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Pentraxin-2 as a marker of renal fibrosis

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Abstract
Back ground: The prevalence of chronic kidney disease (CKD) is rising, making it a major healthcare issue. Kidney fibrosis is the result of the majority of chronic kidney injury, regardless of its cause. Due to its distinct binding profile, pentraxin-2 may accumulate at sites of injury and aid in the non-phlogistic removal of injured tissue. Serum PTX-2 levels may drop in some fibrotic conditions such idiopathic pulmonary fibrosis, nonalcoholic steatohepatitis, and end-stage renal disease as a result of ongoing PTX-2 production and use.
Methods: In a cross-sectional study, 30 healthy people served as control group for the marker only and 60 patients had a reason for a kidney biopsy. The same pathologist assessed the degree of renal fibrosis using the Banff scoring system for glomerulosclerosis (GS) and interstitial fibrosis and tubular atrophy (IFTA). An enzyme-linked immunosorbent test was used to quantify PTX-2, and the results were compared with the patients' biochemical, histological, clinical, and demographic information.
Results: Serum PTX-2 levels decrease significantly in patients group than control group but PTX 2 levels were statistically insignificant between grades of IFTA and GS.
Conclusion: Serum PTX-2 isn't significantly associated with degree of renal fibrosis.

Keywords: Renal fibrosis, interstitial fibrosis and tubular atrophy, glomerulosclerosis, pentraxin 2

Introduction
Renal fibrosis is the common final end point of histological manifestations of virtually all progressive kidney diseases. Most chronic renal damage, regardless of etiology, leads to renal fibrosis [1].
The excessive deposition of extracellular matrix (ECM) components causes renal fibrosis, which results in the loss of renal parenchyma function. This type of fibrosis, which is known as glomerulosclerosis (GS) in the glomeruli, interstitial fibrosis in the tubulointerstitium, and arteriosclerosis/perivascular fibrosis in the vasculature, can impact all histological components of the kidney. Renal outcomes have a strong correlation with the histopathological degree of interstitial fibrosis and tubular atrophy (IFTA) [2].
There is currently little treatment success in reducing renal fibrosis. Renal biopsy is necessary to diagnose kidney fibrosis, which is a significant factor. Furthermore, there are currently no trustworthy biomarkers or non-invasive diagnostic procedures that may be used to track the results of different therapies or to detect kidney fibrosis early [3].
Because of its distinct binding profile, pentraxin-2, also known as serum amyloid P, may accumulate at injury sites and aid in the non-phlogistic removal of damaged tissue. Serum PTX-2 levels may drop in some fibrotic conditions such idiopathic pulmonary fibrosis, nonalcoholic steatohepatitis, and end-stage renal disease as a result of ongoing PTX-2 production and use [4].

Patients and Methods
In this cross-sectional study, 30 healthy people served as the indicators' sole control group, whereas 60 patients over the age of 18 who had a kidney biopsy indication were included. Patients were separated based on their fibrosis degree and pathology, and then they were compared. From July 2021 to January 2023, patients were gathered from Tanta University Hospitals' Nephrology Unit, Internal Medicine Department. Prior to biopsy, patients with malignancy, severe refractory hypertension, uncontrollable bleeding disorders, multiple and bilateral cysts or renal tumors, anatomical kidney anomalies, active renal, perirenal, or

biopsy site infections, a single kidney, a small hyperechoic kidney ,or a single kidney were eliminated. Until a suitable period prior to the procedure, medications that changed the coagulation cascade were not administered. The biopsies had been performed by an experienced nephrologist after informed conset from the patient. After the biopsy, all patients had been kept under observation in the hospital for a day for exclusion of any complications. The patients group had been subjected to the following:

- **Full history taking.**
- **Complete clinical examination**
- **Laboratory investigations including:** Complete blood count, Blood urea, Serum Creatinine, Serum albumin, Serum Cholesterol & Triglycerides, Hepatitis C virus antibody, Hepatitis B virus surface antigen, C3 and C4 levels, ANA & anti-dsDNA, 24 hour protein in urine, Serum Uric acid, Serum PTX-2 level.
- **The eGFR had been determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).**

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

- **Abdominal ultrasound:** For any abnormalities and to guide renal biopsy taking.
- **Blood sampling and laboratory investigations:** Six milliliters of venous blood were collected from each subject using disposable sterilized plastic syringes and delivered into plain vacutainer tubes labeled with the patient's name. The blood was allowed to clot for half an hour in water bath at- 37oc then it was centrifuged for 15 min at 3000 rpm to separate serum. The serum was then stored at-20 oc until analysis. Serum PTX-2 level measured using human Pentraxin -2 ELISA Kit, (Catalog No: 201-12-6958, sunred company, china) .
- **Examination of renal biopsy:** The biopsy specimens were examined by an experienced single pathologist using light and immunofluorescence microscopy. Routine staining analyses, including haematoxylin and eosin, periodic Schiff- methenamine, periodic acid-Schiff reagent, and Masson trichrome staining, were performed. Congo red and methyl violet staining analyses were performed for samples from some patients. Immunofluorescence staining was performed for IgA, IgG, IgM, C3, C4, C1q, and kappa/lambda light chains if indicated. IFTA and GS were scored according to the Banff classification for renal allograft pathology, with scores included no, mild, moderate and severe based on the percentage of cortical parenchyma involved.
- **Statistical analysis**
  The collected data were organized, tabulated and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. For numerical variables, the range mean and standard deviations were calculated. The differences between two mean values were used using student's t test. For categorical variable the number and percentage were calculated and differences between subcategories were tested by chi square and Monte Carlo exact test. We calculated the odds ratio and 95% confidence interval for all variables expected to affect the occurrence of metabolic syndrome in the present study. The correlations between VAI and LAP in one hand and other studied variables were calculated using Pearson's correlation coefficient. We used Recipient – observer – characteristic curve to test the ability of different studied exposure leading to metabolic syndrome. The level of significant was adopted at $p<0.05$.

Results

Patients were then divided according to pathology result in renal biopsy as follows:

- **According to IFTA grades:** No to mild IFTA: 35 patients & Moderate to severe IFTA: 25 patients
- **According to Glomerulosclerosis grades:** No to mild glomerulosclerosis: 41 patients & Moderate to severe glomerulosclerosis: 19 patients

Our study included 60 patients, 21(35%) were males and 39 (65%) were females. The mean age was 35.4 years) and 30 healthy individuals as a control group for the marker only.
In the group with no to mild grade of IFTA the age of studied participants ranged from16 – 54 years with mean age was 31.9±10.49 while in the group with moderate to severe grade of IFTA the age of studied participants ranged from 31 – 63 years with mean age was 40.4±8.89 with statistical significance in between both groups (P =0.004) with no statistical significance regarding gender between both groups (P 0.337) Table (1).

Table 1: Relationship between IFTA grades and sociodemographic data

	No – mild grade (n = 35)	Moderate – severe grade (n = 25)	Test of sig.	P
Age (Years)			U 247.5	0.004*
Mean±SD	31.9±10.49	40.4±8.89		
Min. – Max.	16.0 – 54.0	31.0 – 63.0		
Median (IQR)	31.0 (22.0 – 39.0)	39.0 (33.0 – 46.0)		
Gender			χ^2 0.923	0.337
Male	14	7		
	40.0%	28.0%		
Female	21	18		
	60.0%	72.0%		

IQR, Interquartile range; U, Mann Whitney U test; χ^2, Chi square test.
*$p\leq0.05$ (Statistically significant)

In the group with no to mild grade of GS the age of studied participants ranged from 16 – 54 years with mean age was 32.4±9.84 while in the group with moderate to severe grade of GS the age of studied participants ranged from 31 – 63 years with mean age was 41.9±9.50 with statistical significance in between both groups (P = 0.004) with no statistical significance regarding gender between both groups (P 0.337) Table (2).

Table 2: Relationship between GS grades and sociodemographic data

	No – mild grade (n = 41)	Moderate – severe grade (n = 19)	Test of sig.	P
Age (Years)				
Mean±SD	32.4±9.84	41.9±9.50	U 201.5	0.003*
Min. – Max.	16.0 – 54.0	31.0 – 63.0		
Median (IQR)	33.0 (23.5 – 39.5)	40.0 (34.0 – 48.0)		
Sex				
Male	15 (36.6%)	6 (31.6%)	χ^2 0.143	0.705
Female	26 (63.4%	13 (68.4%)		

IQR, Interquartile range; U, Mann Whitney U test; $\chi^{2,}$ Chi square test.
*$p \leq 0.05$ (Statistically significant)

PTX-2 levels were found to be significantly lower in the case group than in the control group ($p<0.001$) Figure (1).

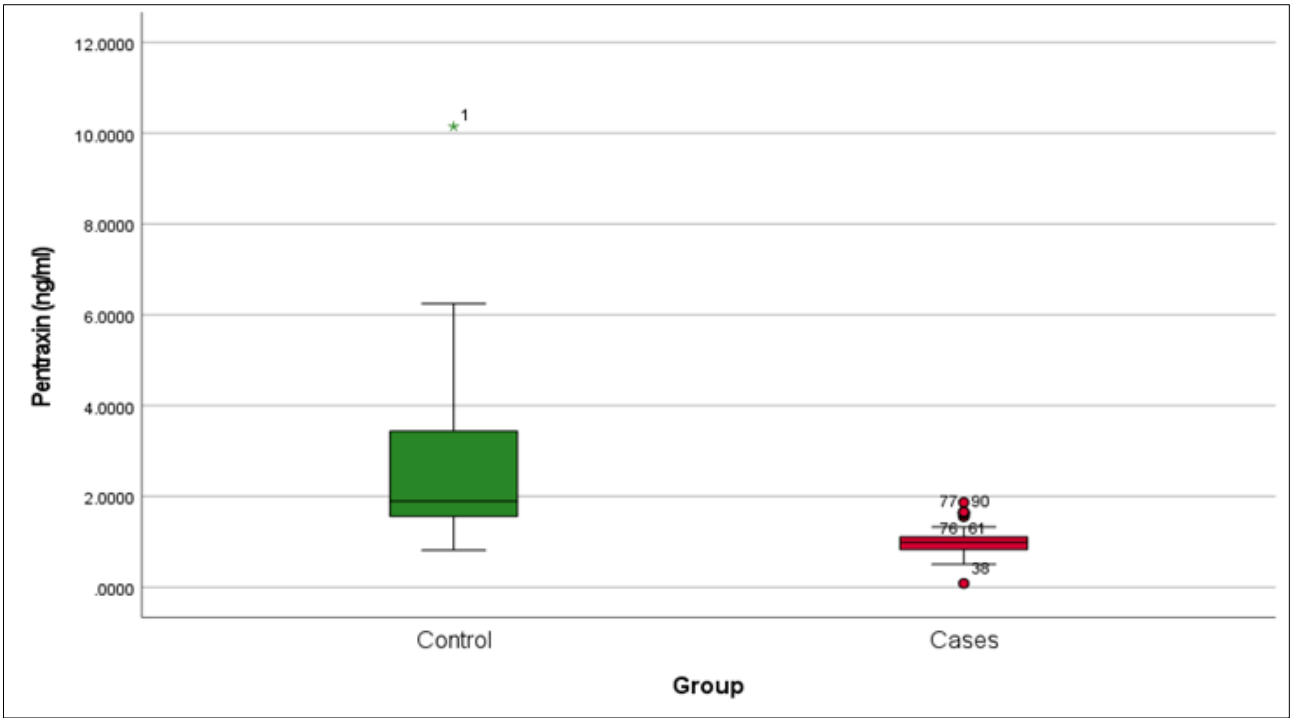

Fig 1: Box plot chart for comparison between cases and controls regarding Pentraxin (ng/ml).

Our study showed that urea (P= 0.002) and Creatinine ($p<0.001$) levels were significantly higher and eGFR ($p<0.001$) was significantly lower in patients with moderate to severe IFTA than patients with no to mild IFTA while other laboratory characteristics showed no statistically significance.

Our study showed that urea (P= 0.037), Creatinine ($p<0.032$), uric acid (P= 0.015), C3 (P= 0.037) and C4 level (P 0.018) levels were significantly higher and eGFR ($p<0.011$) was significantly lower in patients with moderate to severe GS than patients with no to mild GS while other laboratory characteristics showed no statistically significance.

Our study showed that PTX-2 level in no to mild IFTA group ranged from 0.0844 – 1.66 with mean 1.0±0.29 while in the group with moderate to severe grade of IFTA the level ranged from 0.508 – 1.87 with mean 1.1±0.35 with no statistical significance in between both groups (P= 0.776) Figure (2).

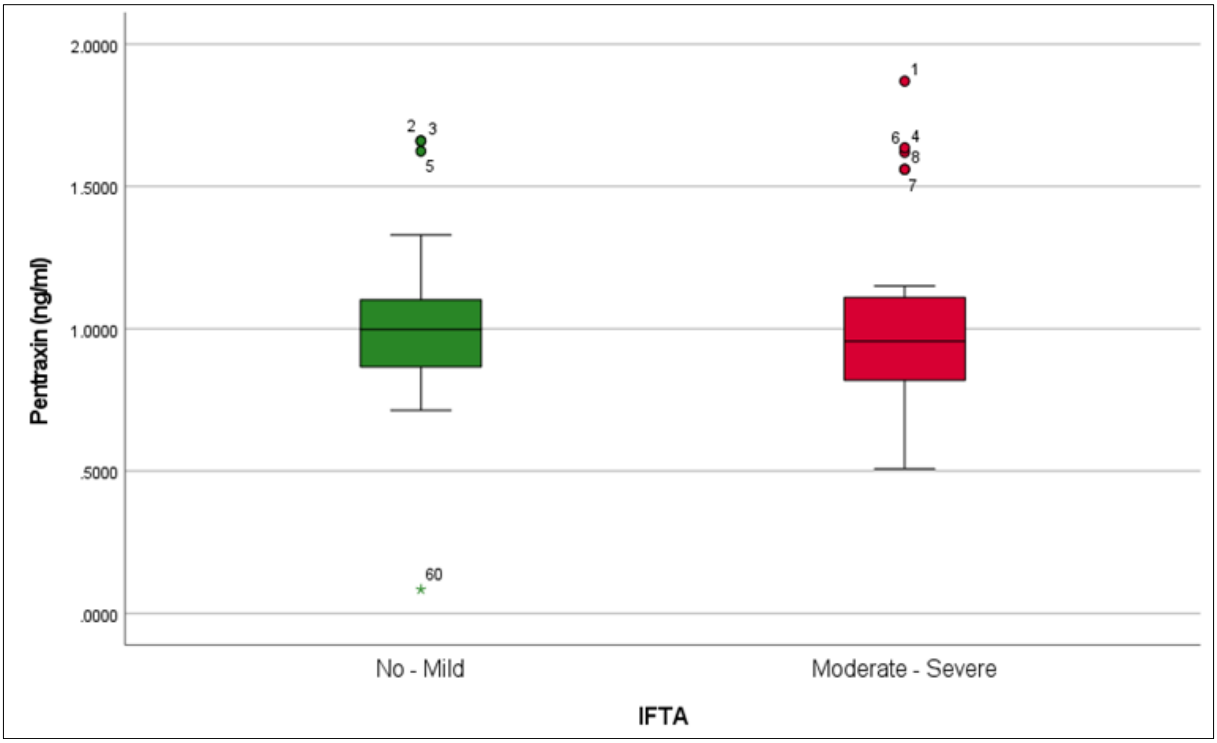

Fig 2: Box plot chart for Relationship between IFTA grades and Pentraxin-2 (ng/ml).

Our study showed that PTX-2 level in no to mild GS group ranged from 0.0844 – 1.87 with mean 1.0±0.30 while in the group with moderate to severe grade of GS the level ranged from 0.508 – 1.636 with mean 1.0±0.33 with no statistical significance in between both groups (P 0.812) Figure (3).

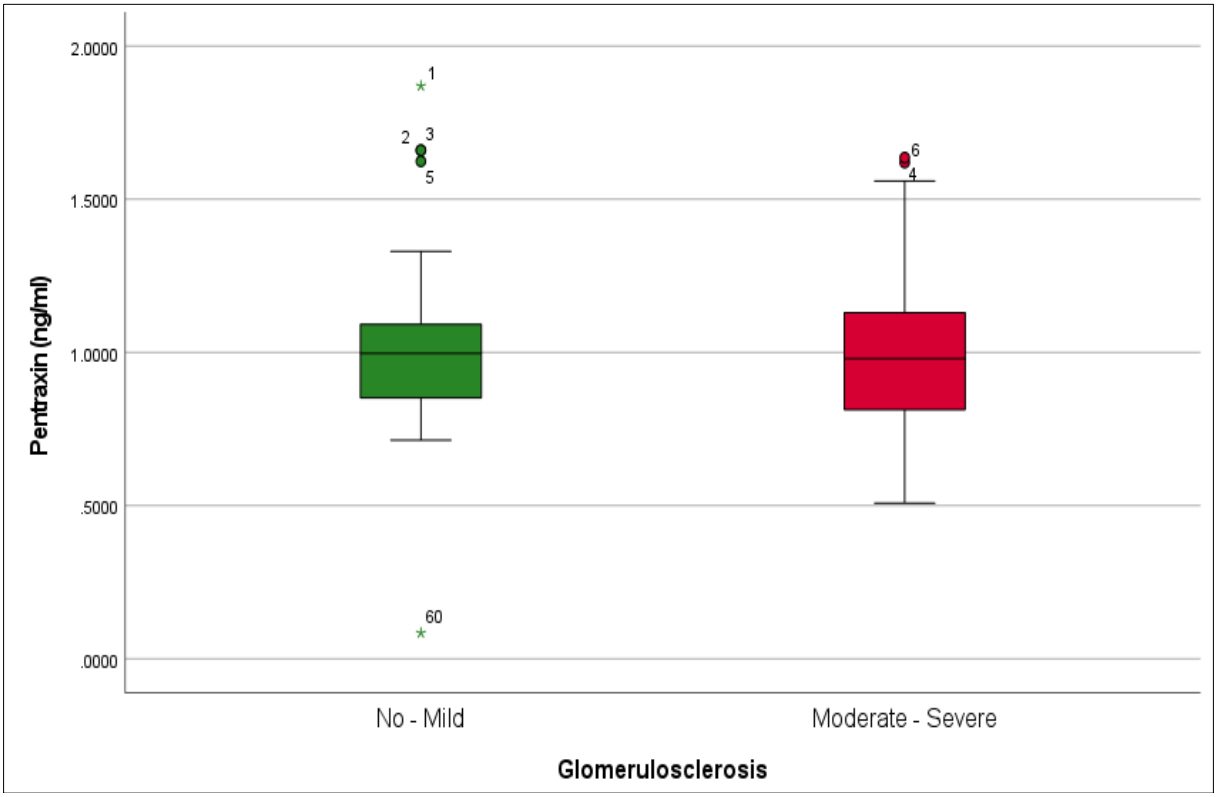

Fig 3: Box plot chart for Relationship between GS grades and Pentraxin-2 (ng/ml).

Discussion

The excessive deposition of extracellular matrix (ECM) components causes renal fibrosis, which results in the loss of renal parenchyma function. This type of fibrosis, which is known as glomerulosclerosis (GS) in the glomeruli, interstitial fibrosis in the tubulointerstitium, and arteriosclerosis/perivascular fibrosis in the vasculature, can impact all histological components of the kidney. Renal outcomes have a strong correlation with the histopathological degree of interstitial fibrosis and tubular atrophy (IFTA) [2].

Urinary retinol binding protein, urine C-type natriuretic peptide, urine angiotensin II signature proteins, and urine and serum type III collagen are among the biological molecules that have been suggested as possible biomarkers for kidney fibrosis; however, none of these have been clinically validated or used. Furthermore, it is unlikely that any of them could be used as a stratification marker [5].

Because of its distinct binding profile, pentraxin-2, also known as serum amyloid P, may accumulate at injury sites and aid in the non-phlogistic removal of damaged tissue. Serum PTX-2 levels may drop in some fibrotic conditions such idiopathic pulmonary fibrosis, nonalcoholic steatohepatitis, and end-stage renal disease as a result of ongoing PTX-2 production and use [4].

In our study as regard PTX-2 there was statistical significance between patients and control group (p<0.001) but there was no significance results between different groups of IFTA or GS. This means that PTX-2 can be used as a predictor for renal fibrosis but it is not ideal to predict the degree of renal fibrosis either with IFTA or GS.

This was in agreement with Basturk et al., (2020) [6] who found in a study included 45 patients and 16 healthy individuals PTX-2 levels were lower in the biopsy group than in the HI group (p=0.12). But in contrast to our study Patients with moderate renal fibrosis had significantly lower serum PTX-2 levels than those in patients with minimal and mild fibrosis (p=0.017 and p=0.010, respectively). The results indicated that PTX-2 levels are significantly lower in patients with renal fibrosis than healthy individuals and declining further in patients with severe fibrosis. Also, Castaño et al., (2009) [7] performed a study about the anti-fibrotic effects of PTX-2 and the potential mechanisms underlying its action. Human serum amyloid P (hSAP) was found to be a natural inhibitor of fibrosis during kidney injury via the down regulation of fibrotic collagen gene transcription. On the contrary, fibrocytes were infrequently seen in injured kidneys following treatment with hSAP proving that fibrocytes do not play a major role in fibrosis. A correlation between loss of kidney function and lower hSAP concentrations has also been reported in mice.

Another study by Nakagawa, (2016) [8] focused on recombinant PTX-2 treatment in mice deficient in the kidney micro vascular basement membrane protein collagen type IV (a) 3. This protein plays a key role in human Alport Syndrome. The mutant mice that received intraperitoneal recombinant human PTX-2 (rhPTX-2) injections for 9 weeks showed an improvement in their lifespan by 420%. RhPTX-2–treated mice showed reduced GS, preserved podocytes numbers in glomeruli, approximately 40% less tubule injury, and attenuated IF also reported decreased numbers of macrophages in the diseased kidneys, enhancement of IL-10 production, and down regulation of secreted proteins associated with fibrosis following rhPTX-2 administration. In a study by Pilling, (2003) [9] assessed the effect of serum amyloid P on the fibrocytes activity and differentiation and found that Purified SAP inhibits fibrocytes differentiation, while depleting SAP reduces the ability of plasma to inhibit fibrocytes differentiation. Compared with sera from healthy individuals and patients with systemic fibrotic diseases, were less able to inhibit fibrocytes differentiation *in vitro* and had correspondingly lower serum levels of SAP. These results suggest that low levels of SAP may thus augment pathological processes leading to fibrosis.

There were some limitations in our study as being cross sectional analysis study so no serial analysis of markers could be measured and the study included small number of patients.

Conclusion

PTX-2 levels are significantly correlated with Prescense of renal fibrosis but not significantly associated with its grades of severity.

Conflict of Interest

There is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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