Thieme

Progranulin and Insulin-like Growth Factor Binding Protein-2 as Biomarkers of Disease Activity and Pathological Changes in Lupus Nephritis

Progranulin und Insulin-ähnliches Wachstumsfaktor-bindendes Protein-2 als Biomarker für Krankheitsaktivität und pathologische Veränderungen bei Lupusnephritis

Authors
Samar H. Goma[1], Marwa Mahmoud Abdelaziz[1], Eman H. El-Hakeim[1], Mona H. El Zohri[2], Sohair K. Sayed[3]

Affiliations
1 Department of Rheumatology, Rehabilitation, and Physical Medicine, Assiut University Hospital, Assiut, Egypt
2 Department of Internal Medicine, Rheumatology Unit, Assiut University Hospital, Assiut, Egypt
3 Department of Clinical Pathology, Assiut University Hospital, Assiut, Egypt

Key words
progranulin (PGRN), insulin-like growth factor binding protein (IGFBP-2), lupus nephritis, pathology

Schlüsselwörter
progranulin (PGRN), Insulin-ähnliches Wachstumsfaktorbindungsprotein (IGFBP-2), lupus nephritis, Pathologie

Bibliography
DOI https://doi.org/10.1055/s-0043-121629
Published online: 27.11.2017
Akt Rheumatol 2019; 44: 121–127

ISSN 0341-051X

Correspondence
Dr. Samar H. Goma
Rheumatology and Rehablitation Department Assiut University Hospital
algalaa street
Assiut 71515
Egypt
Tel.: +20/106/1828 586, Fax: +20/882/310 888
samarhassanein2010@yahoo.com

ABSTRACT

Background Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease, characterised by the production of auto-antibodies and the formation of immune complexes due to the polyclonal activation of T and B lymphocytes, which results in tissue and organ damage. During inflammation, neutrophils and macrophages release serine proteases to cleave progranulin (PGRN) into granulin, which exerts its pro-inflammatory effects that counteract the anti-inflammatory effects of intact PGRN. It is suggested that insulin-like growth factor binding protein-2 (IGFBP-2) is a dependable biomarker of renal deterioration but it is still unclear if it has high sensitivity and specificity for discriminating SLE-caused kidney disease from other-cause kidney disease.
This study aimed to investigate the diagnostic value of PGRN and ILGFBP-2 in patients with lupus nephritis (LN) and the correlation of these biomarkers with disease activity and renal biopsy pathology.
Patients and methods Patients with SLE (n = 25) and chronic kidney disease (CKD) (n = 25), and age- and sex-matched controls (n = 25) were enrolled in the study. Serum PGRN and ILGFBP-2 levels were measured for each group.
Results Disease duration was 4.78 ± 4.26 years in the SLE patients. The mean SLE Disease Activity Index score was 15.04 ± 7.54. All renal biopsy results were class 2, 3, and 5 with a percentage of 32, 24, and 44 % respectively. PGRN and ILGFBP-2 were significantly higher in SLE patients ($p < 0.001$ all) than in the CKD and control groups. All patients with high levels of biomarkers showed higher values of SLE disease activity. No significant difference was noted between active and inactive LN or classes of renal biopsy with PGRN and ILGFBP-2.
Conclusion PGRN and ILGFBP-2 are significantly elevated in SLE compared to CKD and the general population and were associated with the SLE Disease Activity Index but not with active LN or classes of renal biopsy.

ZUSAMMENFASSUNG

Hintergrund Der systemische Lupus erythematodes (SLE) ist eine chronische Autoimmunerkrankung, die durch die Produktion von Autoantikörpern und die Bildung von Immunkomplexen aufgrund der polyklonalen Aktivierung von T- und B-Lymphozyten gekennzeichnet ist, die zu Gewebs- und Organschäden führen. Während der Entzündung können Neutrophile und Makrophagen Serin-Proteasen freisetzen, um

Progranulin (PGRN) in Granulin zu spalten, das seine entzündungsfördernden Wirkungen ausübt, die den entzündungshemmenden Wirkungen von intaktem PGRN entgegenwirken. Es wird vorgeschlagen, dass das Insulin-ähnliche Wachstumsfaktor-Bindungsprotein-2 (IGFBP-2) ein verlässlicher Biomarker für die renale Verschlechterung ist, aber es ist immer noch unklar, ob es eine hohe Sensitivität und Spezifität für die Diskriminierung von SLE-verursachter Nierenerkrankung hat. Ziel dieser Studie war es, den diagnostischen Wert von PGRN und ILGFBP-2 bei Patienten mit Lupusnephritis (LN) und die Korrelation dieser Biomarker mit Krankheitsaktivität und Nierenbiopsie-Pathologie zu untersuchen.

Patienten und Methoden In die Studie wurden Patienten mit SLE (n = 25) und chronischer Nierenerkrankung (CKD) (n = 25), Kontroll- und Geschlechtskontrollen (n = 25) eingeschlossen. Die Serum-PGRN- und ILGFBP-2-Spiegel wurden für jede Gruppe gemessen.

Ergebnisse Die Krankheitsdauer betrug bei den SLE-Patienten 4,78 ± 4,26 Jahre. Die mittlere SLEDisease Activity Index erzielte 15,04 ± 7,54. Alle Nierenbiopsieergebnisse waren Klasse 2, 3 und 5 mit einem Prozentsatz von 32%, 24% bzw. 44%. PGRN und ILGFBP-2 waren signifikant höher bei SLE-Patienten (p <0,001all) als in der CKD und Kontrollgruppen. Alle Patienten mit hohen Biomarkern wiesen höhere SLE-Werte auf. Es wurde kein signifikanter Unterschied zwischen aktivem und inaktivem LN oder Klassen der Nierenbiopsie mit PGRN und ILGFBP-2 festgestellt.

Schlussfolgerung PGRN und ILGFBP-2 sind im Vergleich zu CKD und der Allgemeinbevölkerung signifikant erhöht und mit dem SLEDisease-Aktivitätsindex assoziiert, jedoch nicht mit aktiven LN oder Klassen von Nierenbiopsien.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease [1] characterised by the production of auto-antibodies and the formation of immune complexes due to the polyclonal activation of T and B lymphocytes, which results in tissue and organ damage [2]; SLE also affects multiple organs [3]. The kidney is the most commonly affected organ with 35 % of patients presenting with lupus nephritis (LN) at the time of diagnosis; 50–60 % develop LN during the first 10 years [4] and up to 25 % develop end-stage renal disease within 10 years of the onset of renal symptoms [5].

The incidence of LN is relatively higher in Asian, African, and Hispanic populations [6]. LN is the major cause of morbidity and mortality in patients with SLE because of the secondary effect of immunosuppressive therapies or because of renal failure [4, 7–9].

Routine laboratory investigations such as serum creatinine and proteinuria cannot differentiate between active and stable LN because of a lack of sensitivity and/or specificity [5]. Moreover, biomarkers such as anti-double-stranded DNA antibodies (dsDNA) and complement components 3 and 4 (C3, C4), are neither sensitive nor specific in reflecting concurrent renal activity or predicting impending renal flare [10].

Renal biopsy is the most reliable test for the diagnosis and management of LN but it has drawbacks as it is invasive, with complications such as bleeding and infection. Moreover, it cannot be repeated and reflects only existing pathology but cannot predict renal flare in LN patients [5].

Therefore, it is important to identify biomarkers that have a high specificity for the early diagnosis of LN and can reflect renal activity in follow-up monitoring.

Progranulin (PGRN) is a 593-amino-acid autocrine growth factor present in many cell types, including cells of the immune system, epithelial cells, neurons, and chondrocytes [11]. During inflammation, neutrophils and macrophages are responsible for the cleavage of PGRN into granulin (GRN), which acts pro-inflammatorily to counteract the anti-inflammatory effects of intact PGRN. Moreover, GRN acts with the toll-like receptor 9 (TLR-9) to regulate innate and adaptive immune responses [12]. Active SLE patients have increased TLR9 in the peripheral blood [13]. Thus, providing increased evidence that PGRN plays a role in the pathogenesis of LN [14].

Insulin-like growth factor (IGF) is composed of 2 ligands (IGF1, IGF2), 2 receptors (IGF-1R, IGF-2R), and 6 IGF binding proteins (IGFBP-1 to 6) [15]. IGF-1R acts by facilitating cell proliferation, differentiation, survival, migration, and metabolic processes [16]. The second most abundant IGFBP found in serum is IGFBP-2 which has been found to be a strong diagnostic and prognostic biomarker for several malignant tumours. In addition, IGFBP-2 has been reported to be increased in nephrotic syndrome and to be a predictor of the longitudinal deterioration of renal function in type 2 diabetes [10]. Although the above reports suggest that IGFBP-2 is a dependable biomarker of renal deterioration, it is still unclear if it has high sensitivity and specificity for discriminating SLE-caused kidney disease from other-cause kidney disease.

This study aimed to investigate the diagnostic value of PGRN and IGFBP-2 in patients with lupus nephritis (LN) and the correlation of these biomarkers with disease activity and renal biopsy pathology.

Material and methods

Patients

This study was conducted at Assiut University Hospital, Egypt from December 2015 to May 2016 after approval by the institution's ethics committee.

75 patients were enrolled in this study and were divided into 3 groups. The first group comprised patients with SLE with LN (n = 25) who were diagnosed using the 2012 Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus (SLICC) [17]. The patients were (a) aged 18 years and older and had (b) LN confirmed by renal biopsy. Patients with renal failure were excluded. Each patient underwent a standardised medical history-taking protocol and full physical examination. Serologic profiling of each patient was performed using standard immunoassays later described.

The second group (n = 25), who were patients with chronic kidney disease (CKD) due to causes other than LN, were enrolled as disease controls.

The third group (n = 25) was the control group including age- and sex-matched healthy volunteers.

Informed written consent was obtained from all participants before their participation in the study.

Disease activity

Global disease activity was assessed using the SLE Disease Activity Index (SLEDAI) [18]. In this study, we considered a score of 0 as no activity, 1–5 mild activity, 6–10 moderate activity, 11–19 high activity, and > 20 very high activity [19].

The renal SLEDAI (SLEDAI-R) score (range 0–16) represents the sum of the renal items of the SLEDAI 2000. If present, each of the four SLEDAI-R items receives a score of 4: proteinuria > 0.5 g/day, haematuria and pyuria (both > 5 cells/high-power field), and cellular casts. In this study, we considered SLEDAI-R = 0 as inactive LN and SLEDAI-R > 0 as active LN [20].

Renal pathology

Renal biopsies were reviewed and classified by an experienced renal pathologist, using the 2004 International Society of Nephrology/Renal Pathological Society (ISN/RPS) classification [21]: class I (minimal mesangial LN), class II (mesangial proliferative LN), class III (focal LN), class IV (diffuse LN), class V (membranous LN), and class VI (advanced sclerosing LN).

Laboratory Investigation

7 ml of whole blood was collected from each subject into plain tubes without any additives. After 20 min of incubation at room temperature, the tubes were centrifuged for 10 min at 1000 G. The supernatant was carefully separated, aliquoted, and stored at −80 °C until use. In order to avoid protein degradation from multiple freeze-thaw cycles, each aliquot was retrieved and thawed only once for assays in this study.

Kidney function test, liver function test, and lipid profile were performed with an auto-analyser Cobas c 311 (Roche/Hitachi Cobas c systems, Roche Diagnostics GmbH, Germany). Complete urine analysis was performed using a 10-parameterreagent strip (Polypharma), while proteinuria in a 24-hour urine sample collection was measured on Cobas Integra® 400 plus auto-analyser, and creatinine clearance was calculated [22]. Serum C3 and C4 levels were measured with turbid metric immunoassay using the BN ProSpec® System (Siemens Healthcare Diagnostics Inc.). Antinuclear antibodies (ANAs) were determined using the indirect iunofluorescence technique on Hep2 cells (DiaSorine, HEP2 cell line substrate). Anti-dsDNA IgG autoantibody detection was performed using Alegria® (ORGENTEC Diagnostika). C-reactive protein was detected using the latex agglutination test kit (Biotec Laboratories Ltd, UK).

Measurement of serum PGRN and IGFBP-2 levels

Serum levels of PGRN and IGFBP-2 were measured using the human PGRN ELISA kit (Cat. no.: E-EL-H1578) and human ILGFBP-2 ELISA kit (Cat. no.: E-EL-H0446), respectively, from Elabscience Biotechnology Co. Ltd., according to the manufacturer's manual. The optical density at 450 nm wavelength was measured using a microplate reader Stat Fax® 2100. PGRN and ILGFBP-2 concentration were then calculated according to the standard curve. Serum PGRN levels are expressed as pg/ml and serum ILGFBP-2 levels are expressed as ng/ml.

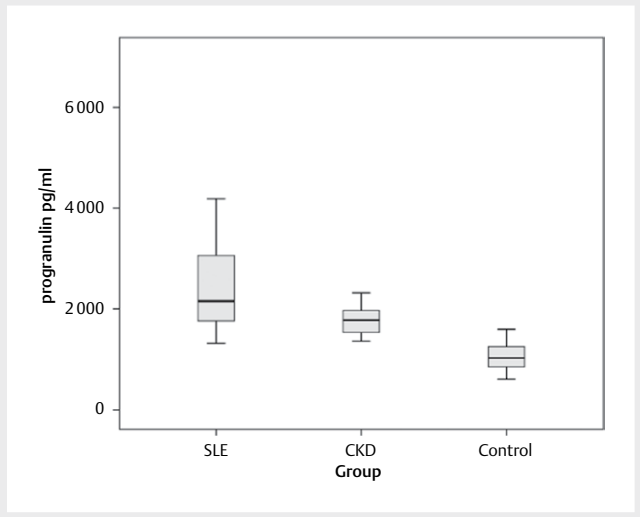
▶ **Table 1** Clinical data of SLE patients.

	SLE (n = 25)
Duration/year	4.78 ± 4.26
Photosensitivity	18 (72 %)
Malar rash	19 (76 %)
Discoid rash	6 (24 %)
Oral ulcers	18 (72 %)
Arthralgia	24 (96 %)
Arthritis	10 (40 %)
Pleuritis	5 (20 %)
Pericarditis	3 (12 %)
Seizures	3 (12 %)
White blood cells 10^9/L	5.68 ± 2.15
Platlets 10^9/L	262.12 ± 97.95
Hemoglobin g/dl	11.1 ± 1.9
ESR mm/h	37.52 ± 24.4
Proteinurea	13 (52 %)
24h protein mg/day	1214.52 ± 1167.93
Urea mg/dL	15.24 ± 20.69
Creatinine mg/dL	98.29 ± 108.99
Creatinine clearance ml/min	81.8 ± 42.25
ANA	25 (100 %)
anti double strand DNA	23 (92 %)
Low C3	10 (40 %)
Low C4	13 (52 %)
SLEDAI score	15.04 ± 7.54
Renal biopsy	
Class2	8 (32 %)
Class3	6 (24 %)
Class5	11 (44 %)

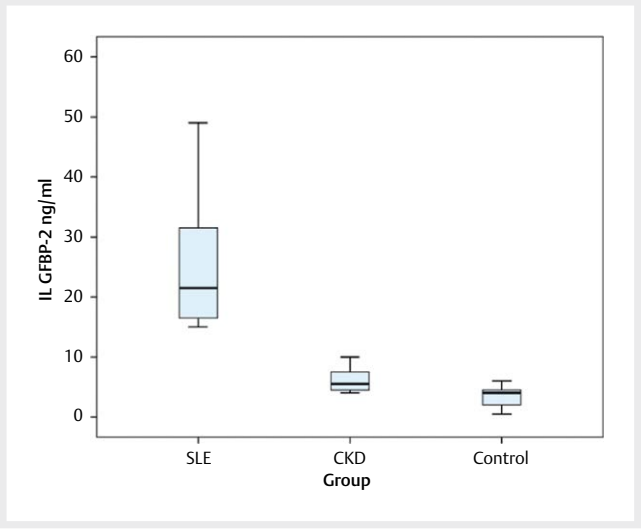
SLE: systemic lupus erythematosus, SLEDAI score: systemic lupus erythematosus disease activity index.

Statistical analysis

The data were tested for normality, using the Anderson-Darling test, and for variances in homogeneity prior to further statistical analysis. Categorical variables are described as number and percentage (N, %), while continuous variables are described as mean and standard deviation (mean, SD). The chi-square and Fisher's exact tests were used to compare categorical variables. Continuous variables were compared using the unpaired t-test and ANOVA. Pearson's correlation was used to assess the correlation between continuous variables. The receiver operating characteristics curve was used to predict cut off values and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and



▶ **Fig. 1** Levels of PGRN in SLE, CKD and control groups. PGRN: progranulin, SLE: systemic lupus erythematosus, CKD: chronic kidney disease.



▶ **Fig. 2** Levels of ILGFBP-2 in SLE, CKD, and control groups. ILGFBP-2: insulin like growth factor binding protein-2, SLE: systemic lupus erythematosus, CKD: chronic kidney disease.

▶ **Table 2** Sensitivity,specificity, and cut-off of PGRN and ILGFBP-2 in the 3 groups vs. each other.

	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
SLE vs. CKD							
ILGFBP-2	1.0	>12.5	100.0	100.0	100.0	100.0	100.0
PGRN	0.718	>2077.5	56.0	84.0	77.8	65.6	71.2
SLE vs. control							
ILGFBP-2	1.0	>6	100.0	100.0	100.0	100.0	100.0
PGRN	0.99	>1594	92.0	100.0	100.0	92.6	94.2
CKD vs. control							
ILGFBP-2	0.844	>4	84.0	68.0	72.4	81.0	76.3
PGRN	0.971	>1336	100.0	88.0	89.3	100.0	94.0

PGRN: progranulin, ILGFBP-2: insulin like growth factor binding protein-2, SLE: systemic lupus erythematosus, CKD: chronic kidney disease, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.

accuracy. A 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS 20.0.

Results

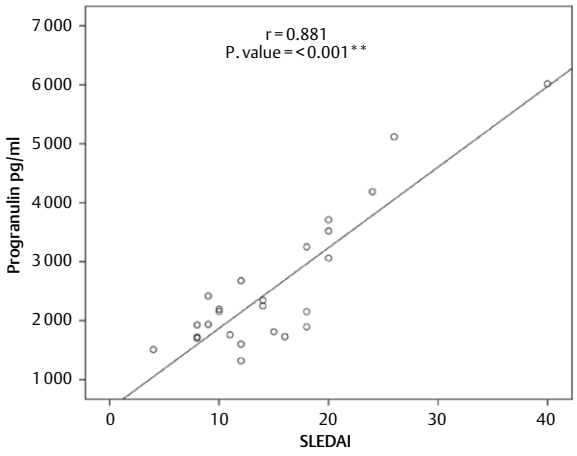
▶ **Table 1** presents the clinical data for SLE patients, who had a disease duration of 4.78 ± 4.26 years. The percentage of patients with photosensitivity was 72 %, malar rash 76 %, discoid rash 24 %, oral ulceration 72 %, arthralgia 96 %, arthritis 40 %, pleuritis 20 %, pericarditis 12 %, seizures 12 %. All the SLE patients were ANA positive, while 92 % were anti-dsDNA positive. The white blood cell count was 5.68 ± 2.15 10^9/L, platelets 262.12 ± 97.95 10^9/L, haemoglobin11.1 ± 1.9 g/dl, and erythrocyte sedimentation rate 37.52 ± 24.4 mm/h. Proteinuria was noted in 52 % of patients and the 24-hour protein was 1214.52 ± 1167.9 mg/day. The mean SLEDAI score was 15.04 ± 7.54. All renal biopsy results were class 2, 3, and 5 with a percentage of 32, 24, and 44 %, respectively.

The mean PGRN level was 2558.92 ± 1170.77 pg/ml for the SLE group, 1814.6 ± 330.28 pg/ml in the CKD group, and 1052 ± 276 pg/ml for the healthy controls, while the mean IGFBP-2level was 26.44 ± 11.55 ng/ml, 6.14 ± 2.25 ng/ml, and 3.3 ± 1.7 ng/ml in the SLE, CKD, and control groups, respectively. Serum PGRN and ILGFBP-2 levels showed a significant elevation in the SLE group in comparison with the CKD and control groups ($p < 0.001$ all). PGRN was significantly higher in the CKD group than in the control group ($P < 0.001$). There was no significant difference between the CKD and control group regarding the serum level of ILGFBP-2(▶ **Figs 1** and ▶ **2**).

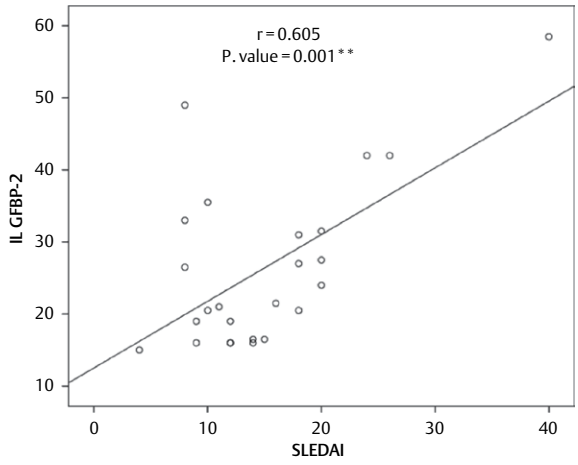
▶ **Table 3** Levelsof PGRN and ILGFBP-2 in relation to SLEDAI score.

	SLEDAI score			P. value
	Moderate	High	Very high	
PGRN pg/ml	1945.6 ± 300	2072.1 ± 545.5	4269.2 ± 1106.8#&	0.002 * *
ILGFBP-2 ng/ml	26.8 ± 11.7	20.1 ± 5	37.6 ± 12.6#&	0.006 * *

* Statistically significant difference ($p < 0.05$); * * Statistically high significant difference ($p < 0.01$); PGRN: progranulin, ILGFBP-2: insulin like growth factor binding protein-2, SLEDAI: systemic lupus erythematosus disease activity index.



▶ **Fig. 3** Correlation between SLEDAI and progranulin. SLEDAI systemic lupus erythematosus disease activity index.



▶ **Fig. 4** Correlation between SLEDAI and ILGFBP-2. ILGFBP-2 insulin like growth factor binding protein -2, SLEDAI systemic lupus erythematosus disease activity index.

▶ **Table 2** shows the cut off, sensitivity, and specificity of PGRN and ILGFBP-2 in the 3 studied groups. This study showed that all SLE patients had moderate, high, or very high disease activity with a positive significant difference between these levels of disease activity and the levels of PGRN and ILGFBP-2 ($p < 0.002$ and < 0.006, respectively) (▶ **Table 3**).

▶ **Figs 3** and ▶ **4** show that there was a significant positive correlation ($p < 0.001$) between PGRN, ILGFBP-2, and SLEDAI. Arthritis, urea, creatinine, creatinine clearance, 24-hour protein, haemoglobin and anti-dsDNA were uncorrelated with both markers, except for the correlation of arthritis with ILGFBP-2 ($p < 0.025$). Moreover, in this study, we found no significant difference between active and inactive LN or classes of renal biopsy with respect to PGRN and ILGFBP-2.

Discussion

SLE is a potentially fatal disease with the deposition of immune complexes and inflammation leading to severe tissue damage [1]. In spite of contemporary treatment using immunosuppressive drugs for LN, results are unsatisfactory regarding disease activity with remission and drug intolerance [9, 23]. Thus, new biomarkers to identify early renal involvement in SLE patients are being soug ht[24–31]. An ideal biomarker should detect disease activity and renal involvement and damage as early as possible to enable prompt treatment and minimise organ damage [32].

In LN, glomerular immune complexes, at their site of deposition on the kidneys, are considered the main mediators of renal involvement. The progression of LN, leading to renal failure, is due to renal infiltration by macrophages, dendritic cells, and T cells [33].

We included a CKD group to evaluate if elevated serum levels of PGRN and IGFBP-2 were involved in the pathogenesis of LN which differs from the pathogenesis of CKD. Our results showed that both markers were elevated in CKD compared to the control group, but were more elevated in LN patients.

Our results showed a significant difference between the 3 groups with respect to PGRN and IGFBP-2, except for ILGFBP-2, where no significant difference was noted between the CKD and control groups. These findings agreed with the findings of some studies on PGRN [14, 34]. Tanaka et al [13] also found higher levels of PGRN in SLE patients than in controls. For IGFBP-2, our findings were in consonance with those of Ding et al [10]. Mok et al found

that IGFBP-2 was significantly elevated in patients with active SLE than in patients with inactive SLE and controls; in this study, SLEDAI ≥6 was considered active SLE [32].

Several studies have reported that the pathway of inflammatory and immune signalling are related to the pathogenesis of LN in which the TLR cascade has an important role [35]. DNA with nucleosomal DNA and immune complexes stimulateTLR-9 on plasmacytoid dendritic cells [9, 36]. Authors found that PGRN was involved in TLR-mediated stimulation in the pathogenesis of LN which is considered a part of disease activity [12–14].

There was a significant increase in PGRN and IGFBP-2 with an increase in the SLEDAI score ($p < 0.002$ and $p < 0.006$ respectively). Moreover, there was no significant difference between PGRN and IGFBP-2 and classes of renal biopsy. For PGRN, our results were consistent with those of Tanaka et al [13] and Wu et al [14]. For IGFBP-2, our results agreed with those of Ding et al [10].

During inflammation, the proteolytic product of PGRN activates the delivery of nuclear auto-antigens to TLR-9 at the endolysosomal compartments. In addition, it helps the interaction between TLR-9 and these auto-antigens, which increases the inflammatory response [12]. That is why PGRN might reflect disease activity in LN.

Our results showed that there was no significant difference between active and inactive LN regarding PGRN and IGFBP-2. Moreover, there was no correlation between arthritis, urea, creatinine, creatinine clearance, 24-hour protein, haemoglobin, and anti-dsDNA, and both markers, except for the correlation of arthritis with IGFBP-2; the reason for these resultare unclear. However, Tanaka et al [13] and Wu et al [14] found a significantly higher serum level of PGRN in active LN compared to inactive LN and non-LN controls, while Ding et al [10] noted a similar pattern with IGFBP-2. Wu et al [14] also found no correlation between PGRN and serum creatinine and 24-hour protein in urine. Ding et al [10] found a correlation between IGFBP-2 and serum creatinine levels. The bioactivity of IGFs is regulated by IGFBPs of which IGFBP-3 is the most abundant form in human plasma, followed by IGFBP-2. IGFBP-1 is the major anabolic factor in human serum and synovial fluid with respect to the proteoglycan synthesis of chondrocytes exposed to these fluids. In arthritis, however, chondrocytes seem to be unresponsive to IGFBP-1, a fact that may be related to the modulation of IGFBP-1 bioactivity by increased levels of IGFBPs [37].

A report showed that IGFBP-2 was elevated in nephrotic syndrome in paediatric patients [38], and in type 2 diabetes[39] as a predictor of the deterioration of renal functions. PGRN plays an important role in early embryogenesis [40], wound healing [41], tumorigenesis [42], and maintenance of neuronal survival [43].

There were some limitations in our study. First, the sample size was relatively small. Secondly, all our patients were from a single institution and of the same ethnic group. Several follow-up studies are needed to estimate levels of PGRN and IGFBP-2 in all SLE patients with and without LN. Moreover, studies could compare these biomarkers with the chronicity index in LN patients.

Conclusion

The present study demonstrated that the serum levels of PGRN and IGFBP-2 were elevated in LN patients and correlated with disease activity but did not correlate with active and inactive LN or with classes of renal biopsy.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Rahman A, Isenberg DA. Systemic lupus erythematous. N Engl J Med 2008; 358: 929–939

[2] Kotzin BI. Systemic lupus erythematosus. Cell 1996; 85: 303–306

[3] Stohl W. Future prospects in biologic therapy for systemic lupus erythematosus. Nat Rev Rheumatol 2013; 9: 705–720

[4] Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine 2006; 85: 147–156

[5] Mok CC. Biomarkers for lupus nephritis: a critical appraisal. J BoimedBiotechnol 2010; 2010: 638413

[6] Ortega LM, Schultz DR, Lenz O et al. Review: Lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions. Lupus 2010; 19: 557–574

[7] Manger K, Manger B, Repp R et al. Definition of risk factors for death, end stage renal disease and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. Ann Rheum Dis 2002; 61: 1065–1070

[8] Cervera R, Khamashta MA, Font J et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003; 82: 299–308

[9] Borchers AT, Leibushor N, Naguwa SM et al. Lupus nephritis: a critical review. Autoimmun Rev 2012; 12: 174–194

[10] Ding H, Kharboutli M, Saxena R et al. Insulin-like growth factor binding protein-2 as a novel biomarker for disease activity and renal pathology changes in lupus nephritis. Clinical and Experimental Immunology 2016; 184: 11–18

[11] Liu CJ. Progranulin: a promising therapeutic target for rheumatoid arthritis. FEBS Lett 2011; 585: 3675–3680

[12] Park B, Buti L, Lee S et al. Granulin is a soluble cofactor for toll-like receptor 9 signaling. Immunity 2011; 34: 505–513

[13] Tanaka A, Tsukamoto H, Mitoma H et al. Serum progranulin levels are elevated in patients with systemic lupus erythematosus, reflecting disease activity. Arthritis Res Ther. 2012; 14: R244

[14] Wu J, Wei L, Wang W et al. Diagnostic value of progranulin in patients with lupus nephritis and its correlation with disease activity. Rheumatol Int 2016; 36: 759–767

[15] Bruchim I, Werner H. Targeting IGF-1 signaling pathways in gynecologic malignancies. Expert OpinTher Targets 2013; 17: 307–320

[16] Forbes BE, McCarthy P, Norton RS. Norton. Insulin-like growth factor binding proteins: A structural perspective. Front Endocrinol (Lausanne) 2012; 3: 38

[17] Petri M, Orbai AM, Alacon GS et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64: 2677–2668

[18] Bombardier C, Gladman DD, Urowitz MB et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arhritis Rheum 1992; 35: 630–640

[19] Petri M, Genovese M, Engle E et al. Definition, incidence and clinical description of flare in systemic lupus erythematosus. Arthritis Rheum 1991; 8: 937–944

[20] Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002; 29: 288–291

[21] Weening JJ, D'Agati VD, Schwartz MM.etal. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004; 65: 521–530

[22] Rock RC, Walker WG, Jennings CD. Nitrogen metabolites and renal function.In fundamentals of clinical chemistry. editor Tiez NW. 3rd edition W.B. Saunders Company; 1987: 669–704

[23] Rovin BH, Zhang X. Biomarkers for lupus nephritis: the quest continues. Clin J Am ScoNephrol 2009; 4: 1858–1865

[24] Frieri M, Samih MA, Dzhindzhikhashvili M et al. Toll-like receptor 9 and vascular endothelial growth factor levels in human kidneys from lupus nephritis patients. J Nephrol 2012; 25: 1041

[25] Panda AK, Parida JR, Tripathy R et al. Mannose binding lectin: a biomarker of systemic lupus erythematosus disease activity. Arthritis Res Ther 2012; 14: R218

[26] Rosa RF, Takei K, Araújo NC et al. Monocyte chemoattractant-1 as a urinary biomarker for the diagnosis of activity of lupus nephritis in Brazilian patients. J Rheumatol 2012; 39: 1948–1954

[27] Kirsztajn G. Serum beta 2-microglobulin/ cystatin C index: a useful biomarker in lupus nephritis. Nephron Extra 2012; 2: 169–176

[28] Singh S, Wu T, Xie C et al. Urine VCAc of renal pathology activity index in lupus nephritis. Arthritis Res Ther 2012; 14: R164

[29] Treamtrakanpon W, Tantivitayakul P, Benjachat T et al. APRIL, a proliferation-inducing ligand, as a potential marker of lupus nephritis. Arthritis Res Ther 2012; 14: R252

[30] Badot V, Luijten RK, van Roon JA et al. Serum soluble interlukin 7 receptor is strongly associated with lupus nephritis in patients with systemic lupus erythematosus. Ann Rheum Dis 2013; 72: 453–456

[31] Wu T, Du Y, Han J et al. Urinary angiotensin- a novel putative marker of renal pathology chronicity in lupus nephritis. Mol Cell Proteomics. 2013; 12: 1170–1179

[32] Mok CC, Ding H, Kharboutli M et al. Axl, ferritin, insulin-like growth factor binding protein 2, and tumour necrosis factor receptor type II as biomarkers in systemic lupus erythematosus. Arthritis care and research 2016; 68: 1303–1309

[33] Bagavant H, Fu SM. Pathogenesis of kidney disease in systemic lupus erythematosus. CurrOpinRheumatol 2009; 21: 489–494

[34] Qiu F, Song L, Ding F et al. Expression level of the growth factor progranulin is related with development of systemic lupus erythematosus. Diagnostic Pathology 2013; 8: 88

[35] Lech M, Anders HJ. The pathogenesis of lupus nephritis. J Am SocNephrol 2013; 24: 1357–1366

[36] Lorenzo G, Desai J, Anders HJ. Lupus nephritis: update on mechanisms of systemic autoimmunity and Kidney immunopathology. CurrOpinNephrolHypertens 2014; 23: 211–217

[37] Neidel J. Changes in systemic levels of insulin-like growth factors and their binding proteins in patients with rheumatoid arthritis. Clin and ExperRheumatol 2001; 1: 81–84

[38] Fled SM, Hirschberg R. Insulin-like growth factor-1 and insulin-like growth factor-binding proteins in the nephrotic syndrome. PediatrNephrol 1996; 10: 355–358

[39] Narayanan RP, Fu B, Heald AH et al. ILGFBP2 is a biomarker for predicting longitudinal deterioration in renal function in type 2 diabetes. Endocr Connect 2012; 1: 95–102

[40] Daniel R, He Z, Carmichael KP et al. Cellular localization of gene expression for progranulin. J HistochemCytochem 2000; 48: 999–1009

[41] He Z, Ong CH, Halper J et al. Progranulin is a mediator of the wound response. Nat Med 2003; 9: 225–229

[42] Bateman A, Bennett HP. The granulin gene family: from cancer to dementia. Bioessays 2009; 31: 1245–1254

[43] Van Damme P, Van Hoecke A, Lambrechts D et al. Progranulin functions as a neurotropic factor to regulate neurite outgrowth and enhanve neuronal survival. J Cell Biol 2008; 181: 37–41