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Assessment of Progranulin as an Early Diagnostic Marker of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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Abstract: Aims: We aimed to investigate progranulin as a diagnostic marker of diabetic nephropathy in patients with type 2 diabetes mellitus. **Methods:** The study included ninety subjects, divided into three groups; 30 patients with type 2 diabetes mellitus with diabetic nephropathy, 30 patients with type 2 diabetes mellitus without diabetic nephropathy and 30 apparently healthy individuals (control group). All personnel were subjected to full history taking, thorough clinical examination, glycated hemoglobin, complete lipid profile, serum creatinine and blood urea and Urinary albumin creatinine ratio. progranulin level was measured for all personals**. Results:** There are statistically significant differences between the three groups regarding age and body mass index with significant difference between every group in comparison with others. Also, there are significant differences between both groups regarding systolic and diastolic blood pressure. There are statistically significant differences between the three groups regarding kidney function tests, glycated hemoglobin and fasting blood glucose. Also, there are significant differences between both groups regarding ALT, AST and serum albumin. There are significant differences between both groups regarding total cholesterol and triglycerides. There is a significant difference between both groups regarding serum progranulin. There are significant differences between both groups regarding type of therapy used and disease duration. There are highly significant positive correlations between serum PGRN and age, urea, creatinine, urinary albumin-to-creatinine ratio, glycated hemoglobin, fasting blood glucose, duration, total cholesterol, triglycerides, systolic and diastolic blood pressure. There are highly significant negative correlations between serum progranulin and BMI, estimated glomerular filtration rate and serum albumin. Multiple stepwise regression analysis demonstrated that only urinary albumin-to-creatinine ratio, duration and diastolic blood pressure were independently associated with serum progranulin. **Conclusion:** Serum progranulin concentrations increased in Egyptian patients with nephropathy. The level of progranulin in patients with type 2 diabetes should be paid high attention and it could be a potential therapeutic target for the management of type 2 diabetes and diabetic nephropathy.

[Fawzy Abdel Fattah Elmessalamy, Hazem Mohamed El Ashmawy, Mohamed Gaber Hamed and Amin Mohamed Amin. **Assessment of Progranulin as an Early Diagnostic Marker of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus.** *Nat Sci* 2019;17(12):87-95]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 13. doi:10.7537/marsnsj171219.13.

Key Words: type 2 diabetes mellitus, diabetic nephropathy, progranulin.

Introduction

Diabetes mellitus is a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism. It results from defects in insulin secretion (type 1), insulin action (type 2), or a combination of these factors, Diabetes is the most common cause of kidney failure, which accounts for more than one-third of all kidney disease patients who are on dialysis **[1].**

Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and pro-inflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat **[2].**

Progranulin (PGRN), also referred to as granulin-epithelin precursor (GEP), proepithelin, PC cell derived growth factor (PCDGF), or acrogranin, was first purified as a growth factor from conditioned tissue culture media. It has been identified from different sources by several independent laboratories. It is a 68.5-kDa secreted growth factor **[3]**.

Diabetic kidney disease (DKD) is a common complication of diabetes, associated with

cardiovascular disease. Increased serum PGRN was observed in macroalbuminuric patients with T2DM. Moreover, PGRN was described as a renal function-dependent adipokine, since elevated serum levels were observed in patients at stage 5 of chronic kidney disease (CKD) **[4]**.

Ezz and Abd El Azeem [5] determined serum progranulin level in Egyptian type 2 diabetic patients and the association between its level with diabetic and renal biomarkers to evaluate it as a predictor marker of diabetic nephropathy. They suggested that PGRN may be considered as a highly sensitive and specific biomarker for diabetic nephropathy.

This study aimed to investigate progranulin as a diagnostic marker of diabetic nephropathy in patients with type 2 diabetes mellitus.

Subjects and methods

This case-control study was conducted on 90 subjects; they were selected from the Outpatient Clinic of Internal Medicine Department, Faculty of Medicine, Zagazig University.

Subjects:

This study included a total number of 90 subjects,30 patients with type 2 DM with diabetic nephropathy, 30 patients with type 2 DM without diabetic nephropathy and 30 apparently healthy individuals (control group).

- **Group 1: Patients with diabetes who have nephropathy:** (30) patients with type 2 diabetes mellitus, complicated with diabetic nephropathy (urinary albumin / creatinine ratio ≥ 2) with age and gender matching.
- **Group 2: Patients with diabetes who have no nephropathy:** (30) patients with type 2 diabetes mellitus, without diabetic nephropathy with age and gender matching.
- **Control group:** (30) normal individuals with age matching as a control.

Inclusion criteria:

- **Age:** above 30 years old
- **Sex:** Male – Female

Exclusion criteria:

- Past history of malignancy.
- Type 1 diabetes mellitus.
- Diabetic macrovascular complications by doing ECG, ECHO and duplex on both LL.
- Other endocrine diseases which affect glucose metabolism and lipid metabolism.
- Chronic hepatitis.
- Primary kidney disease.
- Recent inflammatory disease.
- Acute trauma.
- Taking thiazolidinedione drugs in 3 weeks, pregnancy, and history of drug abuse.

Methods:

- Full history taking (personal and past history).
- General examination and anthroprometric measures.
- Routine laboratory tests (Glycated haemoglobin A1c, serum lipid profiles, kidney function tests, estimated glomerular filtration rate and urinary albumin / ceatinine ratio).
- Detection and measurement of progranulin level by enzyme-linked immunosorbent assay (ELISA) technique.

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human progranulin (PGRN) in samples. Add progranulin (PGRN) to monoclonal antibody Enzyme well which is pre- coated with Human progranulin (PGRN) monoclonal antibody, incubation; then, add progranulin (PGRN) antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, B, the color of the liquid changes into the blue, And at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance progranulin (PGRN) of sample were positively correlated.

Statistical analysis:

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 20. Data were summarized using the arithmetic mean, standard deviation, analysis of variance, correlation study, Mann Whitney U-test, Wilcoxcon-signed rank test, validity of screening test, Student t test and chi-squared test. The threshold of significance is fixed at 5% level (p-value).

The results was considered:

- Significant when the probability of error is less than 5% ($p < 0.05$).
- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Highly significant when the probability of error is less than 0.1% ($p < 0.001$).

The smaller the p-value obtained, the more significant are the results.

Results

There are no significant differences between these groups regarding gender or age (Table 1). There is statistically significant difference between the three groups regarding BMI with significant difference between every group in comparison with others (LSD comparison) (Table 2).

There is statistically significant difference between the three groups regarding BMI. On pair wise comparison, the group with nephropathy showed the

most significant difference with other groups (Table 3). There are significant differences between the three groups regarding HbA1c and fasting blood glucose (Table 4). There are significant differences between both groups regarding serum progranulin. On LSD comparison with the group with diabetic nephropathy had the significant high levels (Table 5).

There are significant differences between both groups regarding ALT, AST and serum albumin. On LSD comparison, there is significant difference between each two groups regarding ALT and AST. The group with nephropathy had the significant lowest serum albumin (Table 6).

There are significant differences between both groups regarding total cholesterol and triglycerides. On LSD comparison, there is significant difference between each two groups regarding lipid profile (Table 7). There are significant differences between both groups regarding systolic and diastolic blood pressure. On LSD comparison, there is significant difference between each two groups regarding systolic blood pressure while the group of patients with nephropathy has the highest significant diastolic blood pressure (Table 8).

There are significant differences between both groups regarding type of therapy used. The largest percentage of patients with nephropathy used insulin while in patients with no nephropathy were on oral antidiabetics. There is significant difference between both groups regarding disease duration (Table 9).

The best cutoff of serum progranulin in diagnosis of nephropathy in diabetic patients is ≥55.5 with AUC 0.986 and sensitivity 93.3%, specificity 86.7%, PPV 78.7, NPV 96.3%, +LR 7.01, -LR 0.08 and accuracy 88.9% ($p<0.05$) (Table 10 and Figure 1).

There are highly significant positive correlations between serum progranulin and age, urea, creatinine, UACR, HbA1c, FBG, duration, total cholesterol, triglycerides, systolic and diastolic blood pressure. There are highly significant negative correlations between serum progranulin and BMI, eGFR and serum albumin (Table 11).

To evaluate the independent factors of PGRN with the factors identified in the above univariate analysis, multiple stepwise regression analysis was done on factors shown significant relation with progranulin level. Oly UAcR (unstandardized β = 0.507, p = <0.001), duration (unstandardized β = 0.379, p = <0.001) and DBP (unstandardized β = 0.131, p = 0.016) were independently associated with serum PGRN (table 12).

Table 1: Demographic criteria of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	F	p
Age					
Mean ± SD	63.53±3.8	64.57± 4.84	66.4 ± 6.66	2.308	0.106
Range	54 - 69	54- 75	54 - 80		
	N (%)	**N (%)**	**N (%)**		
Gender:					
Female	13 (43.3)	13 (43.3)	13 (43.3)	0	1
Male	17 (56.7)	17 (56.7)	17 (56.7)		

Table 2: BMI of studied groups

BMI	Control group	DM with no nephropathy	DM with nephropathy	F	p
Mean ± SD	24.63±1.63	26.7± 1.62	23.8 ± 1.2	29.951	<0.001**
Range	20.8 – 27.1	22.8 – 29.3	21.6 – 26.6		

**p≤0.001 is highly significant BMI: Body Mass Index, DM, Diabetic Mellitus

Table 3: Kidney function test of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	KW	p
Urea					
Mean ± SD	30.43±10.85	38.77± 14.05	97.4 ± 38.41	60.104	<0.001**
Range	13 – 50	15 – 60	56 – 190		
S. creatinine					
Mean ± SD	0.83 ± 0.27	0.9 ± 0.25	2.65 ± 0.25	60.134	<0.001**
Range	0.5 – 1.3	0.5 – 1.3	1.5 – 4.5		
eGFR					
Mean ± SD	105.19±37.5	92.96 ±26.69	27.76 ±11.74	59.711	<0.001**
Range	52 – 188	60.1 – 186.5	10.7 – 52		
UACR					
Mean ± SD	20.47 ± 5.52	22.57 ± 5.28	266.8± 94.54	60.427	<0.001**
Range	10 – 29	14 – 29	140 – 430		

**p≤0.001 is highly significant DM: Diabetes Mellitus, eGFR: Estimated Glomerular Filtration Rate, UACR: Urinary Albumin-to-Creatinine Ratio

Table 4: HbA1c and FBG test of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	KW	p
HbA1c					
Mean±SD	4.99±0.61	8.55± 1.61	10.92 ± 1.8	68.267	<0.001**
Range	4 – 6	6.5 – 13	8 – 15		
Fasting blood glucose					
Mean ± SD	98.8±7.36	148.93±19.97	205.6± 64.24	F=56.103	<0.001**
Range	85 – 111	120 – 190	123 – 354		

**p≤0.001 is highly significant DM: Diabetes Mellitus, HbA1c: Glycated Hemoglobin

Table 5: Progranulin level of studied groups

Progranulin	Control group	DM with no nephropathy	DM with nephropathy	F	p
Mean ± SD	45.63±4.26	50.97 ± 5.16	69.53± 7.84$^{\infty}$	133.231	<0.001**
Range	40 – 60	43 – 60	53 – 82		

**p≤0.001 is highly significant

Table 6: Liver function test of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	F	p
ALT					
Mean±SD	23.27±8.75	30.27 ± 9.86	26.17 ± 7.87	4.276	0.011*
Range	9 – 40	12 – 45	15 – 45		
AST					
Mean±SD	23.7 ± 6.49	31.57 ± 9.9	30.3 ± 6.73	F=8.662	<0.001**
Range	13 – 40	17 – 50	16 – 45		
Albumin					
Mean±SD	4.1 ± 0.57	4.08 ± 0.5	2.8 ± 0.38	70.893	<0.001**
Range	3 – 5	3 – 4.9	2 – 3.4		
Bilirubin					
Mean±SD	0.63 ± 0.27	4.08 ± 0.5	0.6± 0.25	KW=2.814	0.245
Range	0.2 – 1.1	0.3 – 1	0.2 – 1		

**p≤0.001 is highly significant *p<0.05 is significant

Table 7: Lipid profile of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	F	p
Total cholesterol					
Mean ± SD	202.9±35.8	228.9 ±27.05	267.93±33.15	30.892	<0.001**
Range	140 – 285	179 – 283	206 – 321		
Triglycerides					
Mean ± SD	159.43±19.09	179.63 ±27.2	221.43±27.38	48.538	<0.001**
Range	123 – 198	135 – 236	156 – 276		

**p≤0.001 is highly significant

Table 8: Blood pressure of studied groups

	Control group	DM with no nephropathy	DM with nephropathy	F	P
SBP					
Mean±SD	124.33±11.12	135.67±12.51	152.33±21.12	24.584	<0.001**
Range	110 – 140	110 – 150	100 – 190		
DBP					
Mean±SD	79.33 ± 6.53$^{\infty}$	87.5± 9.35	92± 10.64	15.255	<0.001**
Range	70 – 90	70 – 100	70 – 110		

**p≤0.001 is highly significant; DM: Diabetes Mellitus, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table 9: Blood pressure of studied groups

	DM with no nephropathy	DM with nephropathy	Chi square	p
Oral antidiabetics No Yes	 1 (3.3) 29 (96.7)	 15 (50) 15 (50)	Fisher	<0.001**
Insulin No Yes	 19 (63.3) 11 (36.7)	 1 (3.3) 29 (96.7)	Fisher	<0.001**
Duration Mean ± SD Range	 6.13 ± 2.56 2 – 10	 14.1 ± 2.95 9 – 20	MW (-6.507)	<0.001**

**p≤0.001 is highly significant

Table 10: Performance of progranulin in prediction of development of nephropathy in diabetic patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	p
55.5	0.982	93.3	86.7	78.7	96.3	7.01	0.08	88.9	<0.001**

**p≤0.001 is highly significant AUC: Area Uncer Curve, PPV: Positive Predictive Value, NPV: Negative Predictive Value, LR: Likelihood Ratio

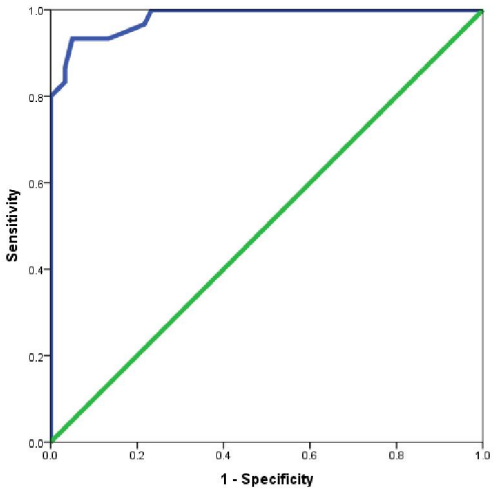

Figure 1: ROC curve showing validity of serum progranulin in prediction of development of nephropathy

Table 11: Correlation between serum progranulin and other study variables in diabetic patients

	r	p
Age	0.584	<0.001**
BMI	-0.321	0.002*
Urea	0.727	<0.001*
Creatinine	0.819	<0.001**
eGFR	-0.687	<0.001**
UACR	0.842	<0.001**
HbA1c	0.716	<0.001**
FBG	0.759	<0.001**
Duration	0.835	<0.001**
S. total cholesterol	0.553	<0.001**
S. triglycerides	0.645	<0.001**
SBP	0.532	<0.001**
DBP	0.393	<0.001**
ALT	0.049	0.65
AST	0.153	0.130
S. albumin	-0.648	<0.001**
S. bilirubin	-0.006	0.953

**p≤0.001 is highly significant *p<0.05 is significant

BMI: Body Mass Index, eGFR: Estimated Glomerular Filtration Rate, UACR: Urinary Albumin-to-Creatinine Ratio, HbA1c: Glycated Hemoglobin, FBG: Fasting Blood Glucose, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table 12: Multiple stepwise regression analysis showing variables independently associated with serum levels of PGRN

	Unstandardized Coefficients		Standardized Coefficients	t	*p*
	Beta	Standard error	Beta		
UACR	0.047	0.008	0.507	6.132	<0.001**
Duration	0.722	0.165	0.379	4.366	<0.001**
DBP	0.119	0.048	0.131	2.459	0.016*

**p≤0.001 is highly significant *p<0.05 is significant
UACR: Urinary Albumin-to-Creatinine Ratio, DBP: Diastolic Blood Pressure

4. Discussion

Diabetic nephropathy represents the most common cause of end-stage renal failure worldwide and accounts for < 40% of all new patients entering end-stage renal disease (ESRD) **[1]**.

To prevent the dreadful consequence, development of new assays for diagnostic of DKD has always been the priority in the research field of diabetic complications **[6]**. DN can be detected before the onset of decreased glomerular filtration rate (GFR) in most patients by detecting abnormal amounts of albumin in the urine. Two stages have been designated: micro-albuminuria (defined as urine albumin between 30 and 300 mg/24 h, 20-200 µg/min on a timed sample, or spot urine albumin to creatinine ratio 30-300 mg/g) and albuminuria, also termed clinicalalbuminuria, macro-albuminuria, and overt nephropathy (>300 mg/24h, >200 µg/min on a timed sample, or spot urine albumin to creatinine [ACR] ratio >300 mg/g) **[7]**. The precision of creatinine-based GFR estimates is limited in hyper-filtration status. These facts make albuminuria and e-GFR less reliable indicators for early-stage DKD **[6]**.

The pathophysiological processes that lead to diabetic nephropathy have notably improved on a genetic and molecular level. Thus, the classic view of metabolic and hemodynamic alterations as the main causes of renal injury in diabetes has been transformed significantly, with clear evidence indicating that these traditional factors are only a partial aspect of a much more complex picture **[8].**

Serum creatinine is considered specific but not very sensitive as its level does not significantly increase until the GFR is reduced to less than 50% of normal. Therefore, new biomarkers are needed for early diagnosis to allow early treatment of DN **[9].**

Due to the limitations of e-GFR and albuminuria in the early diagnosis of DKD, enormous efforts have been made to investigate and validate alternative biomarkers in recent decades. Progranulin (PGRN) is a fascinating multifunctional protein, which has been implicated in cell growth, wound repair, tumorigenesis, neurodevelopment, neurodegeneration. In addition, it is a kind of adipocytokines with important functions in modulation of inflammatory events. Inflammation is a key process in the development of diabetes mellitus and diabetic nephropathy. Therefore, progranulin caught an attention because it is a novel adipokine marker of chronic inflammatory response in type 2 diabetes capable of directly affecting the insulin signaling pathway **[10]**.

It has been suggested that the full length form of the protein (PGRN) has anti-inflammatory action, while released granulins have the opposite effect, increasing the production of pro-inflammatory cytokines. Its proteolytically cleavage by elastase and generates granulin peptides (GRNs) in tissue, some of which enhance inflammation process **[11]**.

Richter et al. [12] and Judit et al. [13] also demonstrated that serum PGRN was associated with the parameters of adiposity, glucose tolerance, insulin resistance, and inflammatory factors. Furthermore, progranulin serum concentrations significantly increase with deteriorating renal function assessed as CKD stage independent of age, sex, and BMI.

The role of progranulin in Egyptian type 2 diabetic nephropathy has not been fully investigated. Therefore, in this study, we aimed to investigate progranulin as a diagnostic marker of diabetic nephropathy in patients with type 2 diabetes mellitus. The presented study included ninety subjects, divided into three groups; 30 patients with type 2 DM with diabetic nephropathy, 30 patients with type 2 DM without diabetic nephropathy and 30 apparently healthy individuals (control group).

All personnel (patients and control) were subjected to full history taking, thorough clinical

examination, HbA1c, complete lipid profile, serum creatinine and blood urea and Urinary albumin creatinine ratio (ACR). Progranulin level was measured for all personals.

In the presenting study, regarding clinico-demographic data, there are statistically significant differences between the three groups regarding age and BMI with significant difference between every group in comparison with others (LSD comparison). There are no significant differences between these groups regarding gender.

Also, there are significant differences between both groups regarding systolic and diastolic blood pressure. On LSD comparison, there is significant difference between each two groups regarding systolic blood pressure while the group of patients with nephropathy has the highest significant diastolic blood pressure.

The gained results revealed that there are statistically significant differences between the three groups regarding kidney function tests, HbA1c and fasting blood glucose. On pair-wise comparison, the group with nephropathy showed the most significant difference with other groups. Also, there are significant differences between both groups regarding ALT, AST and serum albumin. On LSD comparison, there is significant difference between each two groups regarding ALT and AST. The group with nephropathy had the significant lowest serum albumin.

Ezz and Abd El Azeem [5] determined serum progranulin level in Egyptian type 2 diabetic patients and the association between its level with diabetic and renal biomarkers to evaluate it as a predictor marker of diabetic nephropathy. They demonstrated that fasting plasma glucose, postprandial plasma glucose, plasma insulin, HbA1c% and HOMA-IR showed significant increases ($P<0.001$) in type 2 diabetic patients (105.5, 156.05, 55.99, 61.4 and 228.57%, respectively) and diabetic nephropathy patients (151.58, 216.91, 119.55, 150.87 and 464.28 % respectively), compared to normal control subjects. Type 2 diabetic nephropathy patients showed significant increases ($P<0.05$) in FG and PPG, while a high significant increase ($P<0.001$) in plasma insulin, HbA1c% and HOMA-IR values, compared to diabetic patients.

They showed that renal biomarkers (s-creatinine, u-creatinine, s-BUN and A/C ratio) a slight significant change in DM group (20.5, -16.5, 22.6and 48.5% respectively). This change was augmented ($P< 0.001$) in DN group (258.9, -50.48, 254.1and 5938% respectively). Serum total protein and albumin were not significantly changed in both diabetic groups, on the other hand urinary albumin was non-significantly changed in DM group while, it was synergistically increased ($P< 0.001$) in DN group compared to NC group.

In our study, there are significant differences between both groups regarding total cholesterol and triglycerides. On LSD comparison, there is significant difference between each two groups regarding lipid profile.

Ezz and Abd El Azeem [5] showed a slightly significant increase in TAG and V-LDL in DM group (21.1 and 22.4 % respectively) compared to NC group. Dyslipidemia (including high serum TC, TAG, LDL-c, VLDL-C and low HDL-c), were observed in DN group (89, 154.2, 130.6, 136.3 and -32.2% respectively) compared to NC group.

Regarding progranulin level, there is a significant difference between both groups regarding serum progranulin. On LSD comparison, the group with diabetic nephropathy had the significant high levels.

There is evidence that PGRN levels are increased in T2DM when compared to non-diabetic subjects. PGRN is closely related to glucose metabolism. There is a positive correlation between PGRN and HbA1C, fasting plasma glucose and 2 h post-challenge plasma glucose **[14]**. Elevated PGRN concentrations are also observed in impaired glucose tolerance subjects, revealing its role in prediabetic states **[15]**.

During the inflammatory process, progranulin is digested into smaller peptides, called granulins, which are proinflammatory and neutralize the anti-inflammatory effect of intact progranulin. This suggests that PGRN is associated with diabetic nephropathy and may be involved in its pathogenesis **[16]**.

Ezz and Abd El Azeem [5] illustrated that serum progranulin was slightly increased in DM group (39.01%) while e-GFR was non-significantly changed. In DN group, the increase in serum progranulin was augmented (121.2% respectively), while e-GFR was dramatically decreased (68.6%) compared to NC group ($p < 0.001$).

In our study, there are significant differences between both groups regarding type of therapy used. The largest percentage of patients with nephropathy used insulin while in patients without nephropathy were on oral antidiabetics. There is significant difference between both groups regarding disease duration.

The association of PGRN with T2DM is mainly explained by its role in adipose tissue and insulin resistance. Insulin resistance is key feature of type 2 diabetes and can directly result in hyperinsulinemia. Recently, a report shows that PGRN could induce insulin resistance through stimulating IL-6 expression in adipocytes **[17]**.

In our study, the best cutoff of serum progranulin in diagnosis of nephropathy in diabetic patients is ≥ 55.5 with AUC 0.986 and sensitivity 93.3%, specificity 86.7%, PPV 78.7, NPV 96.3%, +LR 7.01, -LR 0.08 and accuracy 88.9% ($p<0.05$). **Ezz and Abd El Azeem [5]** displayed that progranulin provided the highest diagnostic information with area under the curve (AUC) of 1.0, and cut-off value of 105 ng/ml.

In our study, there are highly significant positive correlations between serum progranulin and age, urea, creatinine, UACR, HbA1c, FBG, duration, total cholesterol, triglycerides, systolic and diastolic blood pressure. There are highly significant negative correlations between serum progranulin and BMI, eGFR and serum albumin.

It was reported that other metabolic disorders associated with T2DM have also been linked to PGRN. A positive correlation observed between total cholesterol **[11]**, triglycerides and PGRN suggests a role in dyslipidemia. Patients with metabolic syndrome present higher serum PGRN concentration **[18]**.

Richter et al. [12] demonstrated a positive association between circulating progranulin and components of the metabolic syndrome including insulin resistance, obesity, and dyslipidemia. They suggested that PGRN is associated with obesity, lipid metabolism disorders, and hypertension in Chinese subjects.

It has also been reported that circulating PGRN levels are elevated in patients with type 2 diabetes. Moreover, increased serum PGRN levels are associated with impaired glucose tolerance rather than impaired fasting glucose **[19]**.

Xu et al. [4] investigated the correlation between PGRN and type 2 diabetics with microvascular complications. They demonstrated that serum PGRN levels were positively and markedly correlated with SBP, DBP, BMI, TG, UAER, BUN, CRE, WBC, disease duration, IL-6, and TNF, while correlating negatively and distinctly with eGFR.

To evaluate the independent factors of PGRN with the factors identified in the univariate analysis, multiple stepwise regression analysis was done on factors shown significant relation with progranulin level. The analysis demonstrated that only UAcR, duration and DBP were independently associated with serum PGRN.

Richter et al. [12] reported that progranulin serum levels increased with deteriorating renal function, and the renal elimination was a major route for circulation PGRN. **Xu et al. [4]** evaluated the independent factors of PGRN with the factors identified in the above univariate analysis including SBP, DBP, BMI, TG, UAER, BUN, CRE, eGFR, WBC, disease duration, IL-6, and TNF as independent variables. They demonstrated that only UAER and CRE were independently associated with serum PGRN.

There is little evidence regarding the association of PGRN and DKD in T2DM patients. The pro-inflammatory effects of this adipokine could be involved in the pathway of renal damage, decreasing GFR and increasing albuminuria. When CKD is established, PGRN clearance is reduced and its effects could be potentiated. **Richter et al. [12]** have shown that nephropathy is closely associated. Therefore, reduced renal elimination may be one of the reasons for the elevated circulating progranulin in diabetic nephropathy.

Qu et al. [14] reported the association of PGRN with obesity, with higher serum levels in obese subjects, independently of diabetes. **Nicoletto et al. [20]** evaluated serum and urinary levels of PGRN in patients with T2D and chronic kidney disease (CKD) stages 3-5 and compared to patients with T2D and glomerular filtration rate (GFR; CKD-EPI) >60 mL/min and with control individuals without T2D. They concluded that PGRN serum levels seems to be a marker of obesity and inflammatory state that is affected by decrease in GFR; while urinary PGRN could be a marker of diabetic kidney disease.

Nicoletto et al. [21] investigated the association of serumand urinary PGRN levels with DKD in T2DM. They suggested that serum PGRN depends on eGFR. Serum PGRN is elevated among patients with low eGFR and urinary PGRN correlates with albuminuria. Furthermore, PGRN correlates with adiposity and inflammation markers, and is associated with T2DM. **Ezz and Abd El Azeem [5]** suggested that PGRN may be considered as a highly sensitive and specific biomarker for diabetic nephropathy.

This study has limitations such as small number of subjects, wide further improvements are needed in our future study.

5. Conclusion

We showed that serum PGRN concentrations increased in Egyptian patients with nephropathy. The increased serum progranulin levels were closely related to the progress of diabetic nephropathy, suggesting that PGRN may be considered as a marker for diabetic nephropathy and its severity.

Thus, the level of PGRN in patients with type 2 diabetes should be paid high attention and it could be a potential therapeutic target for the management of type 2 diabetes and diabetic nephropathy. Therefore, early diagnosis of diabetic nephropathy in patients with type 2 diabetes mellitus can help in early treatment and avoid its more serious complication.

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