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ORIGINAL ARTICLE

Serum progranulin levels in axial spondyloarthropathy and relationship with clinical features

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ABSTRACT

Objectives: In this study, we aimed to investigate the serum progranulin (PGRN) levels in patients with axial spondyloarthropathy (AxSpA) and to identify the correlation between disease activity, symptom severity, acute phase reactant (APR), and serum PGNR levels in patients with AxSpA.

Patients and methods: This prospective, cross-sectional study included a total of 152 patients (105 males, 47 females; mean age: 41.8±10.3; range 20 to 65 years) with AxSpA according to the 2009 Assessment of SpondyloArthritis Society (ASAS) criteria who received treatment and 100 healthy individuals (61 males, 39 females; mean age 43.4±14.2; range 20 to 65 years) between February 2018 and February 2019. Serum PGRN levels from the venous blood were analyzed in both groups. The clinical AxSpA assessment scales were used in the patient group. Erythrocyte sedimentation rate and C-reactive protein levels were examined.

Results: The mean serum PGRN level was 6.9±5.4 ng/mL in the patient group and 11.2±6.0 ng/mL in the control group. Serum PGRN level was significantly higher in the control group ($p<0.001$). No significant correlation was found between the PGRN levels and disease activity, symptom severity, duration of disease, and age of the patient ($p>0.05$). Serum PGRN levels were significantly higher in female patients in the patient group ($p<0.01$). In the control group, the serum PGRN levels of individuals with a high body mass index were significantly higher ($p=0.001$).

Conclusion: Serum PGRN levels of patients with AxSpA who are under treatment and follow-up are significantly lower than healthy individuals. Serum PGRN levels in female patients with AxSpA are also significantly higher than male patients. Serum PGRN levels do not seem to be related to disease activity.

Keywords: Acute phase reactants, axial spondyloarthropathy, disease activity, progranulin.

Axial spondyloarthropathy (AxSpA) is a rheumatic disease in the spondyloarthropathy group with symptoms such as spinal inflammation, sacroiliac joint involvement, asymmetric oligoarthritis, dactylitis, and enthesitis, and its main clinical manifestations are low back pain and morning stiffness.[1] Several studies have shown that acute phase reactants (APRs) such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) which are used for the follow-up of disease activity in patients with AxSpA do not reflect follow-up and treatment activation.[2] A relevant study has reported that increasing CRP levels in some patients with AxSpA who have a high disease activity may be related to CRP gene polymorphism.[3] Therefore, the need to search for a more sensitive indicator that would be used in follow-up has emerged.

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Progranulin (PGRN) is a growth factor for glycoprotein excreted by neuron cells, glia cells, chondrocytes, leucocytes, and epithelial cells. It is also excreted by adipose tissue. Studies have shown that high-fat diets increase the PGRN synthesis in adipose tissues. The PGRN is the endogenous ligand of tumor necrosis factor-alpha (TNF-α) receptors. It antagonizes the effects of TNF-α receptors by binding to TNF-α receptors and shows anti-inflammatory effects. Other than its anti-inflammatory effects, it is effective in cases such as wound healing, neuronal recovery, and tumorigenesis.[4] Recently, PGRN has been investigated in immune-mediated inflammatory diseases due to its anti-inflammatory effects. Previous studies have shown that PGRN release increases in case of chronic inflammation process, and has anti-inflammatory effects. The PGRN is degraded by various proteins such as matrix metalloproteinases, A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS-7), elastase, and proteinase-3. *In vivo* studies have shown that granulins, which are the degradation products of PGRN, aggravate acute inflammation and neutralize the anti-inflammatory effect of PGRN.[5,6] The PGRN has been also shown to be a new indicator for chronic inflammation, obesity, type II diabetes, and cardiovascular diseases.[7] Recent studies have demonstrated that serum PGRN increases in immune-mediated inflammatory diseases, such as inflammatory intestinal disease, systemic lupus erythematosus, rheumatoid arthritis (RA), and psoriasis.

In the literature, there is no study examining serum PGRN levels of patients with AxSpA. In the present study, we aimed to investigate the serum PGRN levels in patients with AxSpA and to identify the correlation between disease activity, symptom severity, APR, and serum PGNR levels in patients with AxSpA. In addition, we aimed to examine the correlation between serum PGRN levels and medications used, sex, comorbid presence, and duration of disease.

PATIENTS AND METHODS

This prospective, cross-sectional study was conducted at University of Health Sciences, Bursa Training and Research Hospital, Department of Physical Therapy and Rehabilitation between February 2018 and February 2019. A total of 152 patients (105 males, 47 females; mean age: 41.8±10.3; range 20 to 65 years) with AxSpA according to the 2009 Assessment of SpondyloArthritis Society (ASAS) criteria who received treatment and 100 age- and sex-matched healthy individuals (61 males, 39 females; mean age 43.4±14.2; range 20 to 65 years) were included in the study. Exclusion criteria for the patients diagnosed with AxSpA were pregnancy or lactation, having acute or chronic infection signs, presence of malignancy, and having concomitant secondary rheumatic disease other than AxSpA. In the control group, exclusion criteria were pregnancy or lactation, having acute or chronic infection signs, presence of malignancy, presence of rheumatic diseases. Serum PGRN levels from the venous blood were analyzed in both groups. A written informed consent was obtained from each participant. The study protocol was approved by the University of Health Sciences, Bursa Training and Research Hospital Local Ethics Committee (date-no: 5.12.17 - 2017-18/15). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Assessment parameters and analysis methods

Data including demographic characteristics (age, sex, body mass index [BMI]) and comorbid diseases, duration of disease, and medicine used were recorded.

Clinical AxSpA assessment scales including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), and ASDAS-ESR were used in the patient group. The ESR and CRP levels were analyzed.

The ESR was calculated using the Westergren method via the ALS 100 device (Alaris Medikal ve Laboratuvar Ürünleri San. Tic. Ltd. Şti, Izmir, Turkey), and CRP was calculated with the nephelometric method using the Siemens BN II device (Siemens Healthcare GmbH, Erlangen, Germany). The examination and clinical inquiry of the patients were performed by a single physician.

Blood samples taken from the patient and control groups were centrifuged at 4,000 rpm for 10 min and the sera were separated with a Pasteur pipette and kept at -80°C to measure serum PGRN levels. Human PGRN was measured using the sandwich enzyme-linked immunosorbent assay (ELISA) through a commercially available kit (Boster Biotecnology, CA, USA).

The BASDAI includes six questions on the five basic symptoms of AxSpA (fatigue, spinal pain, arthritis/swelling, localized sensitivity-enthesitis, duration of morning stiffness, severity of morning stiffness). The patients were asked to score these questions between 0 and 10. The score was calculated by adding the total of the first four questions to the average of the last two questions, and dividing it to five. The result was recorded as the BASDAI score (0-10).

The functional capacities of the patients were assessed using the BASFI. The patients were asked to indicate difficulty at a value between 0 and 10 for 10 questions about daily activities. Average value was calculated and recorded as the BASFI score.

The ASDAS measurement was also used to assess disease activity. The ASDAS-CRP and ASDAS-ESR were calculated. The patients were asked to score spinal pain, morning stiffness, global pain, arthritis, and swelling out of 10. The five numeric values were added up and recorded as the ASDAS score. According to this score, ≤1.3 indicates inactive disease; 1.4-2 indicates moderate disease activation; 2.1-3.5 indicates high disease activation; >3.5 indicates very high disease activity.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean and standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. The distribution of variables was assessed using the Kolmogorov-Smirnov test, and parametric tests were used in the analysis of data with normal distribution while non-parametric tests were used in the analysis of data without normal distribution. The Mann-Whitney U test was used for the analysis of data without normal distribution in binary group comparisons, while the Student t-test was used for data with normal distribution. The correlation between continuous variables with normal distribution was assessed using the Pearson correlation test, while the correlation between those without normal distribution was assessed using the Spearman correlation test. The chi-square test was used for the comparison of categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the demographic characteristics between the AxSpA and healthy control groups ($p>0.05$) (Table 1).

The median duration of disease in the patient group was 60 (range, 1 to 444) months. Of the patients, 55 (36.2%) used only non-steroidal anti-inflammatory drug (NSAID), one (0.3%) used only disease-modifying antirheumatic

Table 1. Demographic characteristics of study population

	AxSpA group (n=152)			Control group (n=100)			
	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)							0.832
Sex							0.187
Male	105	69		61	61		
Female	47	40		39	39		
Body mass index (kg/m²)			26.5±4.3			27.23±5.6	0.476

AxSpA: Axial spondyloarthropathy; SD: Standard deviation.

Table 2. Characteristics of patients and assessment parameters

	n	%	Median	Min-Max
Medicine used				
NSAID	55	36.2		
DMARD	1	0.7		
Anti-TNF	61	40.1		
DMARD+NSAID	14	9.2		
Anti-TNF+NSAID	14	9.2		
Anti-TNF+DMARD	5	3.3		
Anti-TNF+DMARD+NSAID	2	1.3		
Variables				
Duration of disease (month)			60	1-444
Spine pain			6	1-10
Peripheral arthritis			3	1-10
Fatigue			5	1-10
Morning stiffness				
0-30 min	107	70.4		
30-60 min	24	15.8		
Longer than 1 h	21	13.8		
ESR (mm/H)			18	2-131
CRP (mg/L)			4.5	3-115
ASDAS-ESR			2.9	1-6.2
BASDAI			3.40	0.1-9.4
BASFI			2.80	0.1-10
Serum PGRN level (ng/mL)			5.26	1.49-25.91

NSAID: Non-steroidal anti-inflammatory drug; DMARD: Disease-modifying antirheumatic drug; TNF: Tumor necrosis factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; PGRN: Progranulin.

drug (DMARD), 61 (40.1%) used only anti-TNF, 14 (9.2%) used DMARD+NSAID, 14 (9.2%) used anti-TNF+NSAID, five (3.3%) used anti-TNF+DMARD, and two (1.3%) used anti-TNF+DMARD+NSAID. Clinical and laboratory data are shown in Table 2.

The mean serum PGRN level was 6.9±5.4 ng/mL in the patient group and 11.2±6.0 ng/mL in the control group. Serum PGRN level was significantly higher in the control group ($p<0.001$) (Table 3).

No significant correlation was found between PGRN levels and disease activity, symptom severity, duration of disease, and age of the patient ($p>0.05$) (Table 4).

Considering the evaluation of the medical treatment received and serum PGRN levels, the use of different medications did not have a significant

Table 3. Serum PGRN levels of study population

	AxSpA group (n=152)	Control group (n=100)	
	Mean±SD	Mean±SD	*p*
Serum PGRN level (ng/mL)	6.9±5.4	11.2±6.0	<0.001

PGRN: Progranulin; AxSpA: Axial spondyloarthropathy; SD: Standard deviation.

Table 4. Correlation analysis results

	Serum PGRN level (ng/mL)	
	r	*p*
Duration of disease	-0.075	0.356
BASDAI	0.023	0.777
ASDAS-ESR	0.048	0.556
ASDAS-CRP	0.037	0.649
BASFI	-0.087	0.286
ESR (mm/H)	0.099	0.224
CRP (mg/L)	-0.060	0.426
Spine pain	-0.14	0.861
Peripheral arthritis	-0.09	0.910
Fatigue	-0.13	0.875
Morning stiffness	0.038	0.641
Duration of disease (month)	-0.39	0.542
Patient's age (year)	-0.75	0.356

PGRN: Progranulin; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functional Index.

effect on the serum PGRN level (p>0.05). In addition, between the patients receiving NSAID and those receiving anti-TNF (n=61), there was no significant difference (p=0.198) (Table 5). The median anti-TNF treatment duration was nine (range, 3 to 78) months.

Considering the correlation between sex and PGRN levels in the patient group, the mean PGRN level was 9.6±6.5 ng/mL in women and 5.7±4.3 ng/mL in men. The serum PGRN levels were significantly higher in female patients (p<0.01). Considering the correlation between sex and PGRN levels in the control group, the mean PGRN level was 11.5±6.4 ng/mL in women and 11.1±5.7 ng/mL in men, indicating no statistically significant difference (p>0.05) (Table 6).

Considering the correlation between the BMI and serum PGRN levels in the patient group, no significant effect of BMI on serum PGRN levels

Table 5. Serum PGRN levels of study population according to medications used

	Serum PGRN value (ng/dL)			
Medicine group	n	Median	Min-Max	*p*
NSAID	55	5.05	1.53-18.57	
DMARD	1	2.37	-	
Anti-TNF	61	5.05	1.64-25.91	
DMARD+NSAID	14	5.72	1.53-25.21	=0.640
Anti-TNF+NSAID	14	4.81	1.52-20.61	
Anti-TNF+DMARD	5	8.27	1.49-17.75	
Anti-TNF+NSAID+DMARD	2	9.89	7.48-12.30	

PGRN: Progranulin; NSAID: Non-steroidal anti-inflammatory drug; DMARD: Disease-modifying antirheumatic drug; TNF: Tumor necrosis factor.

Table 6. Correlation between sex and serum PGRN

	Female		Male		
	n	Mean±SD	n	Mean±SD	*p*
AxSpA group					
Serum PGRN level (ng/mL)	47	9.6±6.5	105	5.7±4.3	<0.001
Control group					
Serum PGRN level (ng/mL)	39	11.5±6.4	61	11.1±5.7	=0.626

PGRN: Progranulin; SD: Standard deviation; AxSpA: Axial spondyloarthropathy.

Table 7. Correlation between serum PGRN and BMI in the patient and control groups

	Serum PGRN level (ng/mL)	
	r	*p*
AxSpA group BMI (kg/m^2)	0.090	0.270
Control group BMI (kg/m^2)	0.325	**0.001**

PGRN: Progranulin; BMI: Body mass index; AxSpA: Axial spondylo-arthropathy.

was found (p>0.05). Considering the correlation between the BMI and serum PGRN levels in the control group, the serum PGRN levels of individuals with a high BMI were significantly higher (p=0.001) (Table 7).

DISCUSSION

In the present study, we showed that serum PGRN levels of patients with AxSpA who were under treatment and follow-up were significantly lower than the control group who did not have any rheumatic disease. We also found that serum PGRN levels were not related to disease activity. The serum PGRN levels in female patients with AxSpA were significantly higher. However, no significant correlation was found between sex and serum PGRN levels in the control group. Although serum PGRN levels of the individuals with a high BMI value in the control group were higher, the same correlation was unable to be found in the patient group.

Having an opinion about AxSpA disease activity, progression and prognosis are particularly important during follow-up. Acute phase response measurements are performed as a part of the clinical routine, since they are not as directive in the follow-up of AxSpA as in diseases such as RA.[3] Since the laboratory values do not always reflect disease activity in AxSpA, scales filled by the patient have been started to be used in clinical studies.[8] This has led to a need for searching a disease-specific molecule in close relation to treatment response.

The PGRN is an autocrine growth factor with 593 amino acids and physiological and pathological duties. It particularly plays a critical role in inflammation, early embryogenesis, preservation of neuronal recovery, wound healing, tumorigenesis, and immune system.[9,10] Recent studies have shown that PGRN binds to TNF receptors. The PGRN shows anti-inflammatory effect by binding to TNFR1/2 receptors competitively and blocking the TNF-α signal pathway.[6] While PGRN shows pro-inflammatory effects in individuals with obesity and insulin resistance, it shows anti-inflammatory effects by inhibiting the effects of TNFα in other cases. Atsttrin, a recombinant protein derivate of PGRN, is regarded as the region responsible for the main anti-inflammatory effect of PGRN.[11] Zhao et al.[11] conducted a study in a rat model to examine the effects of PGRN and Atsttrin and found that contact dermatitis was induced by oxazolone in both PGRN-deprived rats and normal rats, while inflammation and histopathological findings progressed more dramatically in PGRN-deprived rats. Atsttrin at therapeutic doses was systematically given to rats with oxazolone-induced contact dermatitis, and dermatitis symptoms regressed both clinically and histopathologically.

A study examining the correlation between disease activity and PGRN in RA where TNF-α has an active role in the pathogenesis similar to AxSpA assessed 47 patients with RA, 42 patients with osteoarthritis (OA), and 41 healthy controls.[12] Immunohistochemical analysis of PGRN on synovial tissues was carried out. The correlation between PGRN and CRP, disease activity score (DAS28-CRP) and Health Assessment Questionnaire (HAQ) was examined. As a result, this study found that circulating PGRN increased in patients with RA and OA, compared to healthy controls. Synovial fluid in patients with RA was higher than the PGRN levels of patients with OA. PGRN expression was significantly higher in the synovial tissue of patients with RA, particularly in inflammatory infiltrates. The present study found that the serum PGRN levels in patients with AxSpA were higher than healthy controls. The reason for different results compared to the patient group diagnosed with RA may be due to the active biological treatment of 53.9% of 152 patients included in the present study and some of them received anti-TNF treatment at least once in the past.

Johnson et al.[13] measured the PGRN levels in patients with RA who received anti-TNF treatment in their studies. Since PGRN is the natural ligand

of TNF receptors, the correlation between the patients' PGRN levels and response to treatment was examined. Treatment was started in 35 anti-TNF-naïve patients. The DAS28-ESR, DAS28-CRP, and CDAI were calculated and serum PGRN levels were determined at the beginning and follow-up. The PGRN levels significantly decreased after treatment. The DAS28-ESR, DAS28-CRP, and CDAI in the group with a high PGRN were higher that the group with low PGRN. Baseline serum PGRN levels did not provide an insight about the treatment response. Additionally, a positive correlation was found between the decrease in serum PGRN levels and the decrease in ESR, CRP, and DAS28-ESR after starting anti-TNF treatment. This is the only study to assess the PGRN levels after treatment in the long-term. Although the serum PGRN levels before treatment did not predict any response to anti-TNF treatment, serum PGRN levels significantly decreased in line with the treatment.[13] Since the measurements in this study included patients receiving treatment, the similar findings of the study by Johnson et al.[13] conducted with post-treatment group support the present study. No significant correlation was found between serum PGRN levels and duration of disease, medications used, presence of comorbid disease, clinical symptoms, BASDAI, BASFI, ASDAS-CRP, ASDAS-ESR, and APR. Unlike the other studies in the literature, the reason why it is not found to be related in other scales may be due to the suppression of the existing activity.

In a study including patients with psoriasis, biopsies were taken from the lesions of the patients and from the healthy skin areas of the control group, and the PGRN expression was examined.[9] While PGRN was negative in biopsy specimen of 95% of 20 participants in the control group, PGRN synthesis was observed in all epidermal keratinocytes of 34 psoriasis specimen. Additionally, post-treatment serum PGRN levels of 18 patients with psoriasis who received treatment were significantly lower than their pre-treatment PGRN levels. The study examined the TNF-α and interleukin (IL-6) levels in addition to PGRN levels and revealed a positive correlation between PGRN and TNF-α. A negative correlation was found between Psoriasis Area and Severity Index (PASI) and PGRN/TNF-α rate. In other words, PGRN and TNF-α jointly increased in patients with psoriasis; however, as the disease severity increased, PGRN increase was less than TNF-α. It can be interpreted that enough PGRN increase to neutralize the pro-inflammatory effects of TNF-α does not occur. Similarly, there was no correlation between APR, BASDAI, BASFI, ASDAS-CRP, and ASDAS-ESR which are the parameters used to assess the disease severity and serum PGRN levels. Additionally, the fact that serum PGRN decreases with treatment suggests that it plays a role in the pathogenesis of AxSpA disease. Serum PGRN follow-up may be less guiding than APR follow-up for the follow-up of treatment response.

A study which examined the effects of PGRN autoantibodies included 260 patients with psoriatic arthritis and 100 psoriasis patients without psoriatic arthritis. The PGRN autoantibodies were found in 19% (n=50) of the patients with psoriatic arthritis; however, no PGRN autoantibodies were found in 100 psoriasis patients without psoriatic arthritis. The study found that serum PGRN levels of patients with PGRN autoantibodies were low. In psoriatic arthritis patients with PGRN autoantibodies, clinical symptoms such as enthesitis and dactylitis were observed more frequently. Additionally, cytotoxicity was higher in the group with PGRN autoantibodies.[14] In the current study, PGRN levels of the patient group were significantly lower. The low PGRN levels in the patient group may be due to the high level of PGRN autoantibodies. The fact that patients were receiving treatment might have increased the incidence of autoantibody presence.

The PGRN, a new peptide that has recently emerged as an important regulatory adipokine, is associated with the energy homeostasis and obesity in animals and adult humans. A study was conducted to examine the correlation between serum PGRN and obesity. The study included 43 children with obesity and 34 healthy children. Serum PGRN levels were significantly higher in children with obesity. Additionally, serum PGRN levels are in direct proportion to systolic-diastolic blood pressure, total cholesterol, triglycerides, and IL-6. Increased PGRN levels may have a role in the pathological mechanism of childhood obesity.[15] A study examining the diet types of 85 patients found that there was no correlation between serum PGRN total energy and protein, carbohydrate, fat and its derivatives, fiber intake

and diet glycemic index; however, a significant positive correlation was found between saturated fats and serum PGRN levels.[16] Additionally, a positive correlation was found between type II diabetes, waist circumference and BMI, and serum PGRN levels.

A study which examined the correlation between serum PGRN levels of patients with metabolic syndrome, and insulin resistance and autophagic activity found that serum PGRN was significantly higher in the group with metabolic syndrome, compared to the healthy control group.[17] No significant differences were found between sexes. The results of correlation analyses showed significant positive correlations between serum PGRN levels, and BMI, waist circumference. Moreover, serum PGRN levels was found to be in direct proportion to autophagic activity in the omental fat tissue.

The present study found that serum PGRN levels were higher in the female participants in the patient group and participants with a high BMI in the control group. Similar to studies including patients with obesity, a significant correlation was found between BMI and serum PGRN levels in the healthy control group. Considering these studies showing that PGRN is synthesized in fat tissues, it is thought that PGRN can be synthesized at a higher rate in female sex with a more adipose tissue. Due to the AxSpA epidemiology, the number is in favor of male sex in the study and control groups. This might be the reason for the low serum PGRN in the patient group.

Since patients who were receiving treatment were included in the current study, no comparisons between patients before and after treatment were made; maybe, another AS group without on any treatment would give more conclusive results, which is one of the limitations of this study. Additionally, PGRN was examined as a single marker, and PGRN autoantibodies, TNF-α and IL-6 were not studied. This may be considered another limitation of the study. Future studies should examine the correlation between PGRN autoantibodies, TNF-α and IL-6, and treatment received.

In conclusion, low serum PGRN levels in the patient group indicate that it may decrease with treatment, suggesting that it has a role in the pathogenesis of AxSpA disease. This is the first study to examine serum PGRN levels in patients diagnosed with AxSpA. Further studies should be conducted with larger groups before and after treatment including the levels of PGRN, TNF-α, IL-6, and PGRN autoantibodies to further reveal the role of PGRN in AxSpA etiopathogenesis and to examine it as a treatment goal.

Declaration of conflicting interests

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REFERENCES

1. Gran JT, Husby G. HLA-B27 and spondyloarthropathy: Value for early diagnosis? J Med Genet 1995;32:497-501.
2. Ruof J, Stucki G. Validity aspects of erythrocyte sedimentation rate and C-reactive protein in ankylosing spondylitis: A literature review. J Rheumatol 1999;26:966-70.
3. Claushuis TA, de Vries MK, van der Weijden MA, Visman IM, Nurmohamed MT, Twisk JW, et al. C-reactive protein polymorphisms influence serum CRP-levels independent of disease activity in ankylosing spondylitis. Clin Exp Rheumatol 2015;33:159-65.
4. Thurner L, Fadle N, Regitz E, Kemele M, Klemm P, Zaks M, et al. The molecular basis for development of proinflammatory autoantibodies to progranulin. J Autoimmun 2015;61:17-28.
5. Kessenbrock K, Fröhlich L, Sixt M, Lämmermann T, Pfister H, Bateman A, et al. Proteinase 3 and neutrophil elastase enhance inflammation in mice by inactivating antiinflammatory progranulin. J Clin Invest 2008;118:2438-47.
6. Tang W, Lu Y, Tian QY, Zhang Y, Guo FJ, Liu GY, et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science 2011;332:478-84.
7. Kojima Y, Ono K, Inoue K, Takagi Y, Kikuta K, Nishimura M, et al. Progranulin expression in advanced human atherosclerotic plaque. Atherosclerosis 2009;206:102-8.
8. Yanik B, Gürsel YK, Kutlay S, Ay S, Elhan AH. Adaptation of the bath ankylosing spondylitis functional index to the Turkish population, its reliability and validity: Functional assessment in AS. Clin Rheumatol 2005;24:41-7.

9. Huang K, Chen A, Zhang X, Song Z, Xu H, Cao J, et al. Progranulin is preferentially expressed in patients with psoriasis vulgaris and protects mice from psoriasis-like skin inflammation. Immunology 2015;145:279-87.
10. Tanaka A, Tsukamoto H, Mitoma H, Kiyohara C, Ueda N, Ayano M, et al. Serum progranulin levels are elevated in dermatomyositis patients with acute interstitial lung disease, predicting prognosis. Arthritis Res Ther 2015;17:27.
11. Zhao YP, Tian QY, Liu CJ. Progranulin deficiency exaggerates, whereas progranulin-derived Atsttrin attenuates, severity of dermatitis in mice. FEBS Lett 2013;587:1805-10.
12. Cerezo LA, Kuklová M, Hulejová H, Vernerová Z, Kaspříková N, Veigl D, et al. Progranulin is associated with disease activity in patients with rheumatoid arthritis. Mediators Inflamm 2015;2015:740357.
13. Johnson J, Yeter K, Rajbhandary R, Neal R, Tian Q, Jian J, et al. Serum progranulin levels in Hispanic rheumatoid arthritis patients treated with TNF antagonists: A prospective, observational study. Clin Rheumatol 2017;36:507-16.
14. Thurner L, Zaks M, Preuss KD, Fadle N, Regitz E, Ong MF, et al. Progranulin antibodies entertain a proinflammatory environment in a subgroup of patients with psoriatic arthritis. Arthritis Res Ther 2013;15:R211.
15. Wang F, Chen T, Sun L, Lv H, Li X, Shen J, et al. Circulating PGRN levels are increased but not associated with insulin sensitivity or β-cell function in Chinese obese children. Dis Markers 2018;2018:3729402.
16. Nicoletto BB, Sarmento RA, Pedrollo EF, Krolikowski TC, Canani LH. Association between progranulin serum levels and dietary intake. PLoS One 2018;13:e0202149.
17. Li H, Zhou B, Xu L, Liu J, Zang W, Wu S, et al. Circulating PGRN is significantly associated with systemic insulin sensitivity and autophagic activity in metabolic syndrome. Endocrinology. 2014;155:3493-507.