VER
Vascular & Endovascular Review

Evaluating the Relationship Between Nitric Oxide, Lipid Profile and Cardiovascular Risk in Chronic Kidney Disease: A Cross-sectional Study

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ABSTRACT

Background: Chronic kidney disease (CKD) is strongly linked to increased cardiovascular risk, primarily due to endothelial dysfunction (ED) and accelerated atherosclerosis. A major factor contributing to ED is reduced nitric oxide (NO) bioavailability, often resulting from heightened oxidative stress in CKD. As NO plays a critical role in maintaining vascular integrity, its deficiency may exacerbate both renal and cardiovascular complications. This study aimed to assess the association between serum NO levels, lipid profile, and cardiovascular risk in CKD patients.

Materials and Methods: A total of 220 individuals participated in this case-control study, comprising 110 CKD patients [75 males (68.18%), 35 females (31.81%)] and 110 age- and sex-matched healthy controls. Serum NO levels were determined using the Griess reaction method. Biochemical analyses included measurements of urea, creatinine, total cholesterol, triglycerides, HDL-C, LDL-C, and VLDL-C. Cardiovascular risk was evaluated using the cardiac risk ratio. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Statistical analyses were performed using SPSS version 30.0.

Results: CKD patients exhibited significantly higher levels of urea, creatinine, TC, TG, LDL-C, VLDL-C, and cardiac risk ratio as compared to controls ($p < 0.001$). In contrast, HDL-C and NO levels were significantly lower in the CKD group ($p < 0.001$). NO levels showed a positive correlation with eGFR and a negative correlation with creatinine, indicating a link between reduced NO levels and worsening renal function. No significant associations were observed between NO and lipid profile parameters.

Conclusion: The findings suggest that CKD is associated with significant dyslipidemia and reduced nitric oxide levels, both of which may contribute to increased cardiovascular risk. The observed relationships between NO and renal function markers highlight the potential utility of NO as a biomarker for endothelial dysfunction in CKD patients..

KEYWORDS: Cardiovascular risk, chronic kidney disease, endothelial dysfunction, lipid profile, nitric oxide, oxidative stress, eGFR

How to Cite: Shamiunnisha Parveen, Jaya Jain , Rashmi Gulia (2025) Evaluating the relationship between Nitric oxide, lipid profile and cardiovascular risk in chronic kidney disease: A cross- sectional study., Vascular and Endovascular Review, Vol.8, No.18s, 322-327.

INTRODUCTION

Chronic kidney disease (CKD) is a significant global public health issue, with its prevalence rising due to increased life expectancy. CKD patients are at a high risk of progression to end-stage renal disease and cardiovascular disease (CVD) [1,2]. The risk of mortality is notably higher in advanced stages of CKD compared to earlier stages. Multiple risk factors contribute to CKD, including classical ones like hypertension, diabetes, and dyslipidemia, as well as non-classical factors such as inflammation and malnutrition [3].

Nitric oxide (NO) and its metabolites (nitrite and nitrate) are key signaling molecules that regulate blood flow, neurotransmission, and host defense mechanisms. In CKD, endothelial damage and subsequent renal hypoxia disrupt NO production, exacerbating microcirculatory dysfunction. NO metabolites may also serve as biomarkers for evaluating vascular damage in CKD patients [4]. Endothelial dysfunction in CKD results in reduced nitric oxide availability, which is crucial for maintaining vascular tone and regulating blood flow. The reduction in NO production is associated with increased blood pressure and vascular resistance, further exacerbating cardiovascular complications in CKD patients [5,6]. CKD is characterized by systemic low-grade inflammation, which has been implicated in the pathogenesis of both cardiovascular and kidney diseases [7]. This inflammation accelerates atherosclerosis and damages the vascular endothelium, a key factor for both coronary syndrome and CKD progression [1].

Furthermore, chronic kidney disease is linked with dyslipidemia comprised of raised triglycerides and low HDL-C. Studies have found that higher total cholesterol, higher non-HDL-cholesterol and lower HDL-C were significantly associated with an increased risk of developing renal dysfunction. The assessment of lipid profile along with other variables is important for preventing further

progression or formation of CKD. Hence, early determination and management of the risk factors for CKD patients play an important role in development of more effective screening and treatment strategies to reduce mortality and morbidity in these patients. Dyslipidemia among CKD negatively influences the frequency and/or duration of hospitalization [8].

Hence, this study was designed to evaluate the alterations in serum lipid profile and estimation of nitric oxide levels, in order to assess their correlation with cardiovascular risk in CKD patients. By examining these factors, we seek to understand the underlying mechanisms contributing to endothelial dysfunction, renal progression, and cardiovascular complications in CKD patients.

MATERIALS AND METHODS

In this analytical case-control study one hundred ten (n=110) cases of chronic kidney disease were recruited from Medicine Outpatient Department at Index Medical College and Hospital, Indore, Madhya Pradesh from January 2024 to December 2024. Equal number (n=110) of age and sex-matched apparently healthy volunteers were included as controls. Prior to commencement of experimentation, the purpose of study was explained to every participant and informed written consent was obtained. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and in the year 1964 Helsinki's declaration and its later amendments or comparable ethical standards. The ethical clearance was obtained from Institutional Ethical Committee for Human Research (IEC-HR).

CKD was diagnosed according to the Kidney Disease: Initiative and Global Outcomes (KDIGO) guidelines [9]. The effect of possible confounders was eliminated by excluding patients with acute renal failure, acute on CKD, a history of smoking, congestive heart failure, or current pregnancy. Blood samples (5ml of fasting venous blood) were collected in plain vials from each participant under aseptic conditions. After the blood clotted, serum was separated by centrifugation of blood sample at 3000 rpm for 10 minutes and used for estimation of various biochemical parameters.

Measurement of serum Nitric oxide and Biochemical parameters

The NO content was determined using the Griess spectrophotometric assay [10]. Routine biochemical investigations such as kidney function test (urea and creatinine) and lipid profile (including TC, HDL-C and triglycerides) were carried out as per standard laboratory protocols using commercial kits on fully automated clinical chemistry analyzer **(**Erba Mannheim, Germany)**.** LDL-C and VLDL-C levels were calculated using Friedewald's equation [11]. VLDL-C (mg/dL) = Triglycerides / 5. LDL-C (mg/dL) = TC – (HDL-C + VLDL-C).

Statistical analysis:

Data analysis was carried out using the SPSS, version 30.0. Graphs were generated using Graph Pad Prism software, version 10.5. Descriptive statistics, including mean and standard deviation, were calculated for quantitative variables. Group comparisons were conducted using the independent Student's t-test. Pearson's correlation coefficient (r) was used to assess correlations between variables. A p-value of <0.05 was considered statistically significant (S), <0.001 was considered highly significant (H.S).

RESULTS

Renal function, as assessed by estimated glomerular filtration rate (eGFR), was significantly reduced in CKD patients compared to healthy controls ($p < 0.001$). In contrast, serum urea and creatinine levels were significantly elevated in CKD patients relative to controls ($p < 0.001$), indicating marked renal impairment in the CKD group, as shown in **Table 1**.

Table 1 : Comparison of various measured parameters in cases and healthy controls.

Parameters measured	Healthy controls (n=110)	CKD cases (n=110)	p-value
eGFR(ml/min/1.73m^2)	104.4±9.18	26.88±12.56*	<0.001
Urea(mg/dL)	32.70±7.53	109.0±30.31*	<0.001
Creatinine(mg/dL)	0.81±0.16	3.26±1.52*	<0.001

Data are expressed as mean ± SD. Unpaired t-test was applied for comparison. *Significantly different from healthy controls (p<0.001).

A significant reduction in serum nitric oxide levels was observed in CKD patients (13.54±7.10µmol/L) as compared to healthy controls (31.79±12.30µmol/L), indicating significant endothelial dysfunction in the CKD group (**Figure 1)**.

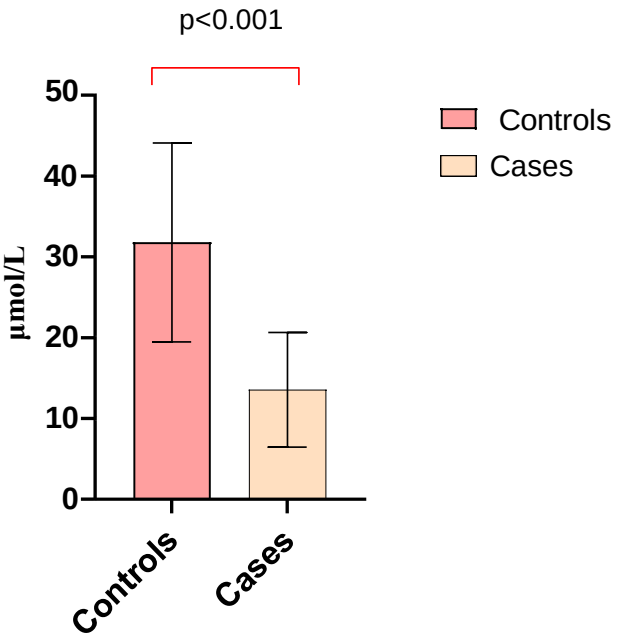

Figure1: Comparison of nitric oxide concentration between CKD and healthy controls

CKD patients exhibited significantly higher total cholesterol, triglycerides, LDL-C, VLDL-C, and cardiac risk ratio, and significantly lower HDL-C, indicating dyslipidemia and increased cardiovascular risk, as presented in **Table 2**.

Table 2: Lipid profile comparison between CKD and healthy controls.

Parameters	Healthy controls (n=110)	CKD cases (n=110)	p-value
TC(mg/dL)	167.50±12.16	201.6±40.67*	<0.001
Triglyceride(mg/ dL)	124.33±31.03	179.9±37.74*	<0.001
HDL-C(mg/ dL)	57.80±15.22	48.05±30.12	0.003
VLDL-C(mg/ dL)	24.86±6.20	35.97±7.54*	<0.001
LDL-C(mg/ dL)	134.56±19.60	189.6±50.71*	<0.001
Cardiac risk ratio	3.11±0.88	5.97±3.24*	<0.001

Data are expressed as mean ± SD. Unpaired t-test was applied for comparison. *Significantly different from healthy control (p<0.001). TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

Correlation analysis revealed a significant positive correlation between nitric oxide levels and eGFR ($r = 0.258$, $p = 0.006$), and a significant negative correlation with serum creatinine ($r = –0.282$, $p = 0.002$), suggesting an association between declining renal function and reduced NO availability. No significant correlations were observed between NO and urea or any of the lipid profile parameters, as detailed in **Table 3**.

Table 3: Correlation of nitric oxide with renal and lipid parameters in CKD patients

NO		
Parameters	**Pearson coefficient (r)**	**p -value**
eGFR	0.258	0.006*
Urea	-0.159	0.097
Creatinine	-0.282	0.002*
TC	0.023	0.805
TG	-0.011	0.906
HDL-C	0.005	0.952
VLDL-C	-0.011	0.906
LDL-C	0.013	0.884
Cardiac risk ratio	0.019	0.840

*Correlation (r) is significant at the 0.01 level (2-tailed). Pearson's correlation was applied to determine the correlation of nitric oxide with renal and lipid parameters in CKD cases. NO; Nitric oxide: TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol

DISCUSSION

Chronic kidney disease remains a major contributor to global morbidity and mortality. A critical factor driving CKD progression is oxidative stress, which is detectable even in early disease stages and is linked to both worsening renal function and elevated cardiovascular risk [12]. Nitric oxide, a reactive gas with vasodilatory, neurotransmitter, and immunomodulatory functions, plays a vital role in vascular health. As reported earlier, in CKD, excess oxidative stress leads to increased generation of reactive oxygen species (ROS), which in turn decreases NO levels [4]. Existing evidence highlights that reduced NO bioavailability and increased oxidative stress are central to both renal and cardiovascular complications [13].

In the present study **(Figure 1),** NO levels were significantly lower in CKD patients as compared to controls, indicating impaired endothelial function. Additionally, CKD patients showed elevated serum urea and creatinine levels and a markedly reduced eGFR in contrast to the control group, reflecting severe renal dysfunction.

The hypothesis that NO levels are decreased in CKD is supported by the findings of the present study. Under normal physiological conditions, endothelial nitric oxide synthase (eNOS) generates NO, promoting vascular protection. However, in CKD, eNOS dysfunction or "uncoupling" may occur, where NO interacts with superoxide radicals to form peroxynitrite, exacerbating oxidative damage and contributing to vascular pathology [14].

In Contrast to our findings several authors have also reported elevated NO levels**,** Meenakshi SR et al. [15] reported elevated NO levels in patients with chronic renal failure undergoing maintenance hemodialysis, attributing this to cytokine-mediated induction of inducible NOS (iNOS) and increased NO release due to platelet activation in uremia. While increased NO levels may initially seem protective, they could promote cytotoxicity and contribute to dialysis-related complications via nitrosative stress similarly, Azouaou LT et al**.** [16] observed elevated NO, possibly reflecting a compensatory mechanism against oxidative stress

Reddy YS et al. [17] reported significantly lower NO across CKD stages, Narawade SY et al. [18] found a consistent reduction in NO among both CKD and ESRD patients, proposing this decrease as a marker of disease progression. Similarly, Purwati DD et al. [19] demonstrated significantly reduced NO levels in non-dialyzed CKD patients, reinforcing the concept of NO deficiency in CKD pathogenesis. Ahmarinezhad Z et al. [20] also found an inverse relationship between NO metabolites and oxidative stress markers in CKD patients.

Lipid profile analysis (**Table 2**) revealed that CKD patients exhibited atherogenic dyslipidemia, characterized by elevated total cholesterol, triglycerides, LDL-C, and VLDL-C, along with reduced HDL-C. This pattern is typical in CKD and contributes to increased cardiovascular risk. Lakshmi MS et al. [21] emphasized the clinical relevance of early lipid derangements such as reduced HDL-C and a low HDL-C/total cholesterol ratio as markers of coronary risk in CKD patients.

In the present study, nitric oxide levels showed a significant positive correlation with eGFR and a negative correlation with serum creatinine, indicating an association between reduced NO availability and declining renal function. However, NO did not show significant correlations with lipid profile parameters or cardiovascular risk ratios. These findings suggest that while NO reduction is closely linked to renal impairment, its relationship with lipid abnormalities in CKD may be limited or influenced by other pathophysiological factors **(Table 3).**rting these findings**,** El-Gamacy et al. [22] documented a decline in NO from early to late

stages of CKD and reported positive correlations with eGFR and HDL-C and negative correlations with urea, creatinine, and lipid parameters in advanced
stages. Batkol K et al. [23] further reported associations between NO metabolites (NOx) and indicators of renal function, inflammation, and vascular injury, suggesting their potential as biomarkers for vascular health in CKD, independent of traditional cardiovascular risk factors. Our findings suggest that reduced nitric oxide (NO) levels are closely linked to declining renal function in CKD, as indicated by their correlation with eGFR and creatinine. While dyslipidemia was evident in CKD patients, NO showed no significant association with lipid parameters, indicating its role is more specific to endothelial dysfunction and renal impairment rather than lipid-related cardiovascular risk.

Existing data suggest that NO regulates many aspects of normal renal homeostasis, and any abnormality in endogenous NO production may lead to nephropathy. It has been reported that exogenous supplementation of L-arginine ameliorated the progression of renal disease in rats with subtotal nephrectomy [24], indicating the potential use of L-arginine as a supplement in CKD patients.

CONCLUSION

This study demonstrated a significant reduction in serum nitric oxide levels in patients with chronic kidney disease, indicating endothelial dysfunction. NO levels showed a significant positive correlation with estimated glomerular filtration rate and a negative correlation with serum creatinine, reflecting an association between declining renal function and reduced NO availability. However, no significant correlations were observed between NO and lipid profile parameters. Additionally, CKD patients exhibited atherogenic dyslipidemia, characterized by elevated triglycerides, total cholesterol, LDL-C, VLDL-C, and reduced HDL-C, contributing to heightened cardiovascular risk. These findings suggest that while NO deficiency is more closely linked to renal dysfunction than to lipid abnormalities, its monitoring may still provide insights into vascular health in CKD. Targeted interventions, including antioxidant therapies, may help mitigate endothelial damage and disease progression.

ACKNOWLEDGMENT

We sincerely thank the faculty, staff, and laboratory personnel of Index Medical College & Hospital, Indore, for their guidance and support. We are also grateful to the study participants and the Institutional Ethics Committee for their valuable cooperation and approval.

Conflicts of interest: None

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