

Can serum progranulin levels be a biomarker following gastric ulcer therapy?

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Abstract

Introduction: Progranulin is a novel growth factor that has several physiological and pathological roles such as cell growth, tumorigenesis, embryogenesis, wound healing, and inflammation.

Aim: To compare the pre-treatment and post-treatment serum levels of the angiogenic factor vascular endothelial growth factor (VEGF), pro-inflammatory cytokine tumor necrosis factor α (TNF- α), and progranulin in peptic ulcer (PU) patients with a healthy control group.

Material and methods: Serum VEGF, TNF- α , and progranulin levels were studied with ELISA in 42 PU patients (antral ulcer (AU): 22, duodenal ulcer (DU): 20) and 15 healthy controls.

Results: The serum progranulin levels before treatment were 4237.35 ± 1091.30 pg/ml in the patients with AU, 4682.64 ± 1501.46 pg/ml in the patients with DU, 3055.66 ± 626.88 pg/ml in the control group, and 4460 ± 1315 pg/ml in the ulcer (AU and DU) group. The serum progranulin levels were 3607.7 ± 869.4 pg/ml in the AU group, 4286.5 ± 1208.78 pg/ml in the DU group, and 3947.1 ± 1094.64 pg/ml in the ulcer group after the treatment. When comparing pre-treatment serum progranulin levels of the AU group, DU group, and ulcer group with the control group there were statistically significant differences ($p < 0.001$, $p < 0.0001$, $p < 0.0001$, respectively).

Conclusions: The disappearance of the difference in terms of post-treatment serum levels of progranulin between the AU group and the control group suggests that serum levels of progranulin can be used as a biomarker of gastric ulcer healing.

Introduction

Peptic ulcer (PU) is defined as a mucosal injury due to acid-pepsin damage, which extends to the submucosa or muscularis propria in the digestive tract and is usually located in the proximal duodenum and stomach. *Helicobacter pylori* (*H. pylori*) infection and frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) are major causes of PU. Anti-secretory agents (H2RAs and PPIs) and successful treatment of *H. pylori* infection form the basis of treatment [1, 2].

Ulcer healing is a complex process modulated by several growth factors and cytokines [3]. Angiogenesis is the principal process for tissue injury and ulcer healing. It is necessary for nutrient and oxygen delivery to the healing site and carries out this by reconstruction

of microvasculature [4]. There are studies that have demonstrated the role of angiogenic growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and prostaglandins in gastroduodenal ulcer healing [5]. Vascular endothelial growth factor is a fundamental regulator of angiogenesis and binds its specific receptors expressed mainly on endothelial cells and initiates endothelial cell proliferation, migration, and microvascular tube formation [6, 7]. It was demonstrated that gastric mucosal injury by ethanol stimulates angiogenesis in the mucosa bordering ulceration and the increase VEGF messenger RNA (mRNA) expression [8].

Tumor necrosis factor α (TNF- α) expression at the ulcer site is increased in the rat stomach. Tissue ne-

crisis and release of leukotriene B attract leukocytes and macrophages. They phagocytise necrotic tissue and release pro-inflammatory cytokines such as TNF- α , interleukins (IL-1 α , and IL-1 β), which activate fibroblasts, endothelial and epithelial cells for angiogenesis and the growth of granulation tissue [9]. Luo *et al.* showed that TNF- α treatment of RGM-1 rat normal gastric epithelial cells resulted in increased cell migration that was dependent on COX-2 protein expression and the secretion of PGE2 [10].

Progranulin, also known as granulin-epithelin precursor (GEP), proepithelin (PEPI), acrogranin, and GP88/PC-cell-derived growth factor (PCDGF), is a 593-amino-acid secretory growth factor that has several physiological and pathological roles such as cell growth, tumourigenesis, embryogenesis, wound healing, inflammation, and neurodegeneration [11–15]. Progranulin has a strong anti-inflammatory effect that was thought to be mediated by inhibition of TNF receptors 1 and 2. It was shown that progranulin enters the injured tissue by the secretion of infiltrating inflammatory cells. It takes place at the early stage of granulation by fibroblast accumulation and neovascularisation [16]. Progranulin expression was studied in transcutaneous wounds until now [15].

Aim

The aim of this study was to compare the pre-treatment and post-treatment serum levels of the angiogenic factor VEGF, pro-inflammatory cytokine TNF- α , and anti-inflammatory growth factor progranulin in PU patients, with healthy control group.

Material and methods

Patients

Forty-two patients who underwent endoscopy for any reason and had PU (antral ulcer (AU) $n = 22$ and duodenal ulcer (DU) $n = 20$) and 15 healthy controls were included in the study between January 2017 and June 2017. Biopsies from antrum, corpus and ulcer margin of patients with AU were taken. The same eradication treatment was given to patients with *H. pylori* (rabeprazole 20 mg b.i.d, bismuth subsalicylate 562 mg b.i.d, metronidazole 500 mg t.i.d, tetracycline 500 mg q.i.d) for 2 weeks. All other PU patients without *H. pylori* were given rabeprazole 20 mg b.i.d. Upper gastrointestinal endoscopy of all patients with AU were repeated 4 weeks after rabeprazole treatment cessation, and *H. pylori* eradication control was performed with gastric biopsy for positive patients. *Helicobacter pylori* eradication control was determined via the stool antigen test with an enzyme immunoassay (EIA) utilising a monoclonal antibody performed at least 4 weeks after the end of therapy in patients with DU and *H. py-*

lori positivity. Biochemical and haemogram parameters were obtained from the laboratory archive.

Serum VEGF, TNF- α , and progranulin ELISA

After PU was detected with upper gastrointestinal system endoscopy 5-ml venous blood samples were taken before and after the treatment. Blood samples from 15 healthy controls and 42 PU patients were obtained with written, informed consent and stored at -80°C until use. Serum VEGF, TNF- α , and progranulin levels were studied with enzyme-linked immunosorbent assay (ELISA) with a commercial ELISA kit (Boster Immunoleader, USA).

Ethics

This study was approved by the Local Ethical Review Board and conducted according to the guidelines laid down in the Declaration of Helsinki.

Statistical analysis

Analysis of the data was done with the IBM SPSS 22.0 packet program. Categorical variables were reported as a proportion or percentage of the total population. Continuous data were presented as mean and standard deviation (SD). The primary outcomes measured were VEGF, TNF- α , and progranulin. Secondary outcomes were whole blood cells and inflammatory markers such as C-reactive protein (CRP). For normality testing, the Kolmogorov-Smirnov test was used. Proportions were compared using the χ^2 or Fisher exact test. For the analysis of differences in continuous variables between two groups, the Mann-Whitney U test was used in cases where the data distribution was non-normal and unpaired t -test was used in cases where the data distribution was normal. Additionally, for the analysis of differences in continuous variables between two dependent groups, the Wilcoxon rank test was used in cases where the data distribution was non-normal. According to distribution status, correlation coefficients were calculated with Pearson and Spearman tests. A p -value ≤ 0.05 was considered statistically significant.

Results

Patients characteristics

Twenty-two patients with AU, 20 patients with DU, and 15 healthy controls were included in the study. There was no difference in terms of age and gender between ulcers (AU and DU) (Table I). *Helicobacter pylori* was found in 17 (51.5%) from the AU group and 16 (48.5%) from the DU group. There was no difference in eradication rates between the two groups after treatment (Table II).

Table I. Patient and control group characteristics

Characteristic	Ulcer (AU and DU) group (n = 42)	AU (n = 22)	DU (n = 20)	Control (n = 15)	P-value*
Age [years]	50.8 ±14.98	53.54 ±14.27	48.33 ±15.47	44.7 ±11.80	0.101
Female sex, n (%)	15 (32.6)	12	3	11 (52.4)	0.123

*P-value shows the difference between ulcer and control group.

Table II. *Helicobacter pylori* positivity before and after treatment

Variable	AU (n = 22)	DU (n = 20)	N = 42	P-value
Hp1(+)	17 (51.5%)	16 (48.5%)	33 (100%)	1.00
Hp1(-)	5 (55.6%)	4 (44.4%)	9 (100%)	
Hp2(+)	7 (63.6%)	4 (36.4%)	11 (100%)	0.384
Hp2(-)	15 (48.4%)	16 (51.6%)	31 (100%)	
Distribution of ulcer cases	22 (52.4%)	20 (47.6%)	42 (100%)	

Hp1(+)- *H. pylori* positive patient numbers before treatment, Hp1(-)- *H. pylori* negative patient numbers before treatment. Hp2(+)- *H. pylori* positive patient numbers after treatment. Hp2(-)- *H. pylori* negative patient numbers after treatment.

Serum progranulin, VEGF, and TNF- α levels

The serum progranulin levels before treatment were 4237.35 ±1091.30 pg/ml in the AU group, 4682.64 ±1501.46 pg/ml in the DU group, 3055.66 ±626.88 pg/ml in the control group, and 4460 ±1315 pg/ml in the ulcer group. The serum progranulin levels were 3607.7 ±869.4 pg/ml in the AU group, 4286.5 ±1208.78 pg/ml in the DU group, and 3947.1 ±1094.64 pg/ml in the ulcer group after treatment. When comparing serum progranulin levels of the AU group, DU group, and ulcer group with the control group, there were statistically significant differences ($p < 0.001$, $p < 0.0001$, $p < 0.0001$, respectively) before treatment. This difference disappeared in the AU group after treatment ($p = 0.117$, $p = 0.002$, $p = 0.009$ in AU, DU, and ulcer group, respectively) (Figures 1 A-C). When AU group and DU group were compared, there was no significant difference in terms of serum progranulin level before treatment ($p = 0.291$), but the difference between the two groups was statistically significant after treatment ($p = 0.048$) (Table III).

When serum VEGF and TNF- α levels of groups were compared with the control group, the differences between pre-treatment and post-treatment were statistically significant. There was a significant difference between AU and DU groups in terms of serum VEGF levels before treatment ($p < 0.019$), and the difference remained unchanged after treatment ($p = 0.14$) (Figures 2 A-C). The differences between the AU and DU groups in terms of serum TNF- α levels were not significant before treatment ($p = 0.787$) or after treatment ($p = 0.507$) (Figures 3 A-C).

It has been observed that serum progranulin, VEGF, and TNF- α values decreased significantly when pre-treatment values of ulcer patients were compared with post-treatment values ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively) (Figures 4 A-C).

Selected laboratory parameters

When comparing some selected laboratory tests such as haemoglobin, iron, iron binding capacity, ferritin, and vitamin B₁₂ between ulcer and control groups a few significant differences were detected. Some differences between the ulcer group and the control group, such as ferritin ($p = 0.016$), iron ($p = 0.041$), iron binding capacity ($p = 0.001$), and PCT ($p < 0.0001$), were found to be discontinued after treatment ($p = 0.167$, $p = 0.290$, $p = 0.056$, and $p = 0.950$, respectively) (Table IV).

Relation with *Helicobacter pylori*

There was no correlation between the presence of *H. pylori* and serum progranulin, VEGF, and TNF- α levels before and after treatment ($p = 0.453$, $p = 0.535$, $p = 0.099$, respectively, before treatment and $p = 0.196$, $p = 0.911$, $p = 0.975$, respectively, after treatment).

Also, there was no correlation between serum progranulin levels and VEGF and TNF- α levels.

Discussion

Progranulin is member of a novel class of growth factors that acts in development, cell cycle progression and cell motility. It has been associated with many biological and pathological events from its discovery to the

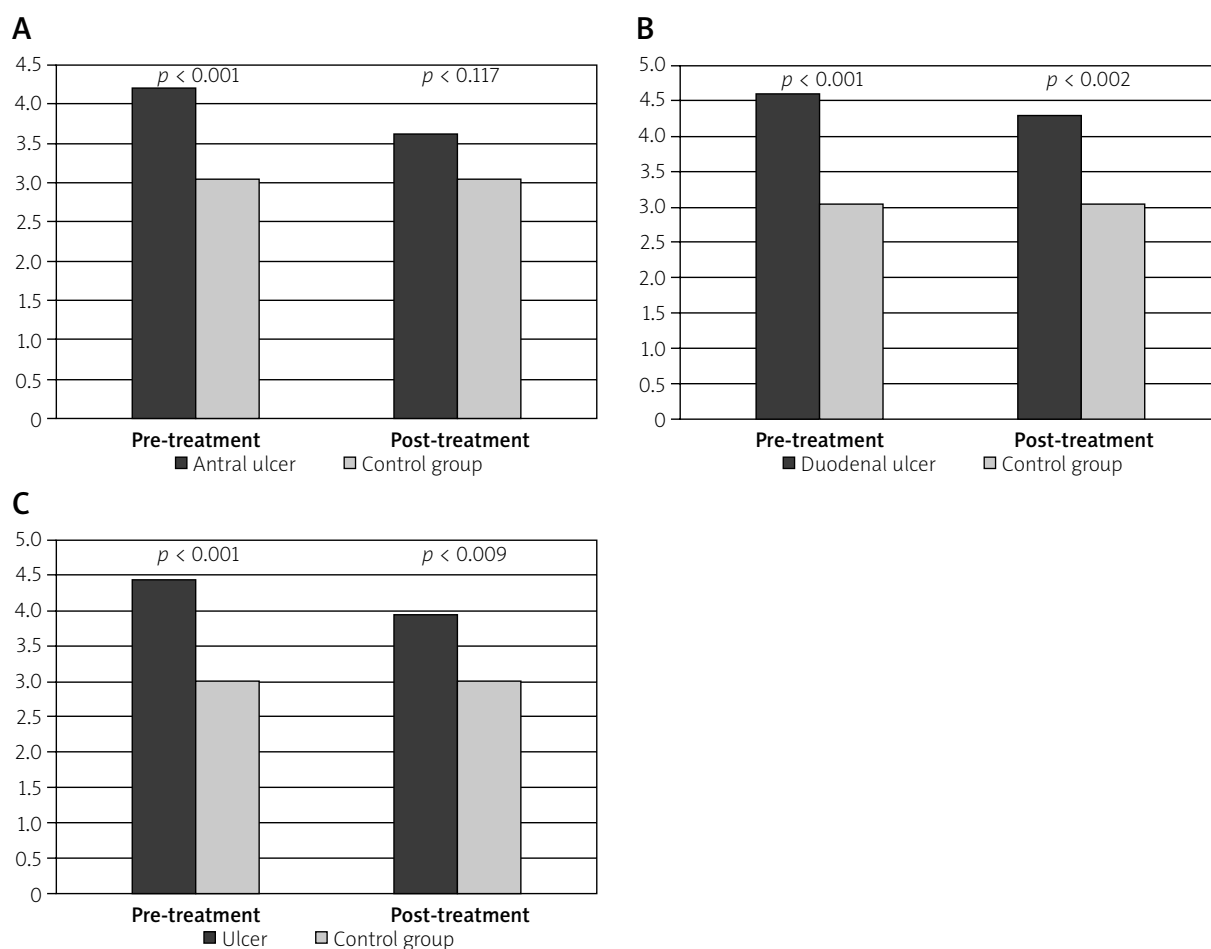


Figure 1. **A** – Comparison of serum progranulin levels between the antral ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (4237.35 ± 1091.30 vs. 3052.66 ± 626.88) – post-treatment (3607.7 ± 869.4 vs. 3052.66 ± 626.88), **B** – comparison of serum progranulin between the duodenal ulcer group and the control group, before treatment and after treatment. Respectively, mean values; re-treatment (4682.64 ± 1501.46 vs. 3055.66 ± 626.88) – post-treatment (4286.5 ± 1208.78 vs. 3052.66 ± 626.88), **C** – comparison of serum progranulin levels between the ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (4460 ± 1315 vs. 3052.66 ± 626.88) – post-treatment (3947.1 ± 1094.64 vs. 3052.66 ± 626.88)

Table III. Comparison of serum progranulin, VEGF, and TNF- α levels between the antral ulcer group and the duodenal ulcer group, pre-treatment and post-treatment

Treatment	Ulcer	Progranulin	P-value*	VEGF	P-value **	TNF- α	P-value***
Pre-treatment	Antral (n = 22)	4237.35 ± 1091.30	0.291	84.6 ± 100.0	< 0.019	283.41 ± 298.05	0.787
	Duodenal (n = 20)	4682.65 ± 1501.46		122.5 ± 101.0		399.91 ± 526.02	
Post-treatment	Antral (n = 22)	3607.7 ± 869.4	0.048	64.5 ± 59.0	0.14	265.5 ± 394.7	0.507
	Duodenal (n = 20)	4286 ± 1208.78		90.24 ± 74.5		328.81 ± 460.7	

VEGF – vascular endothelial growth factor, TNF- α – tumour necrosis factor α . *p – p-value between antral ulcer and duodenal ulcer groups in terms of progranulin levels, **p – p-value between antral ulcer and duodenal ulcer group in terms of VEGF levels, ***p – p-value between antral ulcer and duodenal ulcer group in terms of TNF- α levels.

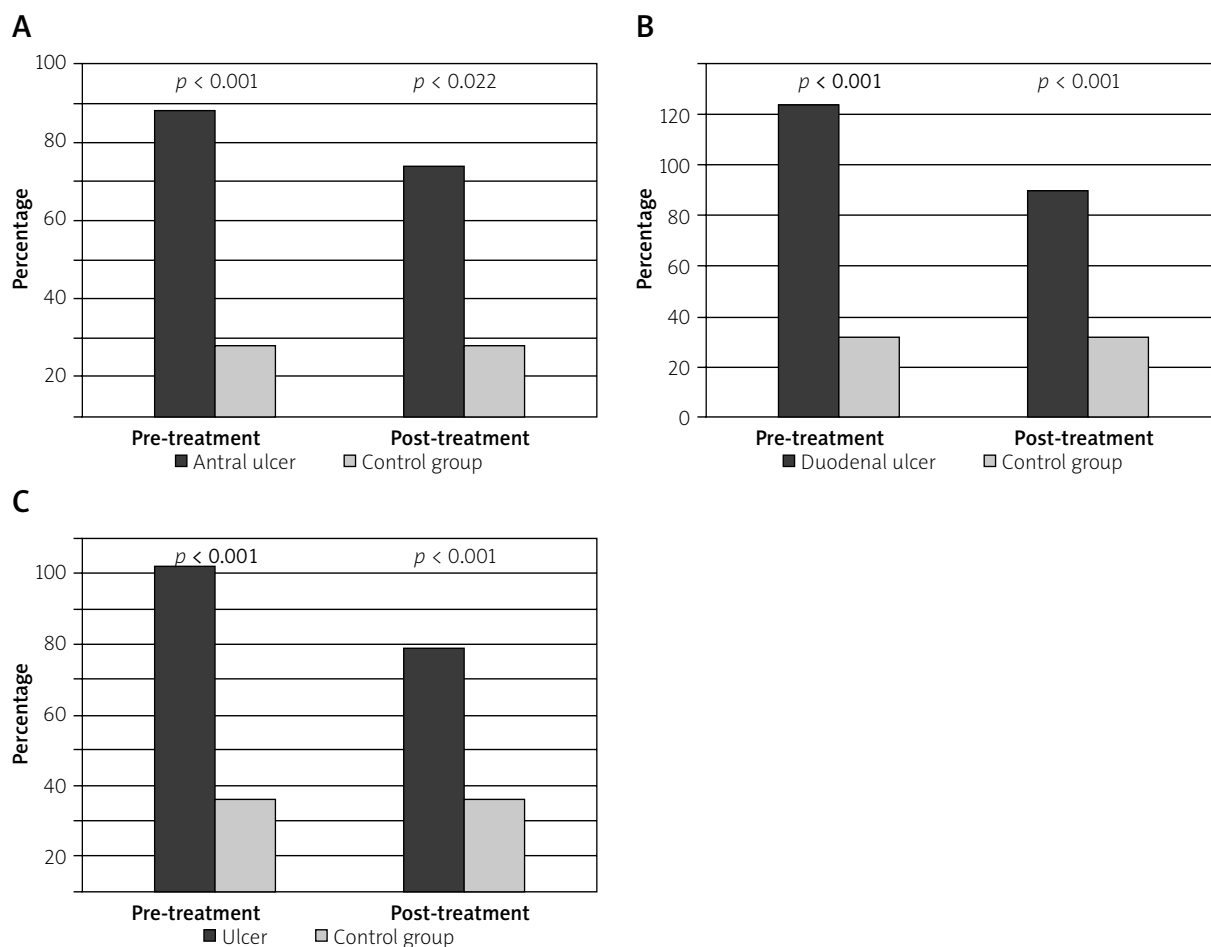


Figure 2. **A** – Comparison of serum VEGF levels between the antral ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (84.6 ± 100.0 vs. 28.38 ± 14.7) – post-treatment (64.5 ± 59.0 vs. 28.4 ± 14.7), **B** – comparison of serum VEGF levels between the duodenal ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (122.47 ± 101.00 vs. 28.38 ± 14.7) – post-treatment (90.24 ± 74.57 vs. 28.38 ± 14.70), **C** – comparison of serum VEGF between the ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (103.55 ± 101.06 vs. 28.38 ± 14.7) – post-treatment (77.37 ± 67.64 vs. 28.4 ± 14.7)

present day, such as diabetes, neurodegeneration, embryogenesis, inflammation, immunity, tumorigenesis, and wound healing [11–15, 17]. Increased progranulin levels in gastric cancer were reported previously [18]. Also, gastritis and gastric cancer had elevated progranulin levels compared with healthy tissue, and it was reported that *H. pylori* infected gastric epithelial cells upregulate progranulin [19]. To our knowledge, this is the first study that shows elevated serum progranulin levels in PU patients and suggests that can be used as a biomarker of healing after treatment in AU patients.

Ulcer healing is a complex process that involves cell migration, proliferation, re-epithelisation, angiogenesis, matrix deposition, and all results in scar formation. All

these processes are managed by several cytokines and growth factors [20]. Epidermal growth factor (EGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and bFGF activate epithelial cell migration and proliferation and accelerate wound/ulcer healing *in vivo* and *in vitro* by binding to their specific receptors [21]. Migration of fibroblasts into the granulation tissue and their proliferation are triggered by growth factors: TGF- β , PDGF, EGF, and FGF and the cytokines TNF- α and IL-1 derived from the inflammatory cells, activated endothelial cells, and macrophages [22]. Angiogenesis (formation of a new microvascular network) is essential for the healing of chronic gastroduodenal ulcers. The growth of granulation tissue and generation of new mi-

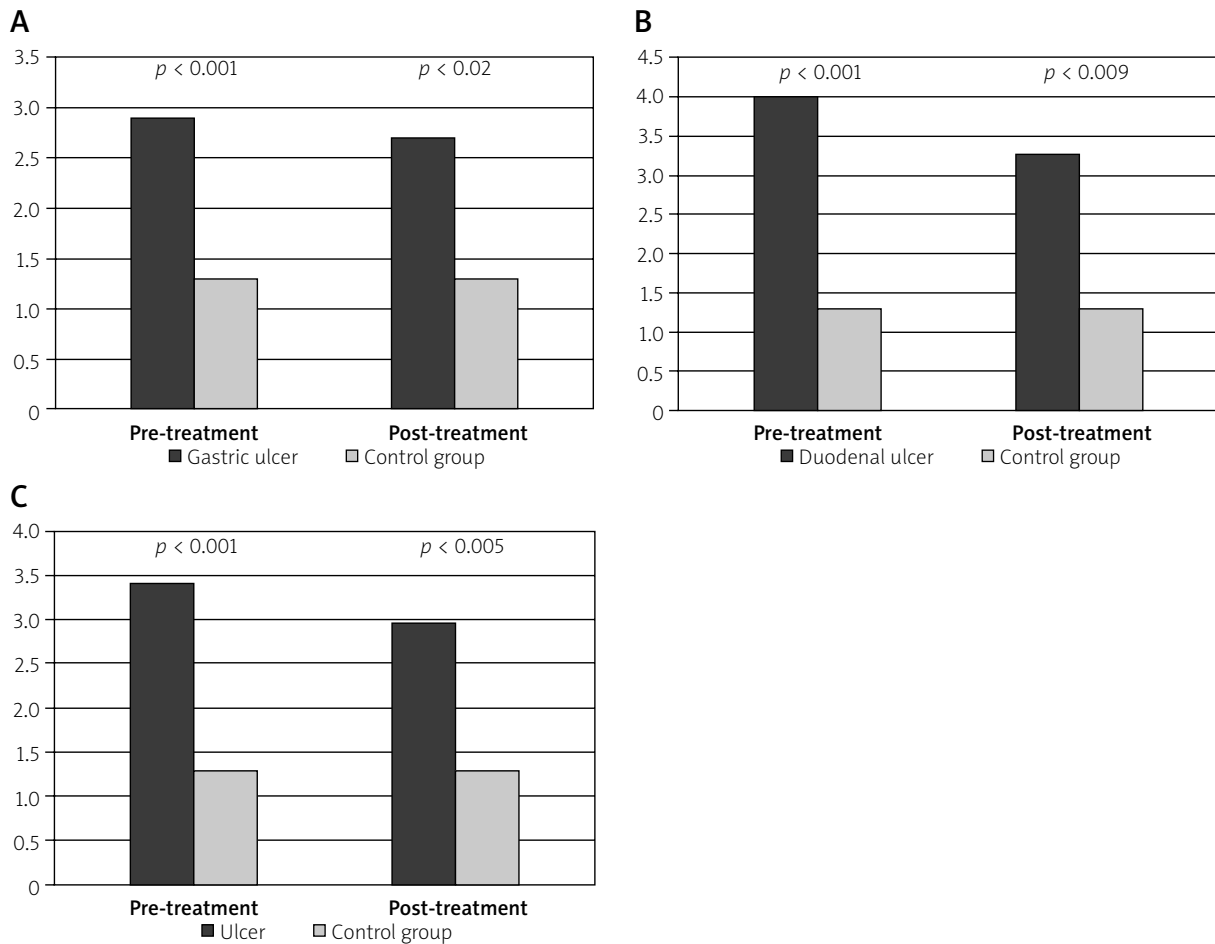


Figure 3. A – Comparison of serum TNF- α levels between the antral ulcer group and the control group, before treatment and after treatment. Respectively, mean values: pre-treatment (283.41 ± 298.05 vs. 130.1 ± 31.02) – post-treatment (265.5 ± 394.7 vs. 130.1 ± 31.02), B – comparison of serum TNF- α between the duodenal ulcer group and the control group, before treatment and after treatment. Respectively, mean values; pre-treatment (399.9 ± 526.02 vs. 130.1 ± 31.02) – post-treatment (328.79 ± 460.74 vs. 130.1 ± 31.02), C – comparison of serum TNF- α between the ulcer group and the control group, before treatment and after treatment. Pre-treatment – post-treatment; Respectively, mean values; pre-treatment (341.66 ± 426.10 vs. 130.1 ± 31.02) – post-treatment (297.14 ± 424.64 vs. 130.1 ± 31.02)

crovessels through angiogenesis is stimulated by bFGF, VEGF, PDGF, angiopoietins, and possibly by other growth factors and cytokines, including IL-1 and TNF- α [23, 24]. IL-1 and TNF- α activate progranulin gene expression in murine embryo fibroblasts. It has been shown that progranulin takes part in multiple steps of wound healing, such as early granulation phase, fibroblast accumulation, and neovascularisation [17]. He *et al.* demonstrated that when applied to a cutaneous wound, progranulin increased the accumulation neutrophils, macrophages, blood vessels, and fibroblasts in the wound in murine transcutaneous puncture wounds. It acts directly on isolated dermal fibroblasts, and endothelial cells promote division, migration, and the formation of capillary-like

tubule structures. It was also shown that after transcutaneous puncture injury progranulin mRNA levels in dermal wound upregulate and remain above baseline for at least 10 days post-injury [15].

Progranulin is a secreted protein and circulating levels can be measured by enzyme immunoassay. Progranulin levels in biological materials are usually low and increase in inflammatory conditions. It was proposed for use as a potential clinical biomarker in several pathologies because of these features [25]. It was recently reported that it can be used as a biomarker for disease activity in some types of cancer such as breast, non-small cell lung carcinoma, high-grade astrocytomas, diabetic microangiopathy, cardiovascular risk detection,

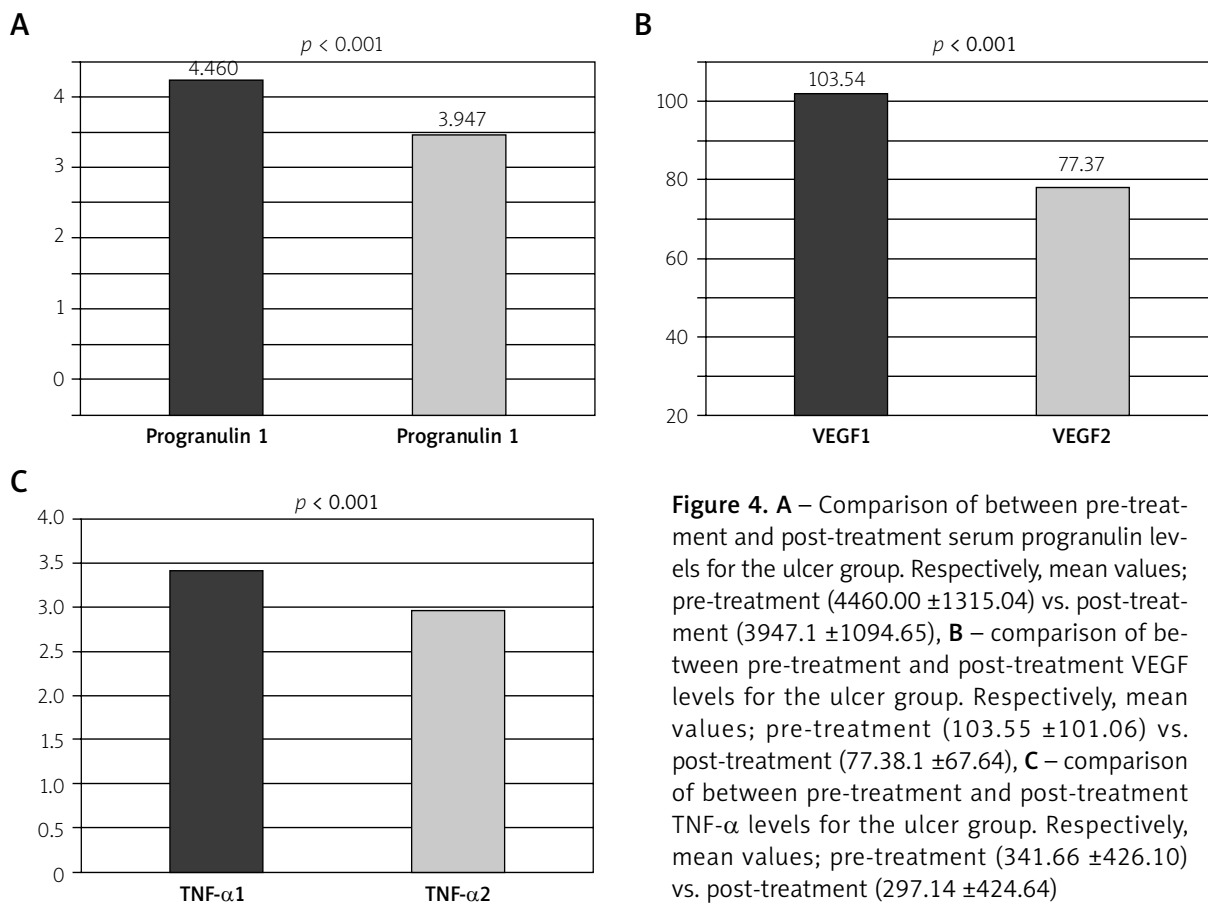


Figure 4. **A** – Comparison of between pre-treatment and post-treatment serum progranulin levels for the ulcer group. Respectively, mean values; pre-treatment (4460.00 ±1315.04) vs. post-treatment (3947.1 ±1094.65), **B** – comparison of between pre-treatment and post-treatment VEGF levels for the ulcer group. Respectively, mean values; pre-treatment (103.55 ±101.06) vs. post-treatment (77.38.1 ±67.64), **C** – comparison of between pre-treatment and post-treatment TNF-α levels for the ulcer group. Respectively, mean values; pre-treatment (341.66 ±426.10) vs. post-treatment (297.14 ±424.64)

Table IV. Comparison of selected laboratory tests between the antral and duodenal ulcer group and the control group before treatment and after treatment

Variable	Pre-treatment			Post-treatment		
	Ulcer (n = 43)	Control (n = 15)	P-value*	Ulcer (n = 43)	Control (n = 15)	P-value**
Hgb [g/dl]	13.69 ±2.09	14.0 ±0.93	0.431	13.87 ±1.72	14.01 ±0.93	0.716
Leukocyte [$\times 10^3/mm^3$]	9.29 ±10.27	7.16 ±0.68	0.138	7.26 ±1.18	7.16 ±0.68	0.34
Platelet [$\times 10^3/mm^3$]	300.32 ±81.99	309.4 ±50.7	0.299	338.10 ±53.73	309.4 ±50.7	0.079
Neutrophils [$\times 10^3/mm^3$]	4.56 ±1.46	3.87 ±0.39	0.186	3.82 ±0.88	3.9 ±0.39	0.467
Lymphocytes [$\times 10^3/mm^3$]	2.29 ±0.59	2.1 ±0.28	0.108	2.09 ±0.28	2.1 ±0.28	0.992
MPV [fl]	8.43 ±1.51	8.47 ±0.48	0.294	8.73 ±0.85	8.5 ±0.48	0.615
RDW (%)	16.11 ±1.82	15.6 ±0.58	0.564	16.39 ±1.1	15.6 ±0.58	0.014
PCT (%)	0.27 ±0.10	0.4 ±0.11	< 0.001	0.40 ±0.12	0.40 ±0.11	0.950
PDW (%)	17.67 ±1.02	15.9 ±0.88	< 0.001	16.70 ±0.92	15.9 ±0.88	0.007
Iron binding capacity [$\mu g/dl$]	429.02 ±96.5	359.9 ±52.3	0.001	406.9 ±69.98	359.9 ±52.3	0.056
B ₁₂ [pg/dl]	260.45 ±51.13	289.46 ±44.4	0.078	270.35 ±45.5	289.5 ±44.4	0.219
Ferritin [ng/ml]	31.6 ±11.84	47.26 ±23.5	0.016	37.5 ±20.94	47.3 ±27.5	0.167
ESR [mm/h]	12.6 ±9.01	12.4 ±6.27	0.936	9.86 ±5.22	12.4 ±6.27	0.171
CRP [mg/l]	0.67 ±0.46	0.55 ±0.26	0.273	0.65 ±0.23	0.55 ±0.26	0.032
Iron [$\mu g/dl$]	56.35 ±25.33	68 ±14.78	0.041	62.37 ±18.2	68 ±14.78	0.290

*p – pre-treatment p-values between ulcer and control groups, **p – post-treatment p-values between ulcer and control groups.

neurogenerative diseases, rheumatoid arthritis, and systemic lupus erythematosus [26].

In our study we found elevated serum progranulin levels in both the gastric ulcer group and the duodenal ulcer group when compared with the control group. There was a statistically significant decrease in terms of serum progranulin, VEGF, and TNF- α levels after treatment in the gastric ulcer, DU, and total ulcer groups. When we compared the gastric ulcer group and the DU group and the ulcer group with the control group in terms of serum progranulin, VEGF, and TNF- α levels before and after treatment we found that the statistically significant difference proceeded except for the serum progranulin levels in the AU group. The disappearance of the difference in terms of post-treatment serum levels of progranulin between the AU group and the control group suggests that serum levels of progranulin can be used as a biomarker of gastric ulcer healing.

The difference in terms of serum progranulin levels after treatment between the AU and DU groups can be attributed to several reasons although none of them explain it exactly. First, the cytokine difference between antral and duodenal ulcers. Previous studies reported that DU patients have higher IL-12A transcription levels and higher Th1 stimulus and showed increased interferon γ (IFN- γ) expression than antral ulcer patients. Also, Th2 mediator IL-4 had increased expression in DU patients than antral ulcer patients. As a result, duodenal ulcer has more upregulated mixed adaptive response pattern when compared with antral ulcer [27]. Second, the difference of the blood flow and morphofunctional status of gastroduodenal mucosa in PU healing. It was shown that mucosal blood flow (MBF) was highest when scar was formed in DU patients, while MBF was highest at the healing phase and decreased in the white scar phase in the gastric ulcer group [28].

The main limitation of our study is the small number of patients and the lack of histological assessment.

Conclusions

This is the first study that reports progranulin may be used as a biomarker in the follow-up of gastric ulcer patients. Future clinical studies involving large numbers of patients and experimental animal studies for histological examination are needed.

Conflict of interest

The authors declare no conflict of interest.

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