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ORIGINAL ARTICLE

Role of serum pentraxin-3 levels in patients with and without diabetic nephropathy

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Abstract

Background Several studies have reported that increased pentraxin-3 (PTX3) levels are associated with impaired renal function in chronic kidney disease (CKD). PTX3 levels increase progressively with diabetic nephropathy (DN) and may be a biomarker for early diagnosis of DN.

Objective The study evaluates serum PTX3 levels and their association with the development of DN. We also aim to find out whether serum PTX3 is a better marker than high-sensitive CRP (hs-CRP) for DN.

Methods In this study, we evaluated serum PTX3 levels in 150 patients which were distributed into three groups that are 50 patients with DN, 50 patients with diabetes mellitus (DM) without DN and 50 controls (not any evidence of DM). DN patients were subdivided: 32 patients with microalbuminuria and 18 patients with macroalbuminuria. Serum PTX3 levels were evaluated using an enzyme-linked immunosorbent assay (ELISA) kit.

Results DN group patients had a higher value of PTX3 ($p < 0.001$) as compared to DM without DN and control groups. hs-CRP levels were higher in DM without DN patients compared to DN patients and controls. PTX3 ($p = 0.33$) and hs-CRP ($p = 0.10$) levels among microalbuminuria and macroalbuminuria patients were statistically not significant.

Conclusion This study concludes that serum PTX3 can be used as a diagnostic marker for DN before the development of apparent chronic kidney disease and PTX3 was found to be a better marker than hs-CRP for diagnosing DN.

Keywords Pentraxin-3 · Diabetic nephropathy · Diabetes mellitus · Hs-CRP · Chronic kidney disease

Introduction

The prevalence of diabetes is increasing worldwide, with the greatest increase seen in countries with low and middle socioeconomic status [1]. It has been estimated that by the year 2045, around 783.2 million people will be diagnosed with diabetes mellitus [2]. Diabetic nephropathy (DN) progressively develops from low-grade renal inflammation and renal fibrosis to end-stage renal disease and is one of the devastating microvascular complications of type 2 DM (T2DM). According to the data from the American Diabetes Association, DN occurs in around one-fourth of T2DM patients which accounts for about half of the cases in developed countries [3].

Pentraxin 3 (PTX3) which is a member of the group containing long and short pentraxins has a structural similarity with C-reactive protein and serum amyloid *p* component [4]. They are secreted in response to injury or inflammation of tissues by several types of cells like endothelial cells, monocytes/macrophages, skeletal muscle and vascular smooth muscle cells [5]. It is elevated in critically ill patients and

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also in myocardial infarction, rheumatoid arthritis, atherosclerosis, small vessel vasculitis and chronic kidney disease (CKD) [5, 6]. In human beings, it has been shown that PTX3 is expressed in the primary proximal renal tubular epithelial cells, primary mesangial cells and renal fibroblasts [6]. A major risk factor for diabetic complications is chronic endothelial inflammation which has a pathogenic role in the advancement of DN [7]. hs-CRP has been described to be a classical marker of inflammation in DN, but since inflammation occurs in several conditions, a more specific marker is needed for the same [7]. It is important to implement different approaches for earlier detection of DN because the application of an early onset biomarker may allow earlier diagnosis of the condition and thus its treatment.

Many studies have demonstrated a strong association between PTX3, endothelial dysfunction and albuminuria in patients with T2DM with proteinuria but normal renal function [7]. Our study aims to estimate the levels of serum PTX3 concentrations in diabetic patients with and without DN and to find out whether it can be utilized as a marker for early diagnosis of the same. It also aims to find out whether PTX3 acts as a better marker than hs-CRP in detecting inflammation caused by DN.

Materials and Methods

This was a prospective case–control study conducted at Amrita School of Medicine, Kochi, Kerala. The study was conducted with the approval of the Ethics Committee of Amrita School of Medicine (ECASM-AIMS-2021–087) and with the written informed consent of the participants. The study was conducted for a period of 1.5 years from January 2021 to July 2022, and blood samples were collected from the Nephrology and Endocrinology OPDs. Controls were those people with no evidence of T2DM who visited the Comprehensive Health checkup section of the hospital.

Inclusion criteria

- Patients aged 40 to 75 years with a diabetic course of 5 to 20 years.
- DN patients with macroalbuminuria (UACR > 20 mg/g) and microalbuminuria (UACR 2–20 mg/g) [8].

Exclusion criteria

- Patients with type 1 DM, primary kidney disease due to any cause other than T2DM, coronary artery diseases, end-stage renal disease, acute and chronic viral infections, acute and chronic bacterial infections, any history of stroke or malignancy, chronic liver disease and immunological disorders.
- Patients on antiproteinuric agents such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Measurements

The venous blood samples were collected under strict aseptic precautions. Samples for estimation of PTX3 were collected in red-coloured vacutainers without anticoagulant. Samples for estimating hs-CRP were collected in heparin-coated green vacutainers. Samples for fasting (FBS) and postprandial blood sugar (PPBS) estimation were collected in sodium fluoride-coated grey vacutainers, and HbA1c samples were collected in EDTA-coated lavender vacutainers. Urine samples for determining albumin-creatinine ratio (ACR) were collected in plain urine collection bottles. Samples for FBS and PPBS were estimated immediately while the samples for estimating PTX3 and hs-CRP were centrifuged, and the serum/plasma was stored at – 20 °C till further testing.

PTX3 levels were estimated using the principle of sandwich-ELISA. The micro-ELISA plate given in the kit was pre-coated with an antibody specific to human PTX3. Samples and standards were added to the plate wells which combined with the specific antibody. A biotinylated detection antibody specific for human PTX3/TSG-14 and avidin-horseradish peroxidase (HRP) was added successively to each well and incubated. Free components were then washed away. Substrate solution was added to each well, and those wells that contained the human PTX3-biotinylated detection antibody-avidin-horseradish peroxidase (HRP) complex turned blue in colour. The enzyme–substrate reaction was stopped by adding a stop solution. The optical density was measured spectrophotometrically at a wavelength of 450 ± 2 nm, and it was proportional to the concentration of PTX3. The concentration of PTX3 was calculated by comparing the OD of the samples to the standard curve. hs-CRP levels were estimated using the principle of particle-enhanced immunoturbidimetric assay. Human CRP was agglutinated with latex particles which were coated with monoclonal anti-CRP antibodies. These aggregates were determined in Roche Cobas-8000 series turbidimetrically.

Statistical analysis

The IBM SPSS 20 (SPSS Inc, Chicago, USA) software was used to do the statistical analysis. The results are represented as mean ± SD for all the continuous variables and frequency and percentage for the categorical variables. In the comparison of the mean difference of numerical variables between groups, the independent sample *t* test was applied for parametric data and the Mann–Whitney *u* test for non-parametric data. The association of categorical variables was obtained by the application of the chi-squared test.

The one-way ANOVA test was applied for the comparison of mean difference of numerical variables for parametric data, and the Kruskal–Wallis test was applied for non-parametric data. Multiple comparison tests were done by using the Bonferroni test. To test the statistically significant relationship between continuous variables and non-continuous variables, the Pearson correlation coefficient and Spearman correlation were computed and its statistical significance was tested using the linear reg *t* test. ROC curve was used to find out the cut-off value of hs-CRP and PTX3 for the diagnosis of DN. The McNemar test was used to check sensitivity, specificity, predictive value positive, predictive value negative and accuracy for the comparison of outcomes of two different methods. Cohen's kappa analysis was used to measure the reliability of two variables. $p < 0.05$ was considered statistically significant.

Results

A total of 150 participants were included in this study of whom 107 were men and 43 were women. The patients were divided into three groups: (i) patients with DN ($n = 50$) (ii) patients with DM without DN ($n = 50$), and (iii) controls, those without any evidence of DM ($n = 50$). DN patients were further subdivided into microalbuminuria ($n = 32$) and macroalbuminuria ($n = 18$) groups based on their calculated UACR levels where macroalbuminuria is defined as UACR > 20 mg/g and microalbuminuria as UACR 2–20 mg/g [8].

The demographic details and biochemical characteristics are presented in Table 1. The mean age was higher in DN patients than in the other two groups. The mean ± SD levels of FBS and median (Q1–Q3) PPBS were significantly higher in DN group ($p < 0.001$) than in the other two groups. The mean HbA1c values were significantly higher in DM without DN group ($p < 0.001$) than in the other two groups. The median (Q1–Q3) serum creatinine levels were higher in DN group than in the other two groups. Table 2 shows the comparison of median (Q1–Q3) levels of hs-CRP and PTX3 in all three groups. hs-CRP levels were higher in DM without DN group while the PTX3 levels were higher in DN patients when compared to the other two groups. In Table 3, median hs-CRP and PTX3 have been compared amongst the microalbuminuria and macroalbuminuria patients. hs-CRP levels were higher in microalbuminuria patients, while the PTX3 levels were higher in those with macroalbuminuria, and both do not show any statistical significance ($p = 0.10$ and $p = 0.33$, respectively).

Table 1 Comparison of demographic details and biochemical characteristics among the three groups

Parameter	DN ($n = 50$)	DM without DN ($n = 50$)	Control ($n = 50$)	*p*
Demographic details				
Age (years)	61 ± 10	59 ± 10	51 ± 10	-
Males ($n = 107$)	38 (76%)	39 (78%)	30 (60%)	-
Females ($n = 43$)	12 (24%)	11 (22%)	20 (40%)	-
Blood glucose levels				
FBS (mg/dL)	157.6 ± 70.8	146.1 ± 43.2	87.2 ± 8.7	< 0.001*
PPBS (mg/dL)	234.8 (223.0–269.0)	220.3 (201.1–267.7)	114.7 (101.4–123.5)	< 0.001*
HbA1c (%)	8.2 ± 1.9	8.9 ± 2.1	5.2 ± 0.2	< 0.001*
Serum creatinine	3.8 (1.9–6.9)	0.9 (0.7–1.1)	0.8 (0.7–0.9)	< 0.001*

The results have been given as mean ± SD, median (interquartile range) and frequencies (percentage) as applicable wherever

DN diabetic nephropathy, *DM without DN* diabetes mellitus without nephropathy, *FBS* fasting blood sugar, *PPBS* post-prandial blood sugar

**p* is highly significant

Table 2 Comparison of PTX3 and hs-CRP levels among the study groups

Parameter	DN ($n = 50$)	DM without DN ($n = 50$)	Control ($n = 50$)	*p*
hs-CRP (mg/L)	7.13 (1.56–27.42)	18.30 (2.10–59.16)	1.59 (0.76–4.72)	< 0.001*
PTX3 (pg/mL)	145.68 (79.83–206.82)	88.91 (61.24–124.14)	69.46 (52.34–95.11)	< 0.001*

The results have been given as median (interquartile range)

DN diabetic nephropathy, *DM without DN* diabetes mellitus without nephropathy, *hs-CRP* high-sensitive C-reactive protein, *PTX3* pentraxin-3

**p* is highly significant

Table 3 Comparison of PTX3 and hs-CRP levels in patients with microalbuminuria and macroalbuminuria

Parameter	Microalbuminuria ($n=32$)	Macroalbuminuria ($n=18$)	p
hs-CRP (mg/L)	6.59 (1.56–13.36)	2.19 (21.62–163.66)	0.10[&]
PTX3 (pg/mL)	135.14 (72.39–196.01)	161.71 (83.95–248.76)	0.33[&]

The results have been given as median (interquartile range)

hs-CRP high-sensitive C-reactive protein, *PTX3* pentraxin-3

[&]p is non-significant

Table 4 Association of hs-CRP and PTX3 in patients with DN and without DN

Parameter		DN (%)	DM without DN (%)	p
hs-CRP	<5.65 ($n=80$)	20 (40%)	60 (60%)	0.021[#]
	>5.65 ($n=70$)	30 (60%)	40 (40%)	
PTX3	<96.25 ($n=84$)	16 (32%)	68 (68%)	<0.001*
	>96.25 ($n=66$)	34 (68%)	32 (32%)	

The results have been given as median (interquartile range)

hs-CRP high-sensitive C-reactive protein, *PTX3* pentraxin-3, *DN* diabetic nephropathy, *DM without DN* diabetes mellitus without nephropathy

*p is highly significant

[#]p is significant

Table 5 Results of sensitivity, specificity, positive predictive value and negative predictive value of PTX3

Statistic	Value	95% CI
Sensitivity	67.14%	54.88 to 77.91%
Specificity	76.25%	65.42 to 85.05%
Positive predictive value	71.21%	61.78 to 79.10%
Negative predictive value	72.62%	65.00 to 79.12%
Accuracy	72%	64.09 to 79.02%

CI confidence interval

Table 6 Correlation between PTX3 and hs-CRP among the groups

Group	n	Correlation between PTX3 andhs-CRP(r)	p
DN	50	0.421	<0.001*
DM without DN	50	0.523	<0.001*
Control	50	-0.093	0.521[&]

DN diabetic nephropathy, *DM* diabetes mellitus without nephropathy, *hs-CRP* high-sensitive C-reactive protein, *PTX3* pentraxin-3

*p is highly significant

[&]p is insignificant

Table 7 Correlation of serum creatinine with hs-CRP and PTX3 among the groups

Group	n	Correlation of serum creatinine with hs-CRP and PTX3(r)			
		hs-CRP	p	*PTX3*	p
DN	50	-0.312	0.02[#]	-0.199	0.16[&]
DM without DN	50	0.176	0.22[&]	0.129	0.37[&]
Control	50	0.144	0.31[&]	0.144	0.31[&]

DN diabetic nephropathy, *DM* diabetes mellitus without nephropathy, *hs-CRP* high-sensitive C-reactive protein, *PTX3* pentraxin-3

[&]p is non-significant

The distribution of hs-CRP and PTX3 respective to DN and DM without DN has been given in Table 4. We observed that out of the 70 patients who had hs-CRP more than 5.65, 30 (60%) belonged to DN group and 40 (40%) belonged to DM without DN group, and this was statistically significant ($p=0.021$). Whereas out of the 66 patients who had PTX3 more than 96.25, 34 (68%) belonged to DN group and 16 (32%) belonged to the DM without DN group. This was found to be highly statistically significant ($p<0.001$).

Table 5 shows the sensitivity (67.14%), specificity (76.25%), PPV (71.21%), NPV (72.62%) and accuracy (72%) of PTX3 with hs-CRP as the gold standard. Based on Cohen's kappa analysis (0.644), there is almost good agreement between PTX3 and hs-CRP in assessing DN ($p<0.001$).

Table 6 represents the correlation analysis of PTX3 and hs-CRP levels amongst the DN and DM without DN groups. A positive moderate correlation is seen in DN group ($r=0.421$) and DM without DN group ($r=0.523$) which was statistically highly significant ($p<0.001$), while a negative low-degree correlation is seen with the control group ($r=-0.093$) and was not statistically significant ($p=0.521$).

Table 7 shows the correlation of serum creatinine with hs-CRP and PTX3 among the three groups. There was a lower negative correlation ($r=-0.312$) between serum creatinine and hs-CRP in DN group which was statistically significant ($p=0.02$) while no correlation was found between serum creatinine and PTX3 ($r=-0.199$) which was not statistically significant ($p=0.16$). There was no significant correlation of serum creatinine with hs-CRP and PTX3 in the other two groups.

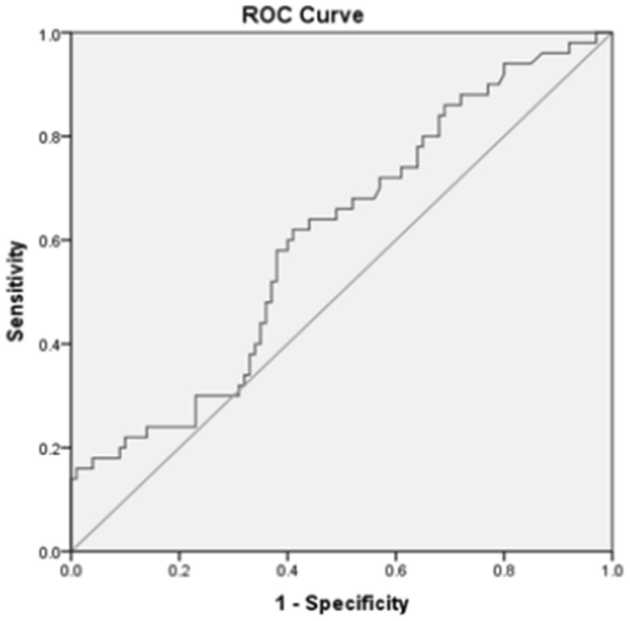

Fig. 1 ROC of hs-CRP between patients with DN and without DN. With AUC 60.4% and cut-off 5.65 and $^{\#}p = 0.039$. ROC, receiver operating characteristic curve; AUC, area under the curve

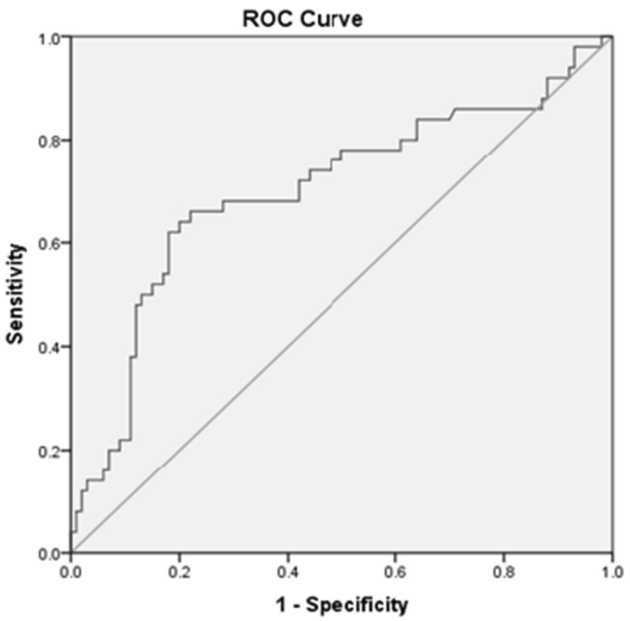

Fig. 2 ROC of PTX3 between patients with DN and DM without DN. With AUC 70.1% and cut-off 96.25 and $^{*}p < 0.001$. ROC, receiver operating characteristic curve; AUC, area under the curve

Figure 1 shows the receiver operating characteristic curve (ROC) of hs-CRP between patients with DN and DM without DN patients which has an area under curve (AUC) of 60.4% and cut-off 5.65 with a $p = 0.039$. Figure 2 shows the ROC of PTX3 between DN and DM without DN patients which has an AUC of 70.1% and cut-off 96.25 with a $p < 0.001$ which was highly significant.

Discussion

DN constitutes a foremost cause of CKD across the globe, and there is a necessity to take effective measures to control and identify early and specific markers to detect the same [9]. Risk factors for DN include increased duration of DM, hypertension, hyperglycemia and dyslipidemia [9].

The demographic and basic biochemical characteristics of the patients are shown in Table 1. Significantly higher levels of FBS and PPBS were observed in the DN group when compared to the other two groups. However, HbA1c levels were higher in DM without DN patients than in DN and controls. Some studies have shown that good glycemic control helps in the prevention of microvascular complications in patients with DM, but certain studies have revealed that there is no significant impact of HbA1c levels on the progression of DN [10]. The median (Q1–Q3) serum creatinine levels were higher in DN group than in the other two groups ($p < 0.001$). Our study observed significantly higher levels of PTX3 ($p < 0.001$) in DN patients than in DM without DN and controls. PTX3 is a marker of local inflammatory reactions and also of innate immunity to cardiovascular and renal diseases [11]. A variety of tissues and cells particularly the cells of innate immunity produce PTX3, in response to proinflammatory indicators and toll-like receptor (TLR) engagement [12]. The interaction of PTX3 with numerous ligands like growth factors, selected pathogens and components of the extracellular matrix plays a part in the activation of the complement system and facilitates the recognition of pathogens by phagocytes [11, 12]. Our results are in agreement with the studies of Uzun et al. [12], Dawood et al. [13], Al-Barshomy et al. [14], El-Senosy et al. [15] and Mezil et al. [16] who also reported that PTX3 levels increase with the advancement of DN. Uzun et al. [12] studied PTX3 and hs-CRP levels in three different groups of diabetic patients and found that the levels of PTX3 increased as the stage of DN progressed while hs-CRP values did not change significantly. Dawood et al. [13] found that PTX3 level is higher in the DN groups than in the control and diabetic without DN groups. Also, they observed a significant difference between the microalbuminuric and macroalbuminuric groups revealing that PTX3 levels increase with the development and progression of DN. In the study by Al-Barshomy et al. [14], serum PTX3 showed a highly significant difference between the nephropathic (microalbuminuric and macroalbuminuric) group and the non-nephropathic group (control and normoalbuminuric). El-Senosy et al. [15] studied the PTX3 levels among normal and microalbuminuric patients in one group and controls in the other group and found that PTX3

levels were higher in the former group of patients. Mezil et al. [16] estimated PTX3 levels among normoalbuminuria, microalbuminuria and macroalbuminuria patients and found that PTX3 levels rise as the disease progresses.

The serum hs-CRP levels were higher in DM without DN (Table 2) than in DN and controls and were statistically significant ($p < 0.001$). hs-CRP belongs to the short pentraxin family which are small pentameric innate immunity effecter proteins also known as acute phase proteins [13]. It is synthesized in the liver and is a marker of systemic inflammation—the probable reason why it was not elevated in DN patients [17]. Since PTX3 is released locally and rapidly, the circulating PTX3 levels could suffer alterations before a detectable increase in the hs-CRP level [17]. This would be of great value for an earlier detection of patients with DN. Similar results were reported by Uzun et al. [12] and Al-Barshomy et al. [14] where no significant association was found between serum hs-CRP levels and the development of DN.

We compared both PTX3 and hs-CRP levels in DN patients (50 patients) with microalbuminuria (32 DN patients) and macroalbuminuria (18 DN patients). Patients with macroalbuminuria had higher levels of PTX3 (161.71 pg/mL) than those with microalbuminuria (135.14 pg/mL) but was not statistically significant ($p > 0.05$). Comparison of hs-CRP levels in these two groups showed the opposite results and again was not statistically significant ($p > 0.05$) (Table 3). Though not significant, our data shows that even though the levels of PTX3 increase along with the disease progression, hs-CRP levels do not show such an association. This could be pointed out to be due to the renal specificity of PTX3 compared to hs-CRP. In the early stages of CKD, inflammatory processes are activated, and since PTX3 is produced and stored in the vasculature, it is rapidly released in response to stimulation by cytokines [17]. Its interaction with P-selectin promotes vascular inflammatory response and endothelial dysfunction [18].

hs-CRP has been extensively addressed in literature in the prediction of microvascular outcomes at different stages in T2DM patients as we have observed in our study [19]. But PTX3 levels rise as diabetes progresses therefore will help in early detection of DN (stages I–III) before the development of overt nephropathy (stages IV and V) and are found to be a better and more reliable marker (12,13,14,15,16).

A moderately positive correlation which was statistically significant ($p < 0.001$) was observed with hs-CRP and PTX3 among DN ($r = 0.421$) and DM without DN patients ($r = 0.523$) (Table 6). However, a negative low-degree correlation ($r = -0.093$) which was statistically not significant ($p = 0.521$) was seen in controls. This shows that when PTX3 levels increase, hs-CRP levels will also increase in DN and DM without DN patients. Correlation of hs-CRP and PTX3 with creatinine did not reveal any significant results. We observed a low negative correlation between hs-CRP and creatinine in the DN group while no correlation was found between serum creatinine and PTX3 in the same group. There was no significant correlation of serum creatinine with hs-CRP and PTX3 in the other two groups. Our results differ with the findings of Al-Barshomy et al. [14] who found a significant positive correlation between serum creatinine and PTX3 and El-Senosy et al. [15] who found a non-significant positive correlation between serum creatinine and PTX3 while no significant correlation between serum creatinine and hs-CRP (Table 7).

A receiver operator characteristic (ROC) curve was constructed to find out the better biomarker amongst the two parameters. The area under the curve (AUC) for hs-CRP was 60.4% with a cut-off of 5.65 (Fig. 1) and that of PTX3 was 70.1% with a cut-off of 96.25 (Fig. 2). hs-CRP levels were more than 5.65 in 30 cases of DN whereas PTX3 was more than 96.25 in 34 cases of DN (Table 4). These findings point towards the specificity of PTX3 in renal diseases. Serum hs-CRP is a marker of systemic inflammation while serum PTX3 is a marker of localized inflammatory response in kidney diseases. Thus, PTX3 can be considered to be a more specific and sensitive indicator of renal damage and can thus be utilized for the early detection of DN [13]. Similar observations were made by Uzun et al. [12], Dawood et al. [13] and Sjöberg [20] who found PTX3 to be a promising biomarker of kidney damage prior to the development of evident CKD.

To find out if PTX3 was an effective marker in DN, we checked for the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PTX3 keeping hs-CRP as the gold standard. PTX3 showed a sensitivity of 67.14%, specificity of 76.25%, PPV of 71.21%, NPV of 72.62% and accuracy of 72%. Cohen's kappa analysis (0.644) reveals almost perfect agreement between PTX3 and hs-CRP in assessing DN with a p value < 0.001 (Table 5).

Conclusion

Serum PTX3 can be used as a marker for the early diagnosis of DN prior to the development of apparent CKD when compared to conventional inflammatory markers like hs-CRP. Further research involving a larger sample size has to be done in this field to elucidate the role of PTX3 as a routine screening tool for DN.

Limitations

One of the limitations of our study was that due to time constraints, we could not check whether serum PTX3 could be used as a prognostic marker of DN. Also, we checked the levels of PTX3 in only the third and fourth stages of DN.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ananyaa Dixit and Sumithra N. Unni C. The first draft of the manuscript was written by Ananyaa Dixit, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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