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Correlation of PON1 rs662 gene polymorphism, Serum Paraoxonase 1 and Calprotectin levels in Chronic Kidney Disease patients in Northern India

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Abstract

Introduction: Chronic Kidney Disease (CKD) is a gradually progressing non-communicable disease, resulting in the identification of patients in many later stages. PON1 levels are affected by the rs662 gene, which may play a significant role in the pathogenesis of CKD. Calprotectin is a novel inflammatory biomarker that may provide better insight into the progression of the disease. The aim of the present study was to identify the association of PON1 rs662 gene polymorphism with the levels of serum PON1 and serum calprotectin in patients with CKD.

Methods: A case-control study was undertaken in a tertiary care hospital in Northern India with 240 participants, with 120 belonging to the case group and 120 to the control group. Venous blood sampling was performed, and the centrifuged serum sample was used for running an ELISA test for PON1, and genotyping was performed using whole blood. Serum gel electrophoresis was performed. Analysis of data was done by using SPSS, version 25.0. Statistical significance was considered with a p-value < 0.05.

Results: The serum PON1 level was significantly lower in the CKD group than in the controls (858.69 ± 168.27 vs 1259.03 ± 333.96 ng/mL; $p<0.0001$). Logistic regression analysis showed that the homozygous GG genotype of PON1 rs662 SNP had a nearly 5-fold increased risk of developing CKD (OR =4.75, 95% CI 2.06-10.89, $p < 0.01$). Serum Calprotectin was significantly higher in the CKD group than in the control group (346.50±65.56 vs 315.93±48.15 ng/mL, $p < 0.05$).

Conclusion: The homozygous GG genotype of PON1 rs662 gene polymorphism was significantly associated with increased CKD susceptibility. Serum PON1 and calprotectin levels may become potential predictive determinants to assist in early intervention and assess the severity of CKD.

Introduction

In the era of new emerging diseases and pandemics spreading worldwide, the toll of non-communicable

diseases acting as co-morbidities has proven to have a significant role in the outcome of the disease in a patient. Chronic kidney disease (CKD) is one of the emerging non-communicable diseases that has led to an increase in morbidity and mortality in recent years. CKD can be defined as kidney damage or glomerular filtration rate (GFR) < 60ml/min/1.73m2 for three months or more, irrespective of the cause. The data on the prevalence of CKD in India is limited. In India, 40-60% of cases of CKD are caused by diabetes and hypertension [1]. The prevalence of CKD in India has been found to be 17.2% in a recent multicentric study, with about 6% having CKD stage 3 or worse [2]. The actual burden of the disease in the Indian population is not known due to the lack of resources, such as the absence of a registry, fewer dedicated centres, and a lack of universal accessibility to renal replacement therapy. It is observed that nearly 50 % of patients with CKD are first seen when the eGFR is <15mL/min/1.73m2 [3]. Thus, there is a need to identify the interactions between various genetic determinants and environmental factors that may provide insight into detecting CKD at an early stage.

Serum PON1, a Ca2+-dependent glycoprotein enzyme with a molecular mass of 44 kDa, is a high-density lipoprotein (HDL) bound enzyme reported to have antioxidant properties [4]. PON1 is crucial in minimizing oxidative stress in the body, which is paramount in causing chronic renal injury. The long arm of chromosome 7 (7q21.3-q22.1) harbours the human Paraoxonase (PON) gene family and includes PON1, PON2, and PON3 [5]. The levels of PON-1 are under genetic regulation. The genetic polymorphisms of the PON1 gene, particularly those in the coding region, may influence the levels and activity of serum enzymes [6]. One such polymorphism is the rs662 gene polymorphism (c.575A>G or p. Gln192Arg or Q192R), which lies on exon 6 and changes glutamine (CAA) to arginine (CGA) at position 192 [7]. In many studies, Q192R polymorphism is considered a genetic biomarker of oxidative stress [8]. Calprotectin, a novel inflammatory biomarker that may provide a better insight into the progression of the disease, is a heterodimeric complex associated with the S100 protein family. It is presumed to play a critical role in the early differentiation of an array of immune cells, such as macrophages, granulocytes, and monocytes [9-10].

The disease burden and lack of studies regarding genetic risk factors associated with CKD in India encouraged us to conduct this study. It aims to determine the role of rs662 PON 1 gene polymorphism in association with serum PON 1 and calprotectin levels in CKD, which may provide a genetic basis for the prevention, early diagnosis, and treatment of the disorder.

Materials and Methods

Study Population

The study was undertaken in a tertiary care hospital in Northern India after prior clearance from the institutional Ethics review board. The total participants in the study was randomly selected: 240 participants (more than 18 years of age) with written informed consent. A nephrologist diagnosed CKD based on medical history, clinical examination, and relevant investigations, including eGFR estimation. Out of 240 study participants, 120 were CKD patients, and 120 were age and gender-matched controls (with no history of diabetes or hypertension and with average GFR values). The exclusion criteria consisted of participants with a recent history of acute infections and sepsis, liver insufficiency, auto-immune disorders, cancer patients, HIV/ COVID-19 infection, and repeated blood transfusions.

The classification system of CKD was given by the Kidney Disease Outcomes Quality Initiative (KDQOI) of the National Kidney Foundation. The system is based on the level of kidney function, which is estimated by the GFR and categorized as G1, G2, G3a, G3b, G4, and G5. G1 has a range greater than 90, G2 has a

range of 60-89, G3a has a range of 45-99, G3b has a range of 30-44, G4 has a range of 15-29, and G5 has a range of <15.

Sample collection

The venous blood sample was drawn preferably from the vein overlying the cubital fossa, following all aseptic precautions, after overnight fasting (8-12 hours). The sample was withdrawn in the order: first in a serum separator tube, then in an EDTA-containing vacutainer, and lastly, in a sodium fluoride grey container (for glucose). The blood in the EDTA vacutainer was stored at -20°C for DNA extraction. The blood in the serum separator tube was allowed to clot and then centrifuged to obtain serum. These serum samples were stored at -80◦C until batch analysis of enzyme assay.

Estimation of Serum PON1

A commercially available ELISA kit manufactured by Shanghai Coon Koon Biotech Co. Ltd. was used for the estimation of serum PON 1, following the manufacturer's instructions. The principle of the test was based on a double antibody sandwich technology enzyme-linked immunoassay for quantitative measurement of serum PON1. The absorbance was measured at 450nm, and a standard curve was obtained, which was used to measure the PON1 concentration of the sample.

Genotyping

The genomic DNA extraction was done from nucleated blood cells using a Himedia DNA extraction kit. The amplification of the DNA was done by using PCR with the forward primer, 5′-GCTGTGGGACCTGAGCACTT-3′, and reverse primer, 5′-ATACTTGCCATCGGGTGAAATG-3′. The total volume of the PCR reaction mixture was 25 µL containing 25-30 ng genomic DNA, 50pmol of each primer, 12.5 µL Go Taq green PCR Master-mix (Promega) containing 50 units/mL Taq DNA polymerase, in a reaction buffer (pH 8.5), 400µM of each dNTP and 3mM MgCl2 and 8.5 µL nuclease-free water using a thermal cycler (Himedia Eco-96). The PCR reaction was run with the initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30s, annealing at 60.4 °C for 30s, then extension at 72 °C for 30s, with a final extension step at 72 °C for 5 min. The final product length of 189bp was incubated with MboI (New England Biolabs) restriction enzyme at 37 °C for 12 hours for digestion. The products of digestion were then resolved on a 1.2% agarose gel electrophoresis for the Q192R genotypes with the AA product length- 156bp and 33bp, AG product length- 189bp, 156bp, and 33bp, and GG product length- 189bp as depicted in Figure 1.

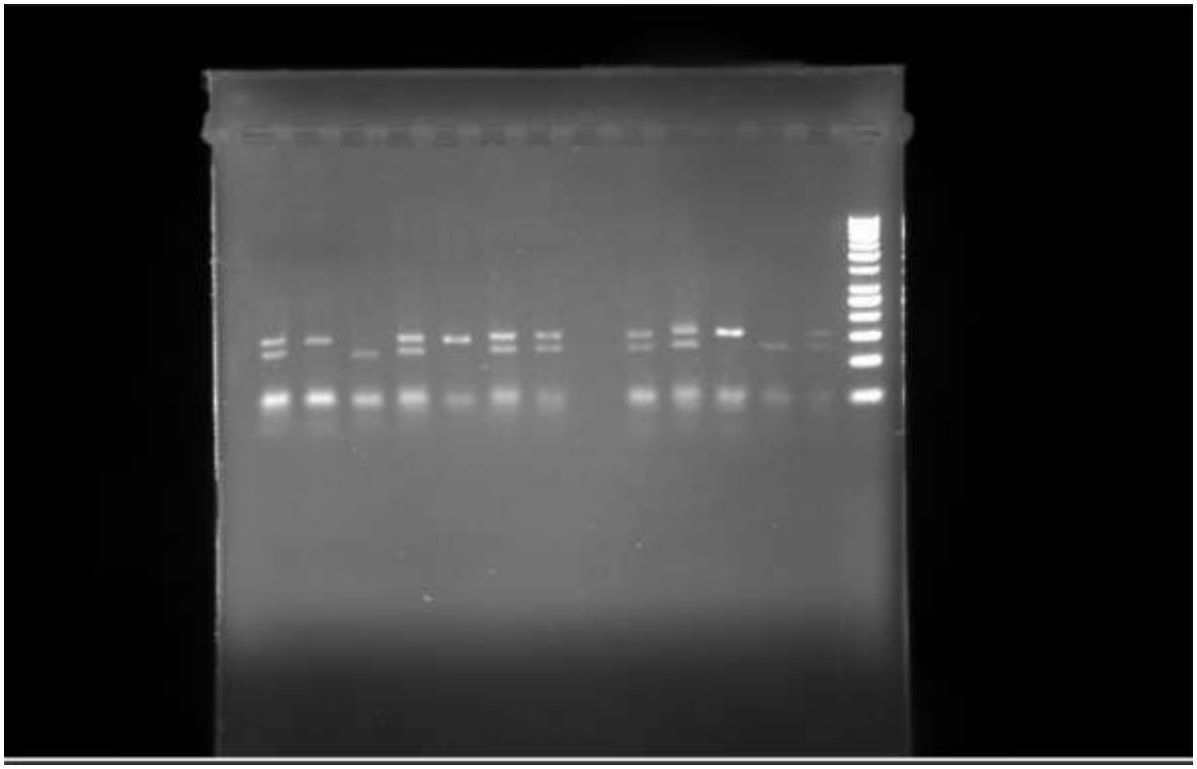

Figure 1. MboI restriction enzyme with the digested PCR products of PON1 gene. Homozygous GG show a single undigested band at 189bp , Homozygous AA show 2 bands at 156bp and 33bp and, Heterozygous AG show 3 bands at 189bp, 156 bp, and 33bp. Lane 1 is DNA Ladder (50bp); Lane 3,12 show AA genotype; Lane 2,5,6,8,9,11,14 represent AG genotype; Lane 4,10,13 are GG genotype.

Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences for Windows (SPSS), version 25.0 (Chicago, IL, USA). Statistical significance was considered with a p-value <0.05. The means of multiple independent groups were statistically compared using Analysis of variance (ANOVA). The Chi-square test was used to evaluate any deviation from the Hardy-Weinberg equilibrium. Odd's Ratio (OR) was estimated to have a 95% confidence interval (CI) to determine the association between genotypes of PON1 gene polymorphism and CKD.

Results

In this study, 240 patients were evaluated for the association between PON1 rs662 gene polymorphism and serum PON1 levels. The categorization of patients as the CKD group and the control group was done based on the estimated glomerular filtration rate, with each group consisting of 120 individuals. The mean age of CKD patients and controls was 40.01±11.12 and 42.18±11.26 years, respectively. Males constituted 81(67.5%) of the CKD group, and females comprised 19(32.5%) of the CKD group. Age and gender matching were done for both cases and the control group. Table 1 depicts the study population based on demographic, clinical, and baseline biochemical characteristics.

Table 1. Study population details on the basis of Demographic, clinical, and biochemical characteristics

Variable	CKD (n=140)	Control (n=140)	P-value
Age, (years)	40.01±11.12	42.18±11.26	>0.05
Males, %	81 (67.5%)	82 (68.3%)	>0.05
Females,%	19 (32.5%)	18 (31.6%)	>0.05
T.Bil, mg/dL	0.56 ± 0.23	0.67 ± 0.23	>0.05
AST, U/L	45 ± 23	46 ± 9	>0.05
ALT, U/L	34 ± 25	47 ± 9	>0.05
ALP, U/L	114 ± 34	86 ± 22	
Urea, mg/dL	122.77±48.42	25.75±13.26	<0.001
Creatinine, mg/dL	3.37±1.58	0.57±0.20	<0.001
e-GFR, mL/min/1.73m^2	26.14±12.16	123.72±21.93	<0.001

Values are expressed as mean ± standard deviation or percentage.
e-GFR-Estimated Glomerular Filtration Rate

In the CKD group, the percentage of diabetes mellitus (DM) patients and hypertensive patients was 76(63.3%) and 63(52.5%), respectively. In the CKD group of patients, serum urea and creatinine levels were significantly higher, whereas the value of e-GFR was significantly lower.
The levels of serum PON1 in CKD patients and controls are shown in Table 2. The levels of serum PON1 were significantly lower in the CKD group as compared to those in the control group (858.69±168.27 vs 1259.03±333.96 mIU/mL, $p < 0.0001$).

Table 2. Serum PON1 level in CKD and control group.

Study Group	PON1(mIU/mL)
CKD	858.69±168.27
Control	1259.03±333.96
P-value	<0.0001

PON1-Paraoxanase1; All values are expressed as mean ± standard deviation.

Serum Calprotectin levels in CKD patients and controls are shown in Table 3. The levels of serum Calprotectin were significantly higher in the CKD group than in the control group (346.50±65.56 vs 315.93±48.15 ng/mL, $p < 0.05$).

Table 3. Serum Calprotectin level in CKD and control group.

Study Group	Calprotectin (ng/mL)
CKD	346.50±65.56
Control	315.93±48.15
P-value	<0.05

All values are expressed as mean ± standard deviation.

The distribution of genotypes and alleles for the PON1 rs662 (Q192R) polymorphism is shown in Table 4. The frequencies of the AA, AG, and GG genotypes in the CKD patient and control group were 36(30%), 56(46.6%), and 28(23.3%) vs. 61(50.83%), 49(40.83%), and 10(8.33%), respectively. Logistic regression analysis showed that the homozygous GG genotype of PON1 rs662 SNP has a 5-fold increased risk of developing CKD in the Indian population (odds ratio OR =4.75, 95% CI 2.06-10.89, $p < 0.01$) with df:2 and effect size:0.19. A significantly higher frequency of the G allele was observed in CKD patients than in controls (OR 2.16, 95% CI 1.48-3.16, $p < 0.001$) with df:1 and effect size:0.15.

Table 4. Genotypic and allelic distribution of PON1 rs662 gene polymorphism in CKD and control group.

	CKD	**Control**	**Test of association**		
Genotype frequency			**P-value**	**OR**	**95% CI**
AA	36 (30%)	61 (50.83%)		Reference	
AG	56 (46.6%)	49 (40.83%)	0.02	1.94	1.10 – 3.39
GG	28 (23.3%)	10 (8.33%)	<0.001	4.75	2.06 –10.89
Total	120	120			
Allelic frequency			**P-value**	**OR**	**95% CI**
A	128 (53.3%)	171 (71.2%)			
G	112 (46.6%)	69 (28.7%)	0.001	2.16	1.48-3.16

OR-Odds ratio; CI-Confidence interval

The inter-genotypic variation of the serum PON1 levels in the CKD and control groups is shown in Table 5. Our results showed that the serum PON1 level in AA, AG, and GG genotypes of the CKD group was 920.89±154.64, 862.90±164.22, and 770.31±159.91 mIU/mL, respectively. In contrast, the respective values in different genotypes were 1357±268.16, 1217±389.3,4 and 560.71±240.26 mIU/mL in the control group. The inter-genotypic difference in the serum PON1 values was statistically significant in both the CKD and the control group.

Table 5. Correlation of serum PON1 levels with genotypes of PON1 rs662 gene polymorphism in CKD patient and control group.

Genotypes »	**AA**	**AG**	**GG**	**P-value**
CKD Group				
N	36	56	28	<0.001
PON1 (mIU/mL)	920.89±154.64	862.90±164.22	770.31±159.91	
Control group				
N	61	49	10	

PON1 (mIU/mL)	1357±268.16	1217±389.34	560.71±240.26	<0.001

All values are expressed as mean ± standard deviation., PON1- Paraoxanase1,

Our study subdivided CKD patients into different subgroups based on the estimated glomerular filtration rate. There was a significant decrease in the mean serum PON1 level, with a decrease in the estimated glomerular filtration rate as per the stages of the CKD group ($p<0.05$) (Table 6). On the other hand, the mean serum calprotectin level significantly increased with the progression of the CKD stage ($p<0.05$) (Table7).

Table 6. PON1 levels of the study sample according to the stages of chronic kidney disease.

Stages of CKD	**N**	**Serum PON1 level (mIU/mL)**	
Stage 3	46	916.70±146.92	P <0.05
Stage 4	56	841.96 ± 164.23	
Stage 5	18	762.52 ± 184.36	

N-number of CKD patients, PON1-Paraoxonase1

Table 7. Calprotectin levels of the study sample according to the stages of chronic kidney disease.

Stages of CKD	**N**	**Serum Calprotectin level (ng/mL)**	
Stage 3	46	317.72±69.83	P <0.05
Stage 4	56	355.88 ± 60.73	
Stage 5	18	390.075± 53.57	

N-number of CKD patients

Discussion:

The domain of CKD adds up to the unseen burden of non-communicable diseases in our country, leading to an evident increase in morbidity and mortality rates. The unacknowledged fact of being unable to identify the disease in its early stages and limited prevalence data requires introspection and the spread of awareness amongst the local masses. The aetiology of CKD is multifaceted, and factors such as comorbid conditions like diabetes, cardiovascular diseases, lifestyle modifications, genetic influences, and stress play a major role. Accordingly, there is a need to evaluate genetic vulnerability and novel biomarkers in suspected individuals for early diagnosis and prognosis of CKD.

Our study found a strong association between hypertension and diabetes as risk factors for CKD. These findings are similar to a study by Adejumo et al. [11], which presented hypertensive nephropathy and diabetic nephropathy as the main risk factors. The studies Alebiosu et al. [12] and Ulasi et al. [13] had similar conclusions. Oxidative damage is the hallmark of the pathogenesis of CKD. PON1, a key antioxidant, is an important defence mechanism against cardiovascular diseases. It is well reported that the concentration and activity of this enzyme are lowered in patients with coronary artery disease [14-16]. However, there is a relative lack of literature regarding serum PON 1 levels in CKD patients. To the best of our knowledge, there are no previous studies on the genotypic and allelic distribution of the PON 1

rs662 gene polymorphism in CKD patients in India. Thus, our study aimed to correlate this specific gene polymorphism with PON1 concentration in CKD patients and controls.

Our study was suggestive of the fact that the serum PON 1 concentration was significantly lower in CKD patients as compared to the control group (858.69 ± 168.27 mIU/mL vs 1259.03 ± 333.96 mIU/mL, p value< 0.0001). There are documented studies that highlight the fact that patients who are undergoing conservative or hemodialysis treatment have reduced PON 1 activity, and this leads to the risk of developing other comorbidities [17-18]. The reduction in the activity and as the concentration of PON 1 in renal failure patients been stated in various studies [19-22]. These findings suggest that uremic toxins might play a role in PON 1 inactivation, leading to its reduced activity.

The PON1 gene is susceptible to certain genetic variations that may affect its functional role in the body. Our study findings highlighted that the occurrence of homozygous polymorphic genotype (GG) was significantly higher in CKD patients as than in the controls, indicating a nearly 4-fold amplified risk of developing CKD in GG genotype individuals. We found that PON1 level was significantly decreased in patients with GG genotype ($p < 0.001$) as compared to its level in AG or AA genotypes, both in the cases and controls, suggesting that it might be a major determinant for decreased PON1 level in CKD patients. Various documented studies associating PON1 Q192R gene variants with CKD have been inconsistent among distinct population groups. A study by Gupta observed that PON 1 activity was lower in the G/G genotype [23]. On the contrary, another study by Ichikawa et al. [24] reported that serum PON1 activity was lower in subjects with the A/A genotype. It has been observed that the Q variant alloenzyme is associated with a more active isoform of PON1 against lipoprotein oxidation [25-26].

The allele ratio in the aggregate population in our study (A: G = 62.3%: 37.7%) corroborated with the global frequency. The frequency of polymorphic allele ‘G’ was found to be 46.6% in the cases, which was much higher than the 28.8% in the controls. It has been reported that the genetic determinants of the PON1 enzyme have a stronger impact than the contributions of the lifestyle risk factors [27]. Hence, the PON1 Q192R gene variant may be considered an important genetic biomarker of the degree of oxidative stress, contributing to the chronic inflammatory state in CKD, acting via modulation of the concentration and activity of the PON1 enzyme [28].

Calprotectin is a calcium-binding protein from the S100 family with immunomodulatory and proinflammatory effects. Calprotectin leads to cellular damage via TLR4/nuclear factor-kappa B (NF-κB) signalling pathway, inducing inflammatory cytokine secretion, endothelial injury, and atherothrombosis via platelet activation [29-30]. In our study, the serum Calprotectin concentration was found to be significantly higher in CKD patients as compared to controls (346.50 ± 65.56 vs 315.93 ± 48.15 ng/mL, p-value < 0.001). Although some studies have associated increased serum calprotectin levels in hemodialysis patients [28-30], nevertheless, there has been no previous study determining the association of serum calprotectin levels in predialysis CKD patients, as per best of our knowledge. Further, regression analysis studies of serum PON 1 level with serum Calprotectin levels highlighted a negative correlation.

Serum PON1 and Calprotectin levels changed significantly with the transition of CKD stages from stage 3 to stage 5 ($p<0.05$), with an inverse relationship between the two parameters. To the best of our knowledge, there are no prior studies that depict the levels of these inflammatory markers in various stages of CKD. Thus, Serum PON1 and calprotectin may also have a prognostic value in determining the severity of CKD.

The limitation of our study was the relatively smaller sample size, which represented only a fraction of CKD patients admitted to a tertiary care hospital in the specified period. Further studies with larger sample

sizes are recommended for the corroboration of our findings.

Conclusions:

Our findings support the association between PON1 rs662(Q192R) gene polymorphism and low PON1 levels in CKD patients. The polymorphic G allele may be responsible for altering the functionality of the PON1 enzyme, leading to an increased risk of CKD. Thus, PON 1 rs662 polymorphism is an important genetic marker, and together with serum PON1 and calprotectin levels, may become a potential predictive determinant to assist in early intervention and determine the severity of CKD, which may help to decrease the burden of the disease.

Acknowledgements

Data are available on reasonable request. The data can be requested from the corresponding author on reasonable request.

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