

Serum and urinary pentraxin-3 levels in type 2 diabetes and its relation to diabetic nephropathy

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Background

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease. Microalbuminuria is the most popular method for detecting the early signs of DN. However, pathological changes occur before the onset of microalbuminuria. So, there is a need for another biomarkers that might provide a sensitive and fast means for identification of the progression of DN. Pentraxin 3 (PTX3) is an acute-phase glycoprotein and a soluble receptor acting as an opsonin. PTX3 protein is expressed in vascular endothelial cells and macrophages. Thereby, its levels may reflect more directly the inflammatory status of the vasculature.

Aim

Evaluation of the levels of serum and urinary PTX3 in type 2 diabetes mellitus (T2DM) patients and its relation to DN.

Patients and methods

Group A: 20 healthy volunteers (control group). Group B: 20 patients with normoalbuminuric T2DM. Group C: 20 patients with microalbuminuric T2DM. Group D: 20 patients with macroalbuminuric T2DM. Also all the participants divided into two subgroups: Group 1: 40 participants with no nephropathy (controls and normoalbuminuric patients). Group 2: 40 patients with nephropathy (microalbuminuric and macroalbuminuric patients).

Results

There was no significant difference among all studied groups with respect to age, sex, lipid profile, urinary PTX3, C-reactive protein, and liver function test. Whereas BMI, hemoglobin level, HBA1C, fasting blood sugar, postprandial blood sugar, serum creatinine, estimated glomerular filtration rate, and 24 h urinary albumin excretion; showed high significant difference among all studied groups.

Serum albumin and total protein levels were highly significantly decreased in macroalbuminuric group as a result of proteinuria compared to the other three groups. Serum PTX3 showed high significant difference between nephropathic (micro and macroalbuminuric) group and non nephropathic group (control and normoalbuminuric).

There were highly significant positive correlations between serum PTX3 and (fasting blood sugar, postprandial blood sugar, HBA1C, and 24 h urinary albumin) significant positive correlation with serum creatinine, whereas there were highly significant negative correlations between serum PTX3 and serum total protein and serum albumin.

Conclusion

Serum PTX3 increased progressively with DN and may be a serum biomarker for early diagnosis of DN. Whereas urinary PTX3 has no relation to DN.

Keywords:

diabetic nephropathy, CRF, pentraxin 3

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Introduction

Diabetes mellitus (DM) is one of the most challenging health concerns of the 21st century [1].

The syndrome 'diabetic nephropathy (DN)' is a microvascular complication of both type 1 and type 2 diabetes [2].

DN is the most common cause of end-stage renal disease (ESRD) and contributes to 57% of patients

with type 2 diabetes mellitus (T2DM). Although T2DM is a preventable and treatable cause of ESRD, the number of ESRD patients caused by T2DM has increased and accounts for more than 50% of incident dialysis patients [3].

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The overall burden for people with DN is extremely high because of the strong associations of DN and cardiovascular disease with ESRD [4].

Microalbuminuria is the most popular method for detecting the early signs of DN [5]. The progression of DN from proteinuria to renal failure is irreversible [6]. Therefore, detection of microalbuminuria as early as possible in the course of the disease is important. The American Diabetes Association (ADA) recommends that all type 2 diabetic patients should do annual microalbumin urine test, starting at the time of diagnosis [7].

The development of clinical nephropathy is insidious, and macroalbuminuria [urinary albumin excretion rate (AER) >300 mg/24 h], the hallmark of the condition, is preceded by a phase of microalbuminuria (UAE 30–300 mg/24 h), which usually lasts 5–10 years. As albuminuria worsens and blood pressure increases, there is a relentless decline in estimated glomerular filtration rate (eGFR) and progression to ESRD [2]. However, pathological changes have been reported to occur before the onset of microalbuminuria and about 20–30% of patients with type 2 diabetes, accompanied by renal insufficiency, showed normoalbuminuria [8].

A sizeable proportion (≥55%) [9]. of DN patients with impaired eGFR (<60 ml min⁻¹ 1.73 m²) were not be diagnosed by albuminuria screening. To overcome these limitations, many clinicians additionally used creatinine in evaluating such patients. However, serum creatinine also depends on creatinine production, extrarenal elimination, and tubular handling [10]. So, there is a need for detecting another biomarkers that might provide a sensitive and fast means for identification of the progression of DN [11].

Pentraxin 3 (PTX3) is an acute-phase glycoprotein and a soluble receptor acting as an opsonin. PTX3 protein is expressed in vascular endothelial cells and macrophages. Thereby, its levels may reflect more directly the inflammatory status of the vasculature [12].

PTX3 is one of the endothelium-specific inflammatory cytokines, representing directly the tissue inflammatory response, especially the one involving the vascular bed. Production of PTX3 is considered to be stimulated in many different tissues under the control of the primary inflammatory signal. In addition to vascular endothelial cells, it can be released by various cell types, such as macrophages, dendritic cells, etc. as a response to tissue damage and inflammation [13,14]. PTX3 escalates the

procoagulant effect of the endothelial cells [15] and reduces the endothelial repair by disabling the effect of the fibroblast growth factor. Furthermore, it accelerates the tissue damage and inhibits angiogenesis [16]. Studies have shown that patients with small-vessel vasculitis or inflammatory conditions, such as coronary artery disease or myocardial infarction have high plasma levels of PTX3 [17,18]. Further, high PTX3 values are related to vascular dysfunction in patients with T2DM [19].

Several clinical investigations have demonstrated that elevated plasma PTX3 levels are associated with cardiovascular and chronic kidney diseases [13,20].

The aim of this work was to study the levels of serum and urinary PTX3 in T2DM patients and evaluate its relation to DN.

Patients and methods

This case-control study was conducted in Internal Medicine, Nephrology Unit and Clinical Pathology Departments in Zagazig University Hospital during the period from October 2016 to October 2017.

Patients

This study was carried out on 80 patients divided into:

- (1) Group A: 20 age and sex matched healthy volunteers (control group).
- (2) Group B: 20 patients with normoalbuminuric T2DM.
- (3) Group C: 20 patients with microalbuminuric T2DM.
- (4) Group D: 20 patients with macroalbuminuric T2DM.

All participants divided into two groups:

- (1) Group 1: 40 participants with no nephropathy (controls and normoalbuminuric patients).
- (2) Group 2: 40 patients with nephropathy (microalbuminuric and macroalbuminuric patients).

Inclusion criteria

Diagnosis of T2DM was based on the ADA diagnostic criteria (2016) and the stages of DN were based on the standard from ADA (2016), annual measurement of urinary albumin and eGFR in patients with type 2 diabetes starting at diagnosis. The T2DM patients were stratified into three subgroups according to

their urinary AER in 24 h urine collections. Normal AER was defined as an AER persistently less than 20 µg/min/24 h, microalbuminuria as an AER between 20 and 200 µg/min/24 h and macroalbuminuria as an AER greater than 200 µg/min/24 h.

Exclusion criteria

Participants who fulfilled one of the following criteria were excluded:

- (1) Liver disease.
- (2) Thyroid disease.
- (3) Any active inflammatory diseases.
- (4) Patients who received insulin therapy for at least 2 years.
- (5) Patients on hemodialysis.
- (6) Patients with history of drug intake including antibiotics, nonsteroidal anti-inflammatory drugs, corticosteroids, or cytotoxic medications at the time of the study.

Methods

All participants were submitted to the following:

- (1) Patient consent for sampling.
- (2) Full history taking: including age, sex, smoking, hypertension, and medications.
- (3) General clinical examination.
- (4) Anthropometric measurements: weight in kilograms, height in meters, and BMI. $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$.
- (5) Laboratory investigations:
 - (a) Routine investigations:
 - (1) Complete blood count.
 - (2) Total cholesterol and triglycerides.
 - (3) Alanine transaminase, aspartate transaminase, and serum albumin.
 - (4) Fasting and random blood glucose.
 - (5) HBA1C.
 - (6) Serum creatinine.
 - (7) Plasma total protein.
 - (8) C-reactive protein (CRP).
 - (9) Calculation of eGFR using MDRD equation $GFR (\text{ml}/\text{min}/1.73 \text{ m}^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ [21].
 - (10) 24 h urinary AER.
 - (11) All routine investigations are obtained from the patients files.
 - (b) Special investigations:

Serum and urinary PTX3 measurement: using a commercial enzyme-linked immunosorbent assay kit

produced by BIOVENDO research and diagnostic products (USA).

Results

There was no significant difference among all studied groups with respect to age, sex, lipid profile, urinary PTX3, CRP, and liver function test. Whereas BMI, hemoglobin level, HBA1C, fasting blood sugar, postprandial blood sugar, serum creatinine, eGFR, and 24 h urinary albumin excretion; showed highly significant difference among all studied groups (Table 1).

There was a high significant difference between macroalbuminuric patients and the other three groups with respect to serum albumin and total protein levels, which were decreased in macroalbuminuric group as a result of proteinuria, other liver function tests showed no significant difference.

CRP showed no significant difference.

There was a significant difference among groups with respect to serum PTX3. It was more in macroalbuminuric group than microalbuminuric group than normoalbuminuric group than control group but urinary PTX3, showed no significant difference among different groups (Table 2, Fig. 1).

With respect to serum PTX3, high significant difference noticed between nephropathic (microalbuminuric and macroalbuminuric) group, and non-nephropathic group (control and normoalbuminuric). With respect to urinary PTX3 there was no significant difference (Table 3, Fig. 2).

There were highly significant positive correlations between serum PTX3 and (fasting blood sugar, random blood sugar, HBA1C) and 24 h AER and significant positive correlation with serum creatinine, whereas there were a highly significant negative correlations between serum PTX3 (serum total protein and serum albumin) and no correlation noticed between serum PTX3, GFR, CRP, urinary PTX3, serum cholesterol, and triglycerides.

Urinary PTX3 level was highly correlated significantly with serum CRP and significantly correlated to serum albumin level otherwise, it shows no correlation with any other parameters (Table 4).

Table 1 Studied parameters among four different groups

	Control (n=20)	Normoalbuminuric (n=20)	Micro albuminuria (n=20)	Macro albuminuria (n=20)	F	P
Age						
Mean±SD	51.3±9.1	52.5±5.21	53.3±5.06	53.0±5.6	0.369	0.776
Range	35–60	45–60	45–60	45–60		
BMI						
Mean±SD	28.7±1.73	30.03±0.95	28.1±1.23	27.3±1.54	13.265	0.00**
Range	25.5–31.5	28–31.3	25.8–30.1	25.2–30.5		
FBS						
Mean±SD	92.4±9.9	150.9±26.8	151.8±33.7	155.6±31.77	24.642	0.00**
Range	76–105	115–195	113–210	118–205		
PPBS						
Mean±SD	119.8±8.6	189.9±20.7	193.4±24.4	193.1±27.8	55.781	0.00**
Range	105–135	162–223	155–245	145–230		
HBA1C						
Mean±SD	4.55±0.38	7.08±0.4	7.25±0.35	7.51±0.52	214.418	0.00**
Range	4–5.1	6.6–8	6.7–8	6.8–8.7		
Serum creatinine						
Mean±SD	0.86±0.25	0.91–0.2	1.01±0.25	1.07±0.21	3.325	0.024*
Range	0.5–1.2	0.5–1.2	0.6–1.4	0.8–1.4		
GFR						
Mean±SD	100.5±7.76	119.0±8.2	105.5±11.1	91.5±9.7	30.492	0.00**
Range	90–115	105–130	90–120	80–110		
24 h (AER)						
Mean±SD	18.6±5.1	18.7±6.1	119.9±38.9	414.5±82.4	321.805	0.00**
Range	10–26	10–27	60–200	300–550		
Total cholesterol						
Mean±SD	190.5±13.4	194.0±15.5	192.5±11.5	189.5±15.1	0.415	0.743
Range	180–220	180–230	180–220	180–230		
Triglycerides						
Mean±SD	167.5±42.0	159.5±39.6	153.5±24.6	164.5±59.9	0.399	0.754
Range	130–240	130–255	130–205	130–330		
HB						
Mean±SD	11.86±0.83	11.49±1.01	11.1±0.8	11.02±0.78	3.738	0.015*
Range	10.3–13.0	10–13	10–12.5	9.7–12		

AER, albumin excretion rate; FBS, fasting blood sugar; GFR, glomerular filtration rate; HB, hemoglobin; PPBS, postprandial blood sugar.
*Significant correlation. **High significant correlation.

Table 2 Serum and urinary pentraxin 3

	Control	Normoalbuminuric	Micro albuminuria	Macro albuminuria	F	P
Serum PTX3						
Control	4.14±1.8 0.9–8	13.02±3.4 8.0–20	15.88±2.91 11.3–20	16.98±2.3 13–20	89.353	0.00**
Urinary PTX3						
Control	4.88±0.72 4–6.2	4.72±0.76 3.9–6	4.95±0.76 3.7–6.7	4.79±0.62 4–5.7	0.389	0.761

PTX3, pentraxin 3. **High significant correlation.

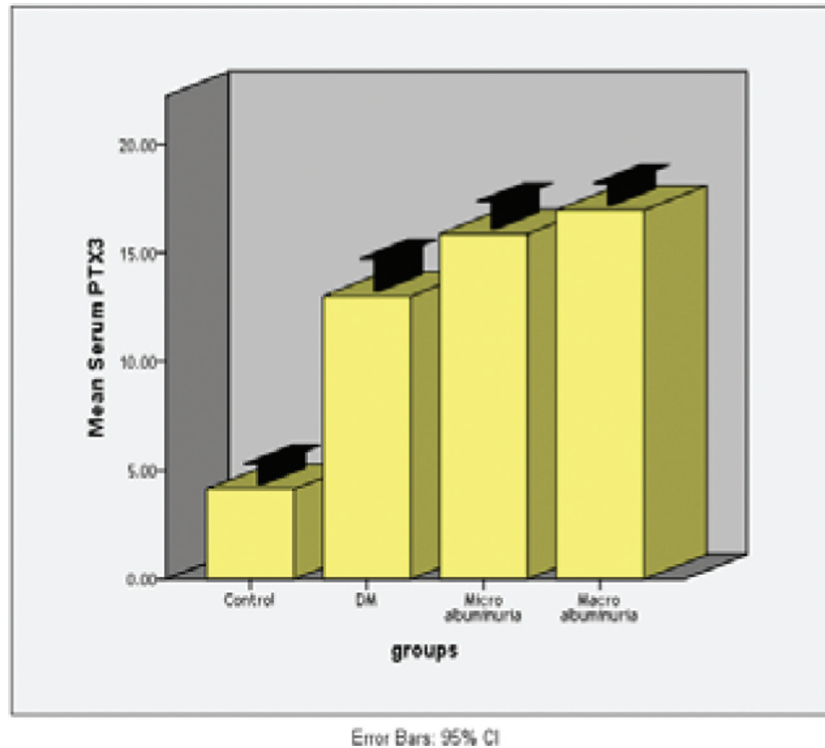
Discussion

Podocyte dysfunction in renal microenvironments is an important feature in the pathogenesis of DN. Podocyte nephrin disintegration in the slit diaphragm has been observed to contribute to loss of protein excretion. Nephren has been shown to act as a protein tyrosine kinase that triggers biologic reaction in maintaining podocyte function and renal filtration capacity in various renal disorders [22]. Lin *et al.* [23] reported

that diabetes lead to reduction of nephren level in conjunction with nephren deacetylation.

Suliman *et al.* [24] studied whether serum PTX3 levels are associated with albuminuria and endothelial dysfunction. They showed that PTX3 is significantly and independently associated with the levels of albuminuria. Moreover, they showed that in patients with type 2 diabetes, both PTX3 and albuminuria are independently associated with ED(Endothelial

Figure 1



Serum pentraxin 3 in different groups.

Table 3 Comparison of pentraxin 3 in nephropathy(micro and macroalbuminuric) and non-nephropathy (control and normalalbuminuric)

	Nephropathy (n=40)	No nephropathy (n=40)	t/ Mann-Whitney	P
Serum PTX3	16.43±2.6 711.3–20.0	8.58±4.2 0.9–20	8.355	0.00**
Urinary PTX3	4.87±0.69 3.7–6.7	4.8±0.74 3.9–6.2	0.436	0.664

PTX3, pentraxin 3. **High significant correlation.

Damage) and carotid intima thickness. Altogether, the strong links among PTX3, albuminuria, and ED suggested a role for PTX3 in the development of atherosclerotic complications in chronic kidney disease.

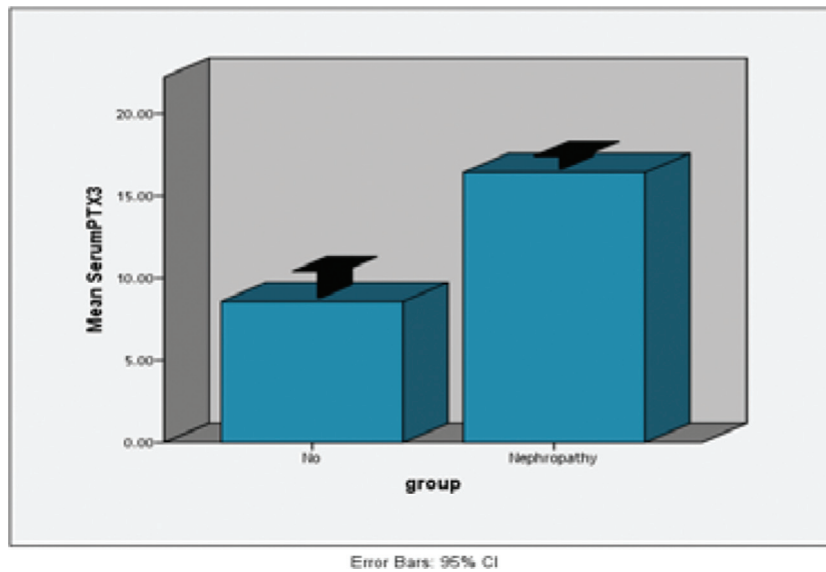
Sun *et al.* [25] showed a crucial role for PTX3 in attenuating renal damage in DN. In mouse hyperglycemia induced nephropathy model, PTX3 treatment showed significantly increased expression of nephrin, acetylated nephrin, and Wilm's tumor-1 protein (WT-1) when compared with control. The number of CD4⁺ T cells, CD8⁺ T cells, Ly6G⁺ neutrophils, and CD11b⁺ macrophages were all significantly lower in the PTX3-treated group than that in the control group in DN. The interleukin (IL)-4 and IL-13 levels in the PTX3- treated group were markedly higher than that in the control group in DN.

Correspondingly, the PTX3-treated group showed increased numbers of Arg1-expressing or CD206-expressing macrophages compared with the control group. Furthermore, inhibition of PTX3-treated macrophages abrogated the alleviated renal damage induced by PTX3 treatment. They documented an innate immunoregulatory role for PTX3 in the kidney inflammatory response against streptozotocin (STZ)-induced DN. PTX3 treatment results in the development of M2 macrophages, which protects kidney from STZ-induced DN.

PTX3 is an acute-phase glycoprotein and a soluble receptor acting as an opsonin. PTX3 protein is expressed in vascular endothelial cells and macrophages. Thereby, its levels may reflect more directly the inflammatory status of the vasculature [12].

In our study, there was no significant difference of DN among groups with respect to age and sex in agreement with Abu Seman [26] but against Yilmaz [19] who found the ages of Turkish T2DM patients with DN (at 42 years old) are younger and their duration of diabetes are shorter. Also, Yamasaki and Kurimuri [27] observed that plasma PTX3 levels between males and females in a healthy Japanese population are different. Moloney *et al.* [28] have demonstrated that DN is 30% more frequent in males than in

Figure 2



Serum pentraxin 3 in nephropathy and non-nephropathy.

females. Gu [29] have also showed that DNA polymorphisms in the genes of sex-determining specific regions are associated with DN with gender-specific effects.

In our research, there was a significant difference among groups with respect to hemoglobin, but there were no statistical significance differences among the studied groups as regards, white blood cells, platelets.

In this study, with respect to all blood glucose parameters (fasting and random blood glucose and HBA1C) a high significant difference was remarked between control group and the other three groups, whereas among normoalbuminuric, microalbuminuric, macroalbuminuric groups, differences were less significant.

This agree with Idogun and Kasia [30] and Assal *et al.* [31] who found that impaired glycemic control by both glycosylated HbA1C and fasting blood glucose is associated with significant elevations in urinary albumin levels. Against our results Kundu *et al.* [32] and Sheikh *et al.* [33] found that impaired glycemic control is associated with significant elevations in urinary albumin levels with respect to glycosylated HbA1C but no significant difference pertaining to fasting blood glucose and postprandial blood glucose. Also Hovind and Tarnow [34] found that increased HbA1C as a marker of chronic hyperglycemia is the most established and unquestioned risk factor for diabetic kidney disease.

In our study there was no statistical significant difference between studied groups with respect to aspartate transaminase, alanine transaminase, total bilirubin

But, there was a high significant difference between macroalbuminuric patients and the other three groups with respect to serum albumin and total protein levels, which were decreased in macroalbuminuric group as a result of proteinuria. In pathophysiology, proteinuria, a marker and potential contributor to renal injury, accompanies DN. Increased glomerular permeability will allow plasma proteins to escape into the urine.

This is supported by Viswanathan *et al.* [35] who found that serum albumin was significantly lower in macroalbuminuric group of DN. Also our study agreed with Jeong *et al.* [36] who found that progression of DN is accompanied by increasing urinary albumin excretion.

In our study there were significant differences between groups with respect to serum creatinine, which was contradictory with El-Hady *et al.* [37] as their study showed no significant difference in serum creatinine level between nephropathic diabetic patient and non nephropathic patients.

Also Abu Seman [26] found no significant difference with respect to serum creatinine level between control group, diabetic non nephropathic group, and DN group.

Table 4 Correlations between serum and urinary pentraxin 3 and other parameters

	Serum PTX3	Urinary PTX3
Serum PTX3		
<i>r</i>	1	-0.109-
<i>P</i>		0.335
Urinary PTX3		
<i>r</i>	-0.109	1
<i>P</i>	0.335	
CRP		
<i>r</i>	0.131	-0.317**
<i>P</i>	0.248	0.004
Total protein		
<i>r</i>	-0.450**	0.042
<i>P</i>	0.000	0.711
Serum creatinine		
<i>r</i>	0.287*	-0.195
<i>P</i>	0.003	0.083
GFR		
<i>r</i>	0.036	0.167
<i>P</i>	0.748	0.139
24 h AER		
<i>r</i>	0.569**	-0.102
<i>P</i>	0.000	0.369
Serum albumin		
<i>r</i>	-0.494**	0.259*
<i>P</i>	0.000	0.020
FBS		
<i>r</i>	0.585**	0.030
<i>P</i>	0.000	0.794
PPBS		
<i>r</i>	0.749**	0.018
<i>P</i>	0.000	0.877
HBA1C		
<i>r</i>	0.810**	-0.038
<i>P</i>	0.000	0.735
Total cholesterol		
<i>r</i>	-0.083	0.186
<i>P</i>	0.462	0.098
Triglycerides		
<i>r</i>	-0.108	0.047
<i>P</i>	0.340	0.680

AER, albumin excretion rate; CRP, C-reactive protein; FBS, fasting blood sugar; GFR, glomerular filtration rate; PPBS, postprandial blood sugar; PTX3, pentraxin 3. *Significant correlation. **High significant correlation.

In our study no statistical difference between studied groups with respect to CRP was found.

In this study, high significant difference was noticed among all groups regarding eGFR by MDRD, it was highest in normoalbuminuric group as a result of hyperfiltration, decreasing from microalbuminuric to macroalbuminuric as a result of nephropathy.

Our study agreed with Chae *et al.* [38] who documented a significant difference between both

nephropathic and non nephropathic groups with respect to eGFR. Also our study agree with Jeong *et al.* [36] who found that progression of DN is accompanied by declining eGFR. In our study there was a significant difference between control group and normoalbuminuric group with respect to eGFR. In agreement with Lu *et al.* [39] and MacIsaac *et al.* [40], who found significant difference between control and normoalbuminuric with respect to eGFR by MDRD. but against [41,42].

In our research, high significant difference noticed regarding urinary albumin in 24 hours, as it was highest in macroalbuminuric group with lowest eGFR and least in normoalbuminuric one with highest eGFR. This could be explained by American Diabetes Association [43] as albuminuria has long been regarded as a marker of the extent of glomerular damage; however, experimental and clinical studies suggest that albuminuria might also contribute to the development and progression of glomerular and tubulointerstitial lesions.

In our research, there was no significant difference with respect to total cholesterol and triglycerides among all studied groups. This is supported by Reverter *et al.* [44], Sigdel *et al.* [45], and Suchitra *et al.* [46]. But Joven *et al.* [47] proved that, with the progression of albuminuria, there is more synthesis of plasma proteins including lipoproteins.

With respect to serum PTX3, high significant difference was noticed between nephropathic group (microalbuminuric and macroalbuminuric) and non nephropathic group (control and normoalbuminuric), as PTX3 level was highly significantly in nephropathic group.

This is supported by Yilmaz [19] who found that in patients with type 2 diabetes and proteinuria with normal renal function, PTX3 was significantly higher than in healthy volunteers.

Another support to our results Suliman *et al.* [24] discovered the strong links between PTX3 and albuminuria. This study showed that PTX3 is significantly and independently associated with the levels of albuminuria. Also, El-Hady *et al.* [37] study proved that serum PTX3 is elevated in microalbuminuric patient than healthy participants and normoalbuminuric patient. Moreover, they showed that in patients with type 2 diabetes, both PTX3 and albuminuria are independently associated with endothelial damage 'ED' and carotid intima thickness.

Yilmaz [19], proved similar association of PTX3 with DN is seen in Turkish patients with T2DM.

Contradictory with our study, Abu Seman [26] examined plasma PTX3 levels in a Malay cohort, including normal participants, T2DM patients with and without DN. Results proved that plasma PTX3 levels in T2DM patients with and without DN were lower as compared with NGT (normal glucose tolerance).

Dubin [48] have demonstrated that there are racial differences of PTX3 in term of association with kidney dysfunction.

Urinary PTX3 showed no significant difference among all groups in contrary to Pang *et al.* [49] who found significantly higher urinary PTX3 levels in active lupus nephritis patients compared to patients in remission and control.

Conclusion

Serum PTX3 increased progressively with DN and may be a serum biomarker for early diagnosis of DN, whereas urinary PTX3 has no relation to DN.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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