JKKI
SCIENTIA EST BASIC VITAE

**JKKI: Jurnal Kedokteran dan Kesehatan Indonesia**
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950

# The correlation between pentraxin-3, matrix metalloproteinase-9, and estimated glomerular filtration rate in patients with chronic kidney disease

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Original Article

**ARTICLE INFO**

***Keywords:***
chronic kidney disease,
pentraxin-3,
matrix metalloproteinase-9,
estimated glomerular filtration rate

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DOI: 10.20885/JKKI.Vol15.Iss1.art8

***History:***
Received: September 24, 2023
Accepted: March 30, 2024
Online: April 29, 2024



## ABSTRACT

**Background**: Chronic kidney disease (CKD) is diagnosed when there is a sustained decrease in the estimated glomerular filtration rate (EGFR) over a period of more than 3 months. While Pentraxin-3 (PTX-3) and Matrix Metalloproteinase-9 (MMP-9) levels increase during the acute phase of the kidney injury, chronic conditions often exhibit alteration in the epithelial mesenchymal transition (EMT).
**Objectives**: This study aimed to elucidate the correlation between serum PTX-3, MMP-9, and eGFR in patients with CKD.
**Method**: Thirty hypertensive patients with CKD stages 3, 4, and 5, aged between 16 and 65 years, were enrolled in the study (15 males and 15 females). Diagnosis of CKD was based on the 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria, utilizing serum creatinine, and CKD-epidemiology Collaboration (CKD-EPI) estimates. Subsequently, serum MMP-9 and PTX-3 levels were quantified.
**Result**: Patients with CKD exhibited significantly higher serum levels of PTX3 and MMP9. Furthermore. a significant negative connection between PTX-3, MMP-9, and EGFR was observed. Additionally, CKD patients displayed a correlation between PTX-3 and MMP-9 concentrations.
**Conclusion**: Plasma levels of PTX-3 and MMP-9 serve as unique, promising, and important markers that contribute to the pathogenesis of CKD.

## INTRODUCTION

Chronic kidney disease refers to an anomaly in kidney structure or function persisting for more than three months. Diagnosis is based on criteria including albuminuria of more than 30 mg/24 hours, urine sedimentation abnormalities, electrolyte imbalances, histological findings, imaging abnormalities, a history of kidney transplantation and a decrease in glomerular filtration rate (GFR) of less than 60 ml/min/1.73 $m^2$. The CKD progression is is irreversible and leads to complications and increasing morbidity and mortality rates.[1,2]

The CKD poses a significant global health burden, ranking as the sixth leading cause of mortality in 2017, with 697.5 million affected individuals and 35.8 million people undergoing hemodialysis.[3] The prevalence of CKD,especially in its end stages requiring renal replacement therapy, is rising, with an estimated 3 million patients currently receiving treatment and projected increases by 50 to 100% by 2030.[4] Data from the Indonesian Nephrology Association (PERNEFRI) in the 2018 Indonesian Renal Registry (IRR) Program, reported a doubling of CKD incidence compared to the previous year and recorded 66,433 new CKD patients in Indonesia. The most common etiologies of CKD are hypertension (36%), diabetes mellitus

(DM) (28%), followed by other causes such as primary glomerulopathy (10%), pyelonephritis (3%), and obstructive nephropathy (3%).[5]

One of the inflammatory marker proteins that play a role in the development of CKD is PTX-3, which belongs to the extended pentraxin group.6 Increased levels of PTX-3 will reduce the synthesis of nitric oxide (NO), thereby inhibiting cell proliferation and inhibiting the effects of fibroblast growth factor-2 (FGF-2) and interacting with P-selectin. Additionally, pentraxin-3 promotes matrix metalloproteinase production, which directly prevents the synthesis of NO, continues to result in increased proteinuria, and accelerates the progression of CKD.[7] One of the MMPs produced by kidney nephron cells, especially in the glomerular basement membrane, is MMP-9. The MMP-9 is a proteinase belonging to the collagenase group that binds to gelatin and breaks down to the gelatin structure, further breaking down collagen fragments denatured by interstitial collagenase. At the glomerular level, inflammatory cell infiltration, the release of inflammatory mediators, and first, as a compensatory measure to lessen excessive collagen production and prevent the development of renal fibrosis, the release of reactive oxygen species (ROS) can boost the synthesis and activity of MMP-9. However, as CKD progresses, MMP-9 activity begins to decrease, which is associated with podocyte loss. Podocyte damage can occur due to adhesion molecule dysfunction, decreased podocyte density, and cell apoptosis due to oxidative stress. As a result, an accumulation of components in the extracellular matrix (ECM) causes increased glomerular permeability, albuminuria, and decreased GFR. Furthermore, there is also activation of the transition from the EMT and the processes of apoptosis and proliferation, which cause foot processes and slit diaphragm in podocytes which lead to the condition of renal fibrosis.[8]

According to Provenzano et al., the increase in MMP-9 levels was estimated to be around 30-50% of CKD stage 4 and 5 patients.[9] Rodríguez-Sánchez et al. found that patients with hypertension and reduced GFR had higher levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) and serum MMP-9.[10] Several experimental animal studies showed MMP-9 expression mainly in the glomerulus and the proximal and distal tubules. Similar research by Valente et al. found that persistent inflammation, characterized by elevated PTX-3 levels, disrupts MMP-9/TIMP-1 balance, promoting renal fibrosis.[11]

Despite numerous studies on CKD progression, few elucidate the initial inflammatory processes involving PTX-3 and MMP-9 markers and their association with degree of kidney damage. Understanding the correlation between serum PTX-3, MMP-9, and eGFR in CKD patients can enhance treatment strategies for GFR decline.[12] Thus, this study aims to comprehensively understand the correlation between serum PTX-3, MMP-9, and eGFR in patients with CKD.

## METHODS

### Study design

This analytical observational investigation was conducted at the biomedical laboratory of the Faculty of Medicine, Andalas University, and the outpatient and inpatient installations of Dr. M. Djamil Hospital Padang from April to September 2022. The study employed a cross-sectional research design.

### Population and sample

The sample size was calculated using the formula for a correlational study, enrolling 30 CKD patients aged between 16 and 65 years old from the outpatient and inpatient Nephrology Departments of Internal Medicine, General Hospital Center Dr. M. Djamil Padang, Indonesia. Inclusion criteria comprised patients willing to provide informed consent and diagnosed with stage 3 to 5 CKD according to the 2012 KDIGO. Exclusion criteria included CKD patients undergoing renal replacement therapy, those with type II DM, using nephrotoxic agents, septic, malignancy, autoimmune disease, cirrhosis of the liver, chronic obstructive pulmonary disease, and acute coronary syndrome (ACS). Sampling was conducted consecutively.

### Data collection

Detailed medical histories, patient age, and other relevant information were collected. Venous blood samples were obtained upon admission to assess biochemical markers and creatinine serum levels, including PTX-3 and MMP-9. Serum separator tubes were used to collect blood samples left to coagulate at room temperature. The serum was isolated by centrifugation at 1,500 g for 10

min before analysis, and it was stored at -80° C for a maximum of one month. Plasma PTX-3 and MMP-9 concentrations were measured using the ELISA Bioassay Technology Lab (Ray BioTech Life Inc, Georgia, USA), with results presented in ng/ml.

**Measurement of eGFR**

The CKD-EPI formula was employed to estimate the eGFR and it is as follows:

GFR = 141 x min (serum creatinine/k.1)$^{\alpha}$ x max (serum creatinine/k.1)$^{-1.209}$ x 0.993$^{age}$ x 1.018 (for female) x 1.159 (for black person).

The k values were 0.7 for female and 0.9 for male patients. The α values were -0.329 for female and -0.411 for male patients. "Min" represented the minimum value of serum creatinine/k or 1, while "max" represented the maximum value of serum creatinine/k or 1.

**Ethics**

Ethical clearance was obtained from the Ethics Committee of Universitas Andalas, Padang, West Sumatra, Indonesia (No. LB.02.02/5.7/117/2022).

**Statistical analysis**

Descriptive analysis was performed on primary data, representing numerical data with mean and standard deviation, and categorical variables with frequencies and percentages. Serum PTX-3 and serum MMP-9 were correlated, and the estimated glomerular filtration rate was represented as the Spearman correlation test in the case of non-normally distributed data or as the Pearson correlation coefficient in the case of normally distributed data. A p-value of less than 0.05 was used to determine the significance of data processed using SPSS 22.0.

## RESULTS

**General Characteristics of the Participants**

Thirty hypertensive patients with CKD stages 3, 4, and 5 were evaluated using serum creatinine levels, the 2012 KDIGO criteria, and the CKD-EPI estimate for diagnosis. The mean serum urea level was 180.77 ± 110.90 mg/dl, and the mean serum creatinine level was 10.58 ± 8.24 mg/dl. Participant characteristics are summarized in Table 1.

Table 1. Characteristics of the participants

| Parameter | n (%) | Mean ± SD |
|---|---|---|
| Sex | | |
| Female | 15 (50) | |
| Male | 15 (50) | |
| Age (years) | | 47.90 ± 13.35 |
| Office SBP (mmHg) | | 154.33 ± 14.78 |
| Office DBP (mmHg) | | 93.00 ± 4.66 |
| Urea (mg/dl) | | 180.77 ± 101.90 |
| Creatinine (mg/dl) | | 10.58 ± 8.24 |

Values are present as mean ± standard deviation (SD); SBP: systolic blood pressure; DBP: diastolic blood pressure.

**ELISA analysis for PTX-3 and MMP-9 serum levels and eGFR by CKD-EPI equation**

Plasma PTX-3 and MMP-9 activities were analyzed by an ELISA kit. The median PTX-3 level was 4.46 (2.68-5.71) ng/ml were shown in Table 2 , while the median MMP-9 level was 201.34 (190.15-279.62) ng/ml. The mean eGFR in CKD patients was 6.00 ml/min/1.73m$^2$, ranging from 1 to 48 ml/min/1.73m$^2$ (Table 2).

**Correlation Between PTX-3, MMP-9 Serum Levels, and eGFR in CKD Patients**

Table 3 illustrates the correlation between the level of serum MMP-9, PTX-3, and eGFR. Serum MMP-9 showed a significant inverse correlation with eGFR in CKD patients (Y = -0.280 MMP-9 +71.662, R = -0.746, p < 0.000), as revealed by linear regression analysis. Similarly, a significant correlation between serum PTX-3 and eGFR in CKD patients was observed (Figure 1).

Table 2. The PTX3, MMP-9 concentrations, and eGFR by chronic kidney disease-epidemiology equation

| Variables | Median (IQR) |
|---|---|
| PTX-3 (ng/ml) | 4.46 (2.68 – 5.71) |
| MMP-9 (ng/ml) | 201.34 (190.15 – 279.62) |
| eGFR (ml/min/1.73m2) | 6.00 (1 – 48) |

eGFR: estimated glomerular filtration rate; PTX-3: pentraxin-3 (PTX-3); MMP-9: matrix metalloproteinase-9, IQR: Interquartile range.

Table 3. Correlation between PTX-3, MMP-9, and eGFR in CKD patients

| Variable | PTX-3 | MMP-9 | eGFR |
|---|---|---|---|
| PTX-3 | | r = -0.477 | r = -0.795 |
| | - | $r^2$ = 0.234 | $r^2$ = 0.587 |
| | | p < 0.008 | p < 0.000 |
| eGFR | r = -0.795 | r = -0.746 | |
| | r2 = 0.587 | r2 = 0.166 | - |
| | p < 0.000 | p < 0.025 | |

eGFR: estimated glomerular filtration rate; PTX-3: pentraxin-3; MMP-9: matrix metalloproteinase-9

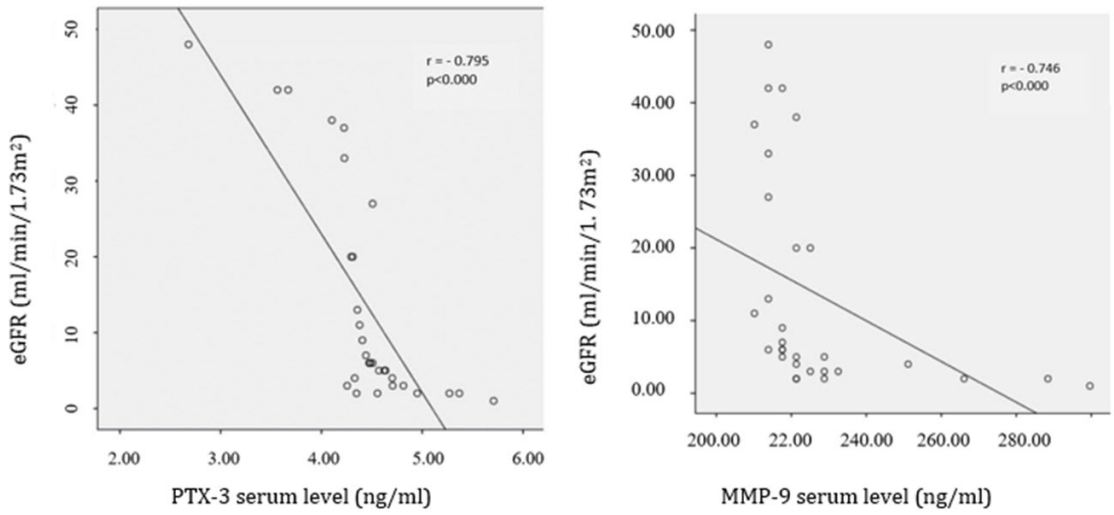


Figure 1. Analysis of the association between serum PTX-3 and eGFR (A) and between MMP-9 and eGFR (B) using linear regression. eGFR: estimated glomerular filtration rate; PTX-3: pentraxin-3

## DISCUSSION

This study was conducted on 30 samples of CKD patients, where the number of male samples was comparable to female samples. This finding aligns with previous study by Hockham et al. which obtained the results of comparing CKD patients based on gender, where slightly more than half of the sample were male, and the rest were female.13 Likewise, research 14 conducted a cohort study with a larger number of CKD population and found that the number of female patients was higher.

Additionally, a study conducted by Golberg and Krause highlighted the significant role of sex hormones in CKD. In his research using experimental animals, it was shown that there is an adverse effect of testosterone and the protective effect of estrogen on kidney damage. Both proximal tubule cells and podocytes experienced increased apoptosis due to the testosterone induction process, which led to increased renal fibrosis, while estrogen was observed to inhibit the process.[15]

The mean age of participants in this study was 47 years , with a majority falling within the 56-65 age range. These findings are consistent with previous research by Hockham et al. with an average patient age of 41 years.[13] While Dubey et al. obtained an average age of 50 years,[16] another study with a larger sample size, conducted by Xu

et al. found that the average age of the stage 3, 4, and 5 CKD groups was 50 years; 48 years, and 50 years.[17] A higher mean age difference compared to this study was reported by Kranowski et al. with a mean age value in CKD patients of 59 years.[18] The difference in this average is due to differences in research inclusion and exclusion criteria. Age is a risk factor for CKD. Renal structure and function changes will worsen with age, even in healthy individuals, such as renal vascularity, filtration process, and tubulointerstitial function. In addition, it is also associated with an increase in the prevalence of CKD etiologies such as DM and hypertension, which also increase with age.[19] The average blood pressure was 93 mmHg at the diastolic level and 154 mmHg at the systolic level. The Joint National Committee (JNC) VIII states that a patient has hypertension if their diastolic blood pressure (DBP) is 90 mmHg or higher and their systolic blood pressure (SBP) is 140 mmHg or higher.[20] This finding aligns to the research of Rodríguez-Sánchez et al., who obtained a mean SBP of 141 mmHg and a mean DBP of 85 mmHg.[10] Liu et al. in their research obtained a mean SBP value of 139 mmHg and DBP 77 mmHg.[14] While Unger et al. obtained a mean SBP of 133 mmHg and a mean DBP of 81 mmHg.[20] These differences are due to differences in sample size and different exclusion criteria.

Sarnak et al. reported that a decrease in GFR < 60 ml/min/1.73m$^2$ is a risk factor for increasing the incidence of cardiovascular disease in the form of new or recurrent cases, thus requiring further evaluation and treatment.[21] This is under data from the IRR in 2017 which places hypertension as the first etiology in CKD patients by 36%.[2] In this study, the mean ureum level was 180.77 mg/dl and the mean creatinine level was 10.59 mg/dl. This study is not much different from a study by Natalia, with a mean ureum level of 145.53 mg/dl, and a mean creatinine level of 3.36 mg/dl.[22] In research by Hockham et al. a higher mean creatinine level was obtained at 249.50 mg/dl and a mean creatinine of 13.70 mg/dl.[13] The difference in means is due to differences in the characteristics of the study sample.

Based on the stage of CKD in this study, there were more patients with stage 5 compared to stages 3 and 4. This is because patients in the final stage of CKD or stage 5, have clinical complaints that encourage patients to seek treatment, so more are found in outpatient and inpatient care compared to CKD patients in stages 3a, 3b, and 4. Based on the glomerular filtration rate (GFR) and the extent of kidney damage, chronic kidney disease is classified into five stages: 1, 2, 3a, 3b, 4, and 5. Stage 5 is a form of total kidney failure in carrying out the main function of metabolic homeostasis and requires renal replacement therapy.[10] In the early stages, CKD does not cause symptoms and signs; even though up to 60% of GFR patients are still asymptomatic, there is an increase in urea and creatinine levels. As the GFR decreases, complaints such as nocturia, weakness, nausea, decreased appetite, and weight loss begin to appear, the patient notices the symptoms and signs of uremia.

The increasing incidence of CKD due to various etiologies, especially in end-stage renal disease (ESRD), will remain a major clinical problem, which requires important attention to prevention to inhibit the progressivity of the disease.[23, 24] High-risk groups for CKD include DM, hypertension, heart disease, structural kidney disease, systemic disease, family history of CKD, old age, and use of nephrotoxic drugs or opportunistic hematuria or proteinuria. Beyond these factors, there are non-traditional factors involved, namely evidence of the role of inflammation and vascular damage in CKD.[25]

A member of the pentraxin subfamily, PTX-3 is an acute and chronic phase protein that contributes to the inflammatory process of chronic kidney disease. Interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) PTX-3 play a role in activating PTX-3, but interleukin-6 (IL-6) or interferon can activate PTX-3. The PTX-3 is also expressed and released from endothelial cells, which is associated with renal fibrosis in chronic CKD.[11] The normal value of PTX-3 is 0.15 - 0.33 ng/ml. In this study, the mean PTX-3 value was 4.45 ng/ml. The median PTX-3 value was 4.46 ng/ml, with a minimum level of 2.68 ng/ml and a maximum of 5.71 ng/ml. Levels of PTX-3 in CKD patients in this study were higher and significant when compared with normal average values. In this study, PTX-3 levels in CKD patients were higher than the normal average value.

Assessed serum PTX-3 levels obtained a median of 5.92 ng/ml.[26] Research results from Wardoyo et

al. obtained a lower median value of 0.93 ng/ml and also used a cut-off value for serum PTX-3 levels of 2.3 ng/ml.[27] Research by Gursu et al. reported a mean value of serum PTX-3 levels in patients who have not undergone hemodialysis (HD) of 1.29 ng/ml, compared to serum PTX-3 of HD patients with a much higher mean value of 3.58 ng/dl.[28] The difference in mean serum PTX-3 levels in this study was due to differences in inclusion and exclusion criteria and treatments on the research samples. Previous research showed that in CKD patients there was an increase in serum PTX-3 levels, as were the findings in this study.

The results of this study showed higher mean serum MMP-9 levels in CKD patients compared to normal values, which is by research conducted by Miljković et al., who also reported an increased MMP-9 value of 376 ng/ml in CKD patients who had not been HD, and in the CKD group that received HD treatment, the MMP-9 value was 304 g/ml.[29]

The study's results differ from research conducted by Mudatsir et al. who reported differences in the mean value of serum MMP-9 in CKD patients and the control group. The decrease in mean MMP-9 was associated with decreased antifibrotic potential in CKD patients with DM comorbid. The difference in the mean value of MMP-9 may be due to differences in the inclusion and exclusion criteria of the study.[30]

Other possibilities that may affect serum MMP-9 levels in this study are hypertension, dyslipidemia, and obesity, which are also causes of renal vascular endothelial damage. Hypertension is closely associated with CKD, which is the cause of glomerulosclerosis, interstitial fibrosis, and atherosclerosis. The MMP-9 in the acute process plays a role in vascular remodeling in the heart and kidney, activating cardiorenal system pathways. However, ECM degradation causes changes in EMT conditions in the form of increased collagen/scarring in conditions of renal fibrosis.[10] The increase in mean serum MMP-9 levels in this study is in line with several previous studies, which show the occurrence of renal fibrosis in CKD patients.

The mean eGFR value in this study was 13.60 ml/min/1.73m$^2$. Dubey et al. obtained a median eGFR value of 29.2 ml/min/1.73m$^2$.[16] This study is different from that conducted by Hockham et al. who obtained a lower mean GFR value of 6.53 ml/min/1.73m$^2$.[13] Liu et al. obtained a mean eGFR of 24.6 ml/min/1.73m$^2$.[14] Previous studies have shown an increase in serum PTX-3 levels in CKD patients. Likewise, many studies have also shown a decrease in eGFR values in CKD patients. In this study, the findings of the analysis demonstrated a high and negative connection, as well as a significant relationship, between PTX3 levels and GFR in individuals with chronic kidney disease. It can be concluded that an increase in PTX-3 in CKD patients causes a decrease in eGFR value.

Pentraxin-3 plays a role in the immunoregulatory mechanism of acute inflammation and chronic kidney damage. PTX-3 levels can be detected normally, but the levels are very low in both serum and tissue. However, the value of PTX-3 increases due to inflammatory stimulation.[31] Research by Dai et al. states that the cause of inflammation in CKD is multifactorial, one of which is due to an imbalance between increased inflammatory production such as due to oxidative stress, acidosis, fluid overload, infection, and comorbidities such as hypertension which will cause a decrease in GFR. Chronic conditions, known as chronic low-grade inflammation, are important from initiation to renal fibrosis.[32]

Increased serum PTX-3 levels were inversely correlated with GFR values in the elderly, and serum PTX-3 levels predicted the incidence of CKD five years in the future.[33] Research by Hung et al. using recombinant PTX3 seen in proximal tubule epithelial cells in mice, found an increase in PTX-3 levels induced by cell migration through the upregulation of EMT in the c-Jun NH2-terminal kinase (JNK)-dependent pathway.[34]

The mechanisms underlying the role of PTX-3 in the reduction of GFR are still unclear; however, the following mechanisms may explain the increase in PTX-3 levels. Firstly, PTX-3 activates and regulates the complement cascade, which functions as a regulator of inflammation in response to stimulation by cytokines. Second, PTX-3 is involved in the regulation of the immune system, which not only protects against certain infections but also against the development of atherosclerotic lesions.[32] Based on the results of this study and several previous studies compared with the theory, the researcher found that as serum

PTX-3 levels increase in CKD patients, there will be a significant decrease in eGFR values.

Serum MMP-9 levels are higher in CKD patients according to earlier research. Moreover, a decline in eGFR levels in CKD patients has been reported in numerous investigations. Serum MMP-9 levels and eGFR values in individuals with chronic kidney disease (CKD) were shown to be significantly correlated in this investigation. The association was quite high and had a negative direction. According to this data, the glomerular filtration rate decreases in CKD patients when MMP-9 levels rise.

Rodríguez-Sánchez et al. reported a correlation between serum MMP-9 activity and decreased renal function in hypertensive patients with impaired function. This research explains that the increase in MMP-9 levels is higher than its inhibitor TIMP-1 as a cause of CKD progressivity, and it appears that the increase in MMP-9 occurs since the early stages of CKD.[10] Research by García-Tejeda et al. stated that there was a relationship between urinary MMP-9 and decreased GFR values.[35]

Li et al. revealed different research findings: they treated diabetic rats after they were streptozotocin-induced, and when they were evaluated in vitro, they discovered increased MMP-9 synthesis along with increased albuminuria, glomerular hypertrophy, and thickening of the glomerular basement membrane. However, as the overexpression of endogenous MMP-9 increased podocyte cell differentiation, compromising podocyte cell integrity and increasing albumin permeability and ECM protein synthesis, the nephropathic alterations in diabetic mice were dramatically mitigated by MMP-9 deletion. It was discovered that MMP-9 increased significantly earlier in diabetic patients than microalbuminuria, suggesting that MMP-9 may be involved in the early onset of CKD, particularly diabetic nephropathy. [36] This work supports the development of treatments that can stop the progression of renal fibrosis in individuals with chronic kidney disease (CKD) and highlights the significance of measuring serum MMP-9 levels and eGFR in these patients.

Previous studies have shown an increase in serum PTX-3 levels in CKD patients. Likewise, many studies have also shown an increase in serum MMP-9 levels in CKD patients. However, so far, no studies have directly linked serum PTX-3 levels with serum MMP-9 levels in CKD patients. So, the author has not found comparative research for this study. The results of the data analysis showed a significant correlation between PTX-3 levels and MMP-9 levels in CKD patients with a positive correlation direction and moderate correlation strength. This shows that the higher the serum PTX-3 level, the higher the serum MMP-9 level in CKD patients.

Several genetic, inflammatory, comorbid, and hormonal factors can influence the increase in renal fibrosis markers. Pentraxin-3 synthesis by the kidney is triggered due to several pathological conditions, including pro-inflammatory cytokines (TNF-α and Interleukin-1 beta (IL-1β)), hypoxia, ROS, profibrotic cytokines, hyperglycemia, acidosis, and angiotensin II which later induces continuous regulation (chronic inflammation) resulting in decreased cell regeneration ability and renal fibrosis. Pentraxin-3 interacts with MMPs either directly or indirectly through NO, leading to the activation and migration of progenitor cells and fibroblasts, followed by ECM repair through vascular remodeling and endothelial dysfunction. Pentraxin-3 alters NO synthesis by reducing NO signaling in blood vessels and increasing MMP-9 production by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) or reducing MMP messenger-RNA (mRNA) stability.[37, 38]

A study like this study reported by Ma et al. assessed the relationship between PTX-3 with CRP and MMP-9 in patients with acute coronary syndrome and proved that there was a positive correlation between PTX-3 and MMP-9 and was significant. An important factor in this inflammatory condition is the process of atherogenesis, which causes PTX-3 activation in smooth muscle cells through atherogenic lipoproteins and endothelial cell tissue factors, as well as monocyte activation that causes the formation of atherosclerotic plaque. Atherosclerotic plaque triggers ECM degradation, which can trigger plaque rupture as the cause of thrombus in myocardial infarction.[39]

Compensatory mechanisms to stop the formation of renal fibrosis and reduce excessive collagen synthesis. However, MMP-9 activity is linked to podocyte loss as CKD worsens. where podocytes detach from the basement membrane. Podocyte loss can occur due to adhesion molecule dysfunction, decreased podocyte density, and cell

apoptosis due to oxidative stress. As a result, an accumulation of components in the ECM causes increased glomerular permeability, albuminuria, and decreased GFR. Furthermore, there is also activation of EMT and apoptotic processes as well as proliferation that causes foot processes and slit diaphragm in podocytes that cause renal fibrosis.8 Limitations of this study were no investigation regarding genetic factors and other inflammatory factors that can also affect serum PTX-3 levels and serum MMP-9 levels in CKD patients and only focuses on the increase in serum PTX-3 and serum MMP-9 levels in CKD patients and does not look at the relationship with other organ/tissue damage conditions .

## CONCLUSION

In individuals with chronic kidney disease (CKD), a modest positive association is observed between serum PTX-3 and serum MMP-9, while a very strong negative correlation exists between serum PTX-3 and serum MMP-9 with eGFR. Future research should therefore investigate additional variables that influence blood PTX-3 and serum MMP-9 levels in CKD patients.

## CONFLICT OF INTEREST

No conflict of interest

## ACKNOWLEDGEMENTS

The researcher would like to thank the Director of the Central General Hospital Dr. M. Djamil Padang, Indonesia, who permitted this research.

## AUTHOR CONTRIBUTION

HH carried out the study conception, data collection, analysis and interpretation of the results, and manuscript preparation. AFD carried out data collection and analysis and interpretation of the results. RA carried out the study design, data collection, and analysis and interpretation of the results.

## LIST OF ABBREVIATIONS

ACS: acute coronary syndrome; CG: Cockcroft gault; CKD: chronic kidney disease; CKD-EPI: chronic kidney disease epidemiology collaboration; DBP: diastolic blood pressure; DM: diabetes melitus; ECM: extracellular matrix; eGFR: estimated glomerular filtration rate; ELISA: enzyme-linked immunosorbent assay; EMT: epithelial mesenchyme transition; ESRD: end-stage renal disease; FGF-2: fibroblast growth factor-2; GFR: glomerular filtration rate; HD: hemodialysis; IL-1: interleukin-1; IL-1β: interleukin-1 beta; IL-6: interleukin-6; IRR: Indonesia renal registry; JNC: joint national committee; JNK: c-Jun NH2-terminal kinase; KDIGO: kidney disease improving global outcomes; MDRD: Modification of Diet in Renal Disease; MMP-9: matrix metalloproteinase-9; mRNA: Messenger RNA; NO: nitric oxide; PERNEFRI: Indonesian nephrology association; PTX-3: pentraxin-3; ROS: reactive oxygen species; SBP: systolic blood pressure; TIMP-1: tissue inhibitor of metalloproteinase-1; TNF-α: tumor necrosis factor alpha.

## REFERENCE

1. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: A review. JAMA. 2019;322(13):1294-1304. DOI: 10.1001/jama.2019.14745.
2. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: Pathophysiological insights and therapeutic options. Circulation. 2021;143(11):1157–72. DOI: 10.1161/CIRCULATIONAHA.120.050686.
3. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33. DOI: 10.1016/S0140-6736(20)30045-3.
4. Bello AK, McIsaac M, Okpechi IG, Johnson DW, Jha V, Harris DCH, et al. International Society of Nephrology Global Kidney Health Atlas: Structures, organization, and services for the management of kidney failure in North America and the Caribbean. Kidney Int Suppl. 2021;11(2):e66–76. DOI: 10.1016/j.kisu.2021.01.001
5. Sertsu A, Worku T, Fekadu G, Tura AK. Prevalence of chronic kidney disease and associated factors among patients visiting renal unit of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia: A cross-sectional study design. SAGE Open Medicine. 2022;10:205031212211169. DOI: https://doi.org/10.1177/20503121221116942.
6. Fiddian-Green RG, Silen W. Mechanisms of disposal of acid and alkali in rabbit duodenum. Am J Physiol. 1975;229(6):1641–8. DOI: 10.1152/ajplegacy.1975.229.6.1641.
7. Zlibut A, Bocsan IC, Agoston-Coldea L. Pen-

traxin-3 and endothelial dysfunction. In: Makowski GS, editor. Adv Clin Chem. Elsevier; 2019. p. 163–79. DOI:10.1016/bs.acc.2019.03.005.
8. Park SJ, Park BS, Yu SB, Kang HM, Kim HJ, Kim IR. Induction of apoptosis and inhibition of epithelial-mesenchymal transition by α-mangostin in MG-63 cell lines. Evid Based Complement Alternat Med. 2018;3985082:1–10. DOI: https://doi.org/10.1155/2018/3985082.
9. Provenzano M, Andreucci M, Garofalo C, Faga T, Michael A, Ielapi N, et al. The association of matrix metalloproteinases with chronic kidney disease and peripheral vascular disease: A light at the end of the tunnel? Biomolecules. 2020;10(1):154. DOI: 10.3390/biom10010154.
10. Rodríguez-Sánchez E, Navarro-García JA, Aceves-Ripoll J, Álvarez-Llamas G, Segura J, Barderas MG, et al. Association between renal dysfunction and metalloproteinase (MMP)-9 activity in hypertensive patients. Nefrología. 2019;39(2):111–222. DOI: 10.1016/j.nefroe.2019.03.006.
11. Valente MJ, Rocha S, Coimbra S, Catarino C, Rocha-Pereira P, Bronze-da-Rocha E, et al. Long pentraxin 3 as a broader biomarker for multiple risk factors in end-stage renal disease: Association with all-cause mortality. Mediators Inflamm. 2019;3295725:1–12. DOI: 10.1155/2019/3295725.
12. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De La Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci. 2020;21(24):9739. DOI: 10.3390/ijms21249739.
13. Hockham C, Bao L, Tiku A, Badve SV, Bello AK, Jardine MJ, et al. Sex differences in chronic kidney disease prevalence in Asia: A systematic review and meta-analysis. Clin Kidney J. 2022;15(6):1144–51. DOI: 10.1093/ckj/sfac030.
14. Liu P, Quinn RR, Lam NN, Al-Wahsh H, Sood MM, Tangri N, et al. Progression and regression of chronic kidney disease by age among adults in a population-based cohort in Alberta, Canada. JAMA Netw Open. 2021;4(6):e2112828. DOI: 10.1001/jamanetworkopen.2021.12828.
15. Goldberg I, Krause I. The role of gender in chronic kidney disease. EMJ. 2016;58–64. DOI:10.33590/emj/10312319
16. Dubey AK, Sahoo J, Vairappan B, Haridasan S, Parameswaran S, Priyamvada PS. Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: A randomized controlled trial. Nephrol Dial Transplant. 2020: 35(1):121-9. DOI: 10.1093/ndt/gfy214.
17. Xu G, Luo K, Liu H, Huang T, Fang X, Tu W. The progress of inflammation and oxidative stress in patients with chronic kidney disease. Ren Fail. 2015;37(1):45–9. DOI: 10.3109/0886022X.2014.964141.
18. Krzanowski M, Krzanowska K, Gajda M, Dumnicka P, Dziewierz A, Woziwodzka K, et al. Pentraxin3 as a new indicator of cardiovascular-related death in patients with advanced chronic kidney disease? Pol Arch Intern Med. 2017;127(3):170-7. DOI: 10.20452/pamw.3944.
19. Tannor EK, Sarfo FS, Mobula LM, Sarfo-Kantanka O, Adu-Gyamfi R, Plange-Rhule J. Prevalence and predictors of chronic kidney disease among Ghanaian patients with hypertension and diabetes mellitus: A multicenter cross-sectional study. J Clin Hypertens (Greenwich). 2019;21(10):1542–50. DOI: 10.1111/jch.13672.
20. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of hypertension global hypertension practice guidelines. Hypertension. 2020;75(6):1334–57. DOI: 10.1161/HYPERTENSIONAHA.120.15026.
21. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Hypertension. 2003;42(5):1050–65. DOI: 10.1161/01.HYP.0000102971.85504.7c.
22. Natalia S, Suangga F, Pramadhani W. Hubungan antara lama menjalani hemodialisa dengan kualitas hidup pasien gagal ginjal kronik di ruang hemodialisa di salah satu RSUD di Batam. An-Najat:Jurnal Ilmu Farmasi dan Kesehatan. 2023:1(2): 108-12. DOI: https://doi.org/10.59841/an-najat.v1i2.162
23. Kovesdy CP. Epidemiology of chronic kid-

ney disease: An update 2022. Kidney Int Suppl. 2022;12(1):7–11. DOI:10.1016/j.kisu.2021.11.003.
24. Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. Am J Nephrol. 2021;52(2):98–107. DOI: 10.1159/000514550.
25. Mihai S, Codrici E, Popescu ID, Enciu AM, Necula LG, Anton G, et al. Inflammation and chronic kidney disease: Current Approaches and recent advances. In: Rath T, editor. Chronic kidney disease - from pathophysiology to clinical improvements. InTech; 2018; DOI: 10.5772/intechopen.72716.
26. Deng H, Fan X, Wang X, Zeng L, Zhang K, Zhang X, et al. Serum pentraxin 3 as a biomarker of hepatocellular carcinoma in chronic hepatitis B virus infection. Sci Rep. 2020;10(1):20276. DOI: 10.1038/s41598-020-77332-3.
27. Wardoyo EY, Nainggolan G. Factors associated with arterial stiffness in chronic hemodialysis patients in Jakarta: The role of hemodialysis frequency and pentraxin 3. Acta Med Indones. 2021;53(2).177-83. https://www.actamedindones.org/index.php/ijim/article/view/1542.
28. Gursu M, Ozturk S, Arici M, Sahin I, Bek SG, Yilmaz M, et al. Characteristics and survival results of peritoneal dialysis patients suffering from COVID-19 in Turkey: A multicenter national study. Kidney Blood Press Res. 2022;47(10):605–15. DOI: 10.1159/000526909.
29. Miljković M, Stefanović A, Bogavac-Stanojević N, Simić-Ogrizović S, Dumić J, Jelić-Ivanović Z et al. Association of pentraxin-3, galectin-3, and matrix metalloproteinase-9/TIMP-1 with cardiovascular risk in renal disease patients. Acta Clin Croat. 2017;56(4):673-80. DOI: 10.20471/acc.2017.56.04.14
30. Mudatsir, Labeda I, Uwuratuw JA, Hendarto J, Warsinggih, Lusikooy RE, et al. Relationship between metalloproteinase-9 (MMP-9) expression and clinicopathology in colorectal cancer: A cross-sectional study. Annals of Medicine & Surgery. 2023;85(9):4277–82. DOI: 10.1097/MS9.0000000000000892.
31. Capra AP, Crupi L, Pantò G, Repici A, Calapai F, Squeri R, et al. Serum pentraxin 3 is a promising biomarker for the long-lasting inflammatory response of COVID-19. Int J Mol Sci. 2023;24(18):14195. https://doi.org/10.3390/ijms241814195.
32. Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-stage renal disease, inflammation and cardiovascular outcomes. In: Ronco C, editor. Contributions to Nephrology. S. Karger AG; 2017 [cited 2024 Mar 19]. p. 32–43. DOI:https://doi.org/10.1159/000479254
33. Sjöberg B, Qureshi AR, Heimbürger O, Stenvinkel P, Lind L, Larsson A, et al. Association between levels of pentraxin 3 and incidence of chronic kidney disease in the elderly. Journal of Internal Medicine. 2016;279(2):173–9. DOI:10.1111/joim.12411
34. Hung TW, Tsai JP, Lin SH, Lee CH, Hsieh YH, Chang HR. Pentraxin 3 activates JNK signaling and regulates the epithelial-to-mesenchymal transition in renal fibrosis. Cell Physiol Biochem. 2016;40(5):1029–38. DOI: 10.1159/000453159.
35. García-Tejeda AU, Sampieri CL, Suárez-Torres I, Morales-Romero J, Demeneghi-Marini VP, Hernández-Hernández ME, et al. Association of urinary activity of MMP-9 with renal impairment in Mexican patients with type 2 diabetes mellitus. PeerJ. 2018;6:e6067. DOI:10.7717/peerj.6067
36. Li SY, Huang PH, Yang AH, Tarng DC, Yang WC, Lin CC, et al. Matrix metalloproteinase-9 deficiency attenuates diabetic nephropathy by modulation of podocyte functions and dedifferentiation. Kidney Int. 2014;86(2):358–69. DOI:10.1038/ki.2014.67
37. Doni A, Stravalaci M, Inforzato A, Magrini E, Mantovani A, Garlanda C, et al. The long pentraxin PTX3 is a link between innate immunity, tissue remodeling, and cancer. Front Immunol. 2019;10:712. DOI: 10.3389/fimmu.2019.00712
38. Garcia-Fernandez N, Jacobs-Cachá C, Mora-Gutiérrez JM, Vergara A, Orbe J, Soler MJ. Matrix metalloproteinases in diabetic kidney disease. J Clin Med. 2020;9(2):472. DOI: 10.3390/jcm9020472
39. Ma R, Zhang W, Wang T, He X, Huang Z, Zhu J, et al. Pentraxin 3, long-expression in mononuclear cells of patients with acute coronary syndrome: Correlation with C-reactive protein and matrix metalloproteinase-9 levels. J. Int Med Res. 2014: 42(3): 677-83. DOI: 10.1177/0300060513507387.