected with *H. pylori* and control group (9.82±5.49 *vs* 7.89±1.84 pg/ml) (Table 4; Figure 4).

Table 2. Differences in serum progranulin levels between patient and the control group.

| Disease	Patients	Control	*P*- value
	Progranulin (ng/ml)	Progranulin (ng/ml)	
	Mean ± SD (Range)	Mean ± SD (Range)	
H. pylori infection	14.96±1.75 (11.46-17.73)	1.29±0.36 (0.67-1.78)	0.000
Hepatitis B	14.22±1.433 (12.18-16.02)	1.29±0.36 (0.67-1.78)	0.000
RA	12.60±3.23 (8.06-15.87)	1.29±0.36 (0.67-1.78)	0.000
Prostate cancer	13.19±1.99 (8.68-15.26)	1.29±0.36 (0.67-1.78)	0.000
Burn wound	13.17±1.59 (10.44-16.03)	1.29±0.36 (0.67-1.78)	0.000

Performed using independent *t* test.
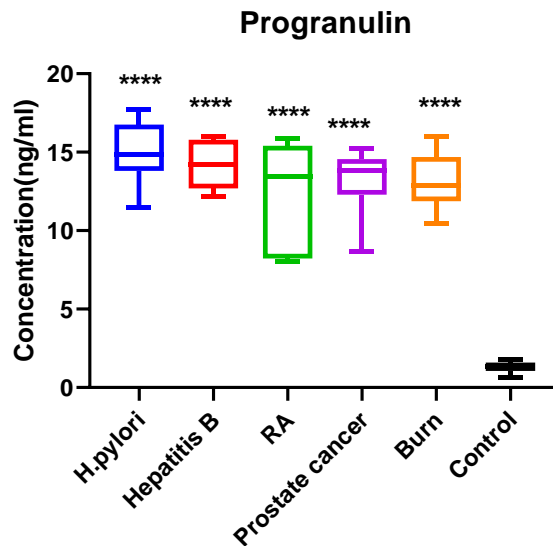
Figure 2. Differences in mean serum progranulin levels (ng/ml) between each patient group and the control group. *P*-value ≤ 0.0001 significant ****.

Table 3. Differences in serum hsCRP levels between patient groups and the control group

Disease	Patients	Control	P- value
	hsCRP (mg/dl)	hsCRP (mg/dl)	
	Mean ± SD (Range)	Mean ± SD (Range)	
H. pylori infection	1.61±2.04 (0.01-6.35)	0.22±0.15 (0.04-0.59)	0.020
Hepatitis B	0.96±1.67 (0.01-5.68)	0.22±0.15 (0.04-0.59)	0.109
RA	4.462±5.29 (0.01-11.38)	0.22±0.15 (0.04-0.59)	0.040
Prostate cancer	3.33±3.43 (0.01-10.64)	0.22±0.15 (0.04-0.59)	0.004
Burn wound	6.07±3.60 (0.01-10.43)	0.22±0.15 (0.04-0.59)	0.000

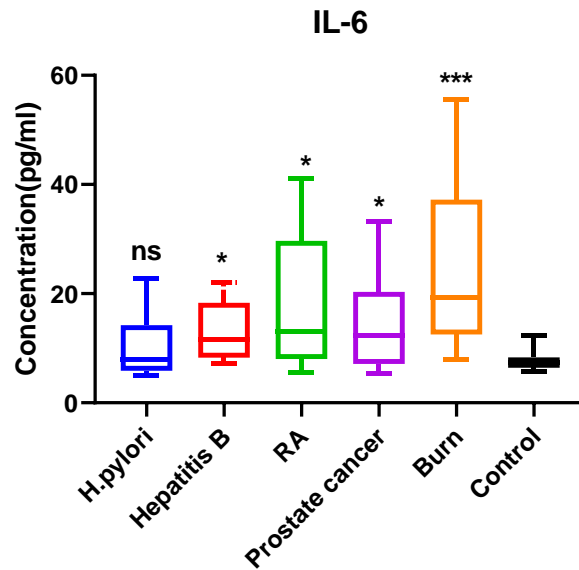Performed using independent *t* test and Mann-Whitney *U* test.
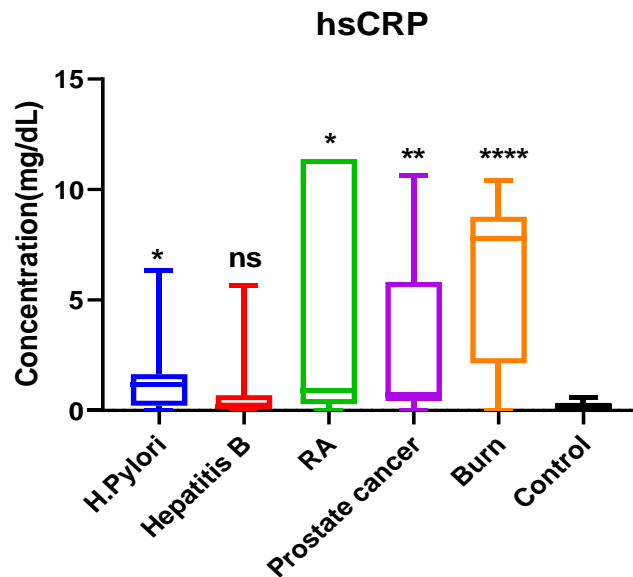
Figure 3. Differences in mean serum hsCRP levels (mg/dl) between each patient group and the control group. *P*-value > 0.05 not significant (ns); *P*-value ≤ 0.05 significant *; *P*-value ≤ 0.01 significant ** and *P*-value ≤ 0.0001 significant ****.

Table 4. Differences in serum IL-6 levels between patient groups and the control group.

Disease	Patients	Control	P- value
	IL-6 (pg/ml)	IL-6 (pg/ml)	
	Mean ± SD (Range)	Mean ± SD (Range)	
H. pylori infection	9.82±5.49 (4.97-22.84)	7.89±1.84 (5.83-12.32)	0.890
Hepatitis B	13.23±5.51 (7.12-22.14)	7.89±1.84 (5.83-12.32)	0.014
RA	17.62±12.49 (5.62-41.18)	7.89±1.84 (5.83-12.32)	0.036
Prostate cancer	14.14±8.09 (5.34-33.26)	7.89±1.84 (5.83-12.32)	0.025
Burn wound	25.52±15.81 (7.96-55.60)	7.89±1.84 (5.83-12.32)	0.001

Performed using independent *t* test and Mann-Whitney *U* test.

IL-6

Figure 4. Differences in mean serum IL-6 levels (pg/ml) between each patient group and the control group. *P*-value > 0.05 not significant (ns); *P*-value ≤ 0.05 significant * and *P*-value ≤ 0.001 significant ***.

Correlation between PRGN and other inflammatory biomarkers

In order to identify the efficiency of PGRN in predicting inflammations, it was necessary to analyze the correlation between serum level of PGRN and common inflammatory biomarkers (hsCRP and IL-6). Table 5 revealed that PGRN levels exhibited positive correlation with hsCRP levels in *H. pylori* group (r = 0.520; P = 0.047) and in RA group (r = 0.772, P = 0.042). However, no significant correlations were observed between those two inflammatory markers in hepatitis B, prostate cancer and burn wound groups (r = -0.453, P = 0.090; r = 0.182, P = 0.517; r = 0.155, P = 0.582 respectively). In addition, PGRN levels were shown to be strongly associated with IL-6 only in RA patient group (r = 0.763, P = 0.046), whereas no important correlations were shown in the rest of studied diseases.

Table 5. Correlations between serum PGRN and common inflammatory biomarkers in different patient groups.

PGRN	hsCRP		IL-6	
Patient groups	*P*-value	*r* -value	*P*-value	*r* -value
H. pylori infection	0.047	0.520*	0.209	0.344
Hepatitis B	0.090	- 0.453	0.304	- 0.362
RA	0.042	0.772*	0.046	0.763*
Prostate cancer	0.517	0.182	0.524	0.179
Burn wound	0.582	0.155	0.108	- 0.432

Performed using person's correlation analysis. *Indicates significant correlation.

DISCUSSION

PGRN is an essential mediator of inflammatory and immune reactions [13]. It has been recently suggested that PGRN's anti-inflammatory properties contribute to a number of inflammatory diseases [14], hence the objective of this study was to assess the efficiency of PGRN as a predictive inflammatory marker in comparison with common pro-inflammatory regulators. For this purpose, PGRN serum levels were estimated in patients with *H. pylori*, hepatitis B, RA, prostate cancer and burn wound.

Regardless to the gender and age, a significant elevation in serum PGRN levels was observed in all studied patient groups compared to those in control group. In line with the findings of current study, several studies indicated that circulating PGRN levels are increased in a variety of illnesses, including renal disease [15, 16], type 2 diabetes [17], cancer [18], COVID19 disease [19] and RA [20].

H. pylori infects more than half of the world's population, and it has been classified by the WHO as a group 1 carcinogen [21]. PGRN expression was greatly increased in gastric epithelial cells after infection with *H. pylori*. However, it is still unclear whether increased production of PGRN represent a protective response to eradicate *H. pylori* infection or it constitutes an adaptive response of the gastric epithelial cells [22]. Ren *et al*. identified a probable method by which PGRN exerts a significant influence on *H. pylori* infection and showed that *H. pylori* infection increased the expression of PGRN, which in turn regulated the expression of CDK4, a target gene of PGRN, via activating the phosphatidylinositol 3 kinases/protein kinase B (PI3K/AKT) signal pathway to competitively interfere with activation of TNF-α mediated inflammatory cascade [23].

On the other hand, when Gong *et al.* looked into the clinical significance of circulating PGRN in individuals with chronic hepatitis B, they observed that these individuals had significantly higher serum levels of PGRN than healthy individuals, indicating that PGRN plays an effective role in the pathogenesis of hepatitis B. [24].

Furthermore, Zhao *et al.* reported that PGRN participates in the progression of associated immunological illnesses that affect joints or arthritis complications like RA by acting as a potent stimulator in response to cartilage differentiation [25]. In 2014, Yamamoto and colleagues used ELISA to quantify the serum PGRN levels of patients with RA and observed a remarkable rise in PGRN levels when compared to controls which were not influenced by sex or age. As well as, they showed that the serum PGRN could be a valuable tool for tracking the progression of the disease in RA patients [26]. Likewise, Cerezo *et al.* showed elevated PGRN expression at localized inflammation and suggested a connection between PGRN levels, illness activity and functional impairment in RA patients [20].

Regarding the PGRN in cancer, previous studies have reported significant biological effects of PGRN on several cancer types. It was found to regulate the carcinogenesis due to its enhancement of cell growth, migration, invasion, angiogenesis, malignant transformation, resistance to anticancer medications, and immune avoidance [27]. Multiple human cancers, including those of the breast, ovarian, endometrium, cervix, liver, kidney, prostate, and brain, have been associated with elevated PGRN levels, where PGRN works as an autocrine growth factor by regulating the motility and invasion of transformed cells [28]. In breast cancer, glioblastoma, and ovarian cancer, high PGRN expression levels have been associated with an aggressive phenotype and a bad prognosis [18, 29]. Otherwise, Monami *et al.* sided with the hypothesis that PGRN might be critical in the progression of prostate cancer than in its initiation [30]. In a study of serum PGRN levels in men with prostate cancer, Greither *et al.* found that the levels are significantly different between healthy individuals and patients with prostate cancer [31]. The level was also correlated to the age and the prognosis of patients, with younger patients (≤66 years), had a significantly better overall survival than elder patients [31].

Moreover, inflammation and injury cause PGRN to be strongly expressed. Burn damage/ wound healing is a coordinated cell process including cytokines and regulatory growth factors [32]. According to a previous study, PGRN caused a greater buildup of fibroblasts, blood vessels, neutrophils, and macrophages in the wound. It

stimulates cell division, migration, and the development of tubules resembling capillaries by directly influencing isolated dermal fibroblasts and endothelial cells. Consequently, PGRN is likely a growth factor related to wounds [33].

In this study, although the serum levels of PGRN, IL-6 and hsCRP were increased in all patient groups, correlation serum levels of PGRN with the traditional biomarkers (hsCRP and IL-6) exhibited positive correlation only with hsCRP in *H. pylori* and RA patient groups, as well as with IL-6 in RA patient group, while no significant correlations were found with the rest of studied diseases. In general, inflammatory biomarkers serve as measures of the immune system's health, increased their levels may support evidence of ongoing illness processes and generate snapshots of complicated immune responses to the environment of acute and chronic inflammations. Limited or no prior data are available regarding correlations between PGRN and different inflammatory biomarkers in acute and chronic inflammations such as those included in the current study. According to Cerezo *et al.*, there was no correlation between serum PGRN levels and CRP levels in RA [20]. Meanwhile, Baillet *et al.* studied 813 RA patients and concluded that IL-6 and CRP were strongly correlated [34]. IL-6 is rapidly produced during immunological responses to infection and tissue damage, and the uncontrolled expression of IL6 exerts a pathological impact on autoimmune disease and chronic inflammation [35]. On the other hand, a study by Feng *et al.* [36] revealed that in the critically ill patients, the CRP serum levels elevated as the clinical picture deteriorated and reached a significant difference. Therefore, in patients with RA, the increased levels of PGRN that positively correlated with both hsCRP levels and IL-6 levels may predicting poor outcomes.

CONCLUSIONS

The results of the current study suggested that PGRN is an effective nonspecific inflammatory indicator of acute and chronic inflammations that resulted from different etiologies. It had also a higher predictive effect than hsCRP and IL-6 which are commonly used as inflammatory predictive markers. This study provided updated information to guide future studies. It is recommended that such studies with a larger sample size should be carried out to establish the role of PGRN as a marker for the prediction of inflammations and their sequels.

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AUTHOR CONTRIBUTIONS

NWM and ZNE contributed to the design of the study. OAN and ZNE carried out the laboratory measurements. NWM and SFJ analyzed the results. NWM and OAN wrote the article. SFJ contributed to the interpretation of the findings and took the lead in revising the manuscript. NWM and SFJ approved the final version of the manuscript to be published.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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