RESEARCH PAPER

Serum Paraoxonase-1: A Key Modulator of Lipid Abnormalities and Atherosclerotic Risk in Early Stage Chronic Kidney Disease

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ABSTRACT:
Background Chronic kidney disease (CKD) is associated with significant disturbances in lipid metabolism and increased oxidative stress, both of which contribute to the development of cardiovascular disease. High-density lipoprotein (HDL) is functionally linked to the antioxidant enzyme paraoxonase-1 (PON1), which plays a crucial role in protecting lipoproteins from oxidative modification. In CKD, PON1 activity is known to decline, thereby enhancing atherogenic risk.
Aim To evaluate serum paraoxonase-1 (PON1) levels and examine their association with dyslipidaemia and renal function in patients with Stage 2 CKD.
Materials and Methods A case control study was conducted among Stage 2 CKD patients (n = 45), aged 30–60 years, attending Saveetha Medical College and Hospital. Patients with type 2 diabetes mellitus, obesity, or hypertension were included. Individuals with acute inflammatory conditions or end-stage renal disease were excluded. Serum renal and lipid parameters were analyzed using an automated dry chemistry analyzer, while PON1 levels were estimated by sandwich ELISA. Statistical analysis was performed using SPSS version 15.0.

Results All CKD patients (100%) demonstrated significantly reduced serum PON1 levels (<3.1 ng/mL). Compared to healthy controls, CKD patients showed significantly elevated serum urea, creatinine, uric acid, triglycerides, total cholesterol, LDL, and VLDL levels ($p < 0.01$). In contrast, HDL and serum PON1 levels were significantly decreased ($p < 0.01$). Reduced PON1 levels showed a strong correlation with impaired lipid metabolism and markers of renal dysfunction.

Conclusion Serum PON1 activity is markedly reduced in Stage 2 CKD patients and is associated with oxidative stress and dyslipidaemia-driven atherogenesis. PON1 may serve as a valuable biomarker and a potential therapeutic target for early cardiovascular risk reduction in patients with CKD.

Keywords: Chronic kidney disease Stage 2, Serum Paraoxonase 1, Dyslipidaemia, Oxidative stress, Cardiovascular disease, HDL, LDL

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by progressive loss of renal function accompanied by a profound dysregulation of lipid metabolism. Individuals with CKD, including those in stage 2, exhibit a distinct pattern of dyslipidemia marked by increased plasma triglyceride concentrations, reduced high-density lipoprotein (HDL) levels, and an accumulation of highly atherogenic small, dense low-density lipoprotein particles[1 , 2].Importantly, these lipid abnormalities are not merely quantitative but extend to qualitative impairments in lipid particle composition and function, further heightening the risk for developing premature atherosclerosis [3,4] .Among the cardioprotective mechanisms mediated by HDL is its antioxidant activity, primarily conferred by paraoxonase 1 (PON1), an HDL-associated enzyme synthesized in the liver [5]. PON1 exerts a pivotal protective effect against atherogenesis via hydrolyzing lipid peroxides and impeding oxidative modification of LDL particles—a process integral to foam cell formation and atherosclerotic plaque development [6]. Notably, serum PON1 activity has emerged as a potential biomarker reflective of systemic oxidative stress burden and cardiovascular risk, with lower PON1 activities consistently associated with increased incidence of major cardiovascular events.In

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CKD patients, multiple interrelated mechanisms converge to compromise both lipid homeostasis and the antioxidative defences of HDL. Oxidative stress, inflammation, and uremic toxins prevalent in CKD diminish the activity and concentration of PON1, thereby impairing HDL's capacity to detoxify oxidized lipids and maintain endothelial function [7]. Recent meta-analytic evidence indicates a marked reduction in both paraoxonase and aryl esterase activities of PON1 across all stages of CKD, with a pronounced decline observed as CKD progresses. This decline in PON1 activity magnifies the susceptibility of LDL and other apolipoprotein B-containing particles to oxidative modification, potentiating the generation of pro-inflammatory, pro-atherogenic lipid species [8,9]. Consequently, the interplay between altered lipid profiles and impaired PON1-mediated antioxidant defence constitutes a central axis in the pathogenesis of atherosclerosis in CKD stage 2 patients. The loss of PON1 activity not only facilitates lipid peroxidation but also propagates inflammatory cascades within the vascular wall, fostering the development and progression of atherosclerotic lesions.

MATERIALS AND METHODS:

Participants:

Inclusion criteria: CKD stage 2 patients aged 30–60 years, with diagnosed dyslipidaemia per NKF KDOQI guidelines and comorbid conditions like type 2 diabetes mellitus, obesity, or hypertension.

Exclusion criteria: End-stage renal disease, acute infections, inflammatory diseases.

Sample Collection:

Blood Samples will be collected from two chronic kidney disease 2 patients from Saveetha Medical College and Hospital. 10 ml of blood will be collected from the antecubital vein under aseptic conditions. Serum is separated after centrifugation. Handle and store specimens in stoppered containers to avoid contamination and evaporation. Refrigerated at - 20 ˚ C (long-term storage)

Biochemical Analysis:

Renal function tests (urea, creatinine) and lipid markers measured via Vitros 5600 dry chemistry analyzer. Lipid profile estimation included total cholesterol (CHOD–PAP method), triglycerides (GPO–PAP method), and HDL cholesterol (indirect precipitation method). LDL and VLDL cholesterol were calculated using the Friedewald formula, excluding samples with triglycerides >400 mg/dL. All assays were performed following the manufacturer's instructions with appropriate quality control, and reference ranges were as per standard clinical laboratory guidelines. Serum PON1 levels assessed using sandwich ELISA. The assay procedure involves running all standards and samples in duplicates or triplicates with a standard curve for each assay. First, 100 µL of standard diluent, standards, and samples are added to the respective wells and incubated for 80 minutes at 37 °C. After washing the plate four times, 100 µL of biotinylated antibody working solution is added and incubated for 50 minutes at 37 °C, followed by another wash. Then, 100 µL of Streptavidin-HRP conjugate is added, incubated for 50 minutes, and washed again. Next, 100 µL of TMB substrate is added, and the mixture is incubated for 10 minutes at 37 °C without shaking. The reaction is stopped with 100 µL of stop solution, changing the colour from blue to yellow. Absorbance is read at 450 nm within 10–15 minutes. The mean absorbance values of standards are plotted against concentration to generate a standard curve, from which sample concentrations are determined, with dilution adjustments as necessary.

Statistical Analysis:

One-way ANOVA, conducted using SPSS v15.0. P-values < 0.05 are considered statistically significant.

Ethical clearance:005/04/2024/IEC/SMCH

RESULTS:

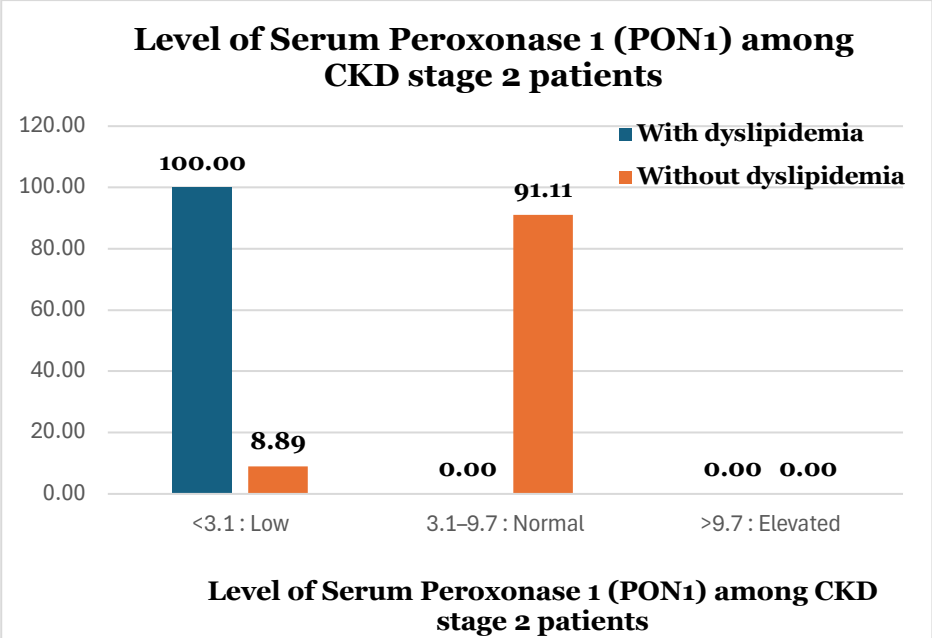
Table 1 presents the frequency and percentage distribution of Serum Paraoxonase 1 (PON1) levels in patients with CKD Stage 2. Among all patients (n = 45), 100% exhibited low PON1 levels (< 3.1 ng/mL), while none had normal or elevated levels.

Table 1: Frequency and percentage distribution of levels of Serum Paraoxonase 1 among CKD stage 2 patients with and without dyslipidaemia.

Level of Serums	Serum Paraoxonase 1 (PON1)			
	With dyslipidaemia		Without dyslipidaemia	
	F	%	F	%
Low	45	100.00	4	8.89
Normal	0	0.00	41	91.11
Elevated/High	0	0.00	0	0.00

These findings highlight a consistent reduction in antioxidant enzyme activity among CKD Stage 2 patients, suggesting a strong association with oxidative stress and dyslipidaemia.

Figure 1: Distribution of Serum Paraoxonase 1 (PON1) Levels among CKD Stage 2 Patients



Overall, the control group exhibited a strongly favourable biochemical profile, with optimal antioxidant enzyme activity and minimal oxidative damage, thereby providing a reliable baseline for comparison with CKD patient groups.

Figure 2: Percentage distribution of levels of Serum Paraoxonase 1 in the control group

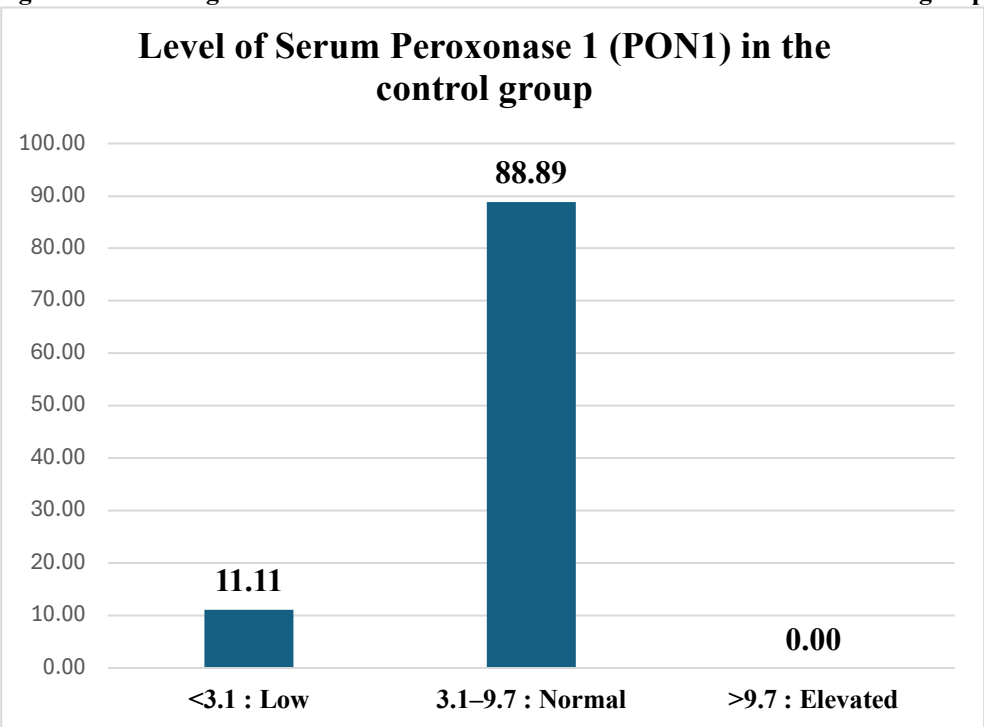


Table 2: Comparison of Biochemical Parameters between CKD Stage 2 Patients and Control Group

Table 2 shows the comparative analysis of renal and lipid profile parameters, including Serum PON1 levels, between CKD Stage 2 patients and healthy controls.

Parameter	Control (Mean ± SD)	CKD Stage 2 (Mean ± SD)	P-value
Urea (mg/dL)	26.27 ± 7.23	75.13 ± 7.36	< 0.01
Creatinine (mg/dL)	0.72 ± 0.35	1.24 ± 0.18	< 0.01
Uric Acid (mg/dL)	4.28 ± 1.33	5.77 ± 1.79	< 0.01
Triglycerides (mg/dL)	87.09 ± 10.33	164.78 ± 2.70	< 0.01
Total Cholesterol (mg/dL)	114.84 ± 17.19	217.00 ± 3.66	< 0.01
HDL Cholesterol (mg/dL)	61.00 ± 6.46	31.16 ± 9.31	< 0.01
VLDL Cholesterol (mg/dL)	18.36 ± 4.82	36.04 ± 7.36	< 0.01
LDL Cholesterol (mg/dL)	73.60 ± 8.94	147.89 ± 3.91	< 0.01
Serum PON1 level (ng/mL)	4.05 ± 0.78	0.95 ± 0.26	< 0.01

Table 3: Level of Serum Paraoxonase 1 among the CKD 2 patients across stages with and without dyslipidaemia.

Stages	Status of dyslipidaemia	Serum Paraoxonase 1 ng/ml			Mean difference	F-value	p-value
		Mean	S. D	Variance			
Stage 2	With	0.848	0.081	0.007	4.485173	162.8548	< 0.01
	Without	5.333	1.694	2.870			
	Without	5.674	1.589	2.526			
Control group		4.054047	0.784814	0.615933	-	-	-

Table 3 presents the comparison of Serum Paraoxonase 1 (PON1) levels (ng/mL) among CKD patients across stages, differentiating between those with and without dyslipidaemia, along with values for the control group. Patients with CKD Stage 2 showed significantly elevated levels of urea, creatinine, uric acid, triglycerides, total cholesterol, VLDL, and LDL compared to the control group ($p < 0.01$). Conversely, HDL and Serum PON1 levels were significantly decreased in the CKD group. These results indicate marked dysregulation of both renal and lipid metabolic parameters and reduced antioxidant defence in patients with CKD Stage 2. Understanding these mechanistic links is of considerable clinical relevance, as strict control of dyslipidaemia and strategies to preserve or enhance PON1 activity may offer promising therapeutic avenues for reducing cardiovascular morbidity and mortality in early-stage CKD.

DISCUSSION:

Patients with chronic kidney disease (CKD), even at early stages such as CKD stage 2, exhibit profound alterations in lipid metabolism that collectively create a highly atherogenic environment. These changes include increased serum triglycerides, the accumulation of small, dense low-density lipoprotein particles, and a significant reduction in both the concentration and functional quality of high-density lipoprotein (HDL). Notably, these lipid abnormalities go beyond simple dysregulation, encompassing structural and compositional alterations in lipoproteins that promote their oxidation and removal from circulation via non-traditional pathways, thereby predisposing patients to premature atherosclerosis PON1, a key HDL-associated esterase synthesized in the liver, is recognized as a crucial determinant of HDL's antioxidative and anti-inflammatory properties . In functional terms, PON1 hydrolyzes oxidized phospholipids and lipid peroxides present on both LDL and HDL particles, impeding the oxidative and inflammatory cascade that underlies atherogenesis . Experimental and epidemiological evidence demonstrate that reduced PON1 activity translates into impaired detoxification of lipid hydroperoxides, thereby facilitating oxidative modification of LDL— a critical event in foam cell formation and plaque development . Indeed, lower serum PON1 activity is consistently associated with augmented systemic lipid peroxidation and increased cardiovascular risk, underscoring its antiatherogenic potential [10].

The pathophysiological context of CKD is especially relevant here, as mounting evidence from meta-analyses has shown a striking reduction in both the paraoxonase and aryl esterase activities of PON1 in patients with CKD compared to healthy controls [11]. This decline in antioxidant defence is linked not only to intrinsic renal impairment but also to factors such as uremic toxins, inflammation, heightened oxidative stress, and disturbances in gut microbiota, all of which are prevalent in CKD and compound oxidative burden [12]. As CKD progresses, this reduction in PON1 activity becomes more pronounced, which aligns with the stepwise increase in atherosclerotic complications noted clinically in later stages of CKD.Hybridizing these mechanisms, it becomes clear that reduced PON1 activity in CKD patients acts in concert with the altered lipid profile to amplify atherogenic risk. CKD-related dyslipidaemia especially the preponderance of LDL and dysfunctional HDL provides abundant substrate for lipid peroxidation, a process only partially checked by the diminished antioxidant capacity of low-activity PON1. Once lipoproteins are oxidized, their uptake by vascular macrophages and subsequent foam cell transformation are accelerated, triggering both local

arterial inflammation and systemic oxidative stress. The deficiency of functional PON1 thus not only accelerates LDL oxidation but also undermines HDL's traditional roles in reverse cholesterol transport and endothelial protection [13]. Furthermore, genetic polymorphisms and environmental modulators of PON1 (e.g., dietary phytochemicals) may also influence its functional expression and activity, suggesting a spectrum of susceptibility to atherosclerosis among CKD patients [14]. This underlines the emerging notion that therapeutic strategies to boost PON1 activity, whether by pharmacological agents or nutritional intervention, hold promise for augmenting antioxidant defences and mitigating cardiovascular risk in CKD. Importantly, the present findings position PON1 not merely as a marker but a mechanistic link between renal dysfunction, disordered lipoprotein metabolism, and accelerated atherogenesis [15]. The growing number of patients, the high stakes of the end-stage renal disease movement, and the limited visibility of persistent kidney infection (CKD) place a significant burden on the healthcare system [16]. A measure of small dense low-density lipoprotein particles, which are strongly linked to a number of metabolic and vascular disorders, is the ratio of triglycerides (TG) to high-density lipoprotein (HDL) cholesterol [17]. ROS levels surpass the body's antioxidant capacity, and oxidative stress results in aberrant apoptosis and inflammation. ROS are increased by metabolic syndrome and dyslipidaemia[18]. Interventions targeting the preservation or enhancement of PON1 activity, alongside established lipid-lowering therapies, may therefore represent a dual-pronged approach to reducing the incidence of cardiovascular events in early-stage CKD.

CONCLUSION:

The present study underscores the crucial role of serum paraoxonase 1 (PON1) in modulating the altered lipid profile and its significant contribution to early atherogenesis in patients with chronic kidney disease (CKD) stage 2. Compelling evidence confirms that even in early-stage CKD, patients display prominent dyslipidemia, including elevated triglycerides, increased small, dense LDL, and impaired HDL function, which collectively promote a pro-atherogenic environment. Central to this process is a reduction in PON1 activity, an enzyme bound to HDL that facilitates its antioxidative and anti-inflammatory functions. The diminished activity of PON1 in CKD stage 2 leads to increased oxidative modification of both LDL and HDL particles, further amplifying lipid peroxidation, endothelial dysfunction, and vascular inflammation, hallmarks of early atherosclerotic lesion formation.

CONFLICT OF INTEREST:

No conflicts of interest regarding this investigation**.**

AUTHOR CONTRIBUTION

The conception and design of the study, data collection, and laboratory experiments. Prepared the initial draft of the manuscript, analysed and interpreted the results, reviewed relevant literature, and were involved in the statistical analysis, data interpretation, and subsequent revision and finalisation of the manuscript.

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