Original Research Paper

Volume - 15 | Issue - 10 | October - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Medicine

EVALUATION OF ASSOCIATION OF DYSLIPIDEMIA AND ATHEROGENIC INDEX OF PLASMA WITH VARIOUS CHRONIC KIDNEY DISEASE: A CROSS-SECTIONAL STUDY

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ABSTRACT **Background:** Chronic kidney disease (CKD) is associated with increased cardiovascular risk, partly due to dyslipidemia. Patients often develop lipid abnormalities early, which worsen with disease progression. **Objective:** To evaluate the association between dyslipidemia, atherogenic index of plasma (AIP), and severity of ckd. **Methods:** A cross-sectional study was conducted among 90 CKD patients. Lipid profile, estimated glomerular filtration rate (eGFR), and AIP were measured and correlated with CKD stages. **Results:** The mean age of participants was 55.2 years, with a male predominance (61.1%). Most were in stage 5 CKD (43.3%), followed by stage 4 (34.4%) and stage 3 (22.2%). Mean AIP values increased with CKD stage. AIP showed a significant negative correlation with eGFR ($r = -0.518$, $p<0.001$). Total cholesterol, triglycerides, HDL, VLDL, and AIP were significantly associated with CKD stages, while LDL was not. **Conclusion:** Dyslipidemia worsens with CKD progression and is reflected by higher AIP values. Stage 5 CKD carries the highest atherogenic risk, highlighting the importance of early monitoring and intervention.

KEYWORDS : Chronic kidney disease, Dyslipidemia, Atherogenic index, eGFR

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as either kidney damage or decreased kidney function with decreased glomerular filtration rate (eGFR) for more than three or more months.[1] Individuals with CKD are at an increased risk for cardiovascular disease compared to the general population.[2] Lipoprotein(a) (Lp(a)) is a cholesterol-rich particle existing in human plasma, first described by Berg in 1963.[3]

CKD, with its high prevalence, morbidity and mortality is an important public health problem. CKD and other noncommunicable diseases have often been ignored in the face of persistent challenges from and competition for resources for communicable diseases and high infant and maternal mortality.[4] The reported prevalence of CKD in different regions ranges from <1% to 13%, and recently data from the International Society of Nephrology's Kidney Disease Data Center Study reported a prevalence of 17%.[5]

The most widely used criteria are a decreased glomerular filtration rate (GFR <60 mL/min per 1.73 m^2) or urinary albumin creatinine ratio ≥30 mg/g. Patients with CKD are at an increased risk of premature mortality, independently of the criterion (GFR or albuminuria) used for diagnosis.[6-10] In CKD leading factor for morbidity and mortality is cardiovascular disease. The risk of cardiovascular complications is increases as CKD progresses. Dyslipidemia is one of the leading risk causes for cardiovascular complication in normal healthy individual as well as in CKD.[11]

At the earlier stages of CKD, patients develop both quantitative and qualitative abnormalities in lipoprotein metabolism which usually follows a worsening course as renal function deteriorates regardless of the aetiology of CKD. Early in CKD, there are alterations in apolipoproteins, lipid transfer proteins, lipolytic enzymes and lipoprotein receptors. As renal function declines, triglyceride (TG) concentrations increase and high-density lipoprotein cholesterol (HDLc) concentrations decline and become dysfunctional, while levels of low-density lipoprotein cholesterol (LDL-C) remain within the normal range or become slightly low.[12-14]

Furthermore, there is progressive accumulation of small less dense and oxidised LDL particles, decreased concentration of apolipoprotein A-containing lipoproteins and increased concentrations of TG-rich apolipoprotein B-containing lipoproteins as glomerular filtration rate (GFR) declines (Stages 4 and 5). Together these, abnormalities contribute to the risk of arteriosclerotic cardiovascular diseases which adversely affects the progression of renal disease and contributes to cardiovascular morbidity and mortality.[15]

In Chronic Kidney disease, reduced HDL causes declined reversed cholesterol transport system. Most of the studies are done to find a best indicator for atherogenic factor in blood which can calculate the cardiovascular risk and also helpful for monitoring the treatment response. It revealed that atherogenic index of plasma (AIP) will be good predictor for assessing the risk factor of cardiovascular disease.[16] Atherogenic index of plasma reveals the association between atherogenic and protective lipoprotein and it is also related to dimension of pre atherogenic and antiatherogenic lipoprotein level. Based on the AIP value cardiovascular risk will be assessed. AIP value lower than 0.11 consider low risk, If AIP ranges between 0.11-0.21 considered as an intermediate risk and AIP value >0.21 is considered as high risk.[17]

Furthermore, renal dysfunction is associated with disturbance of metabolism in lipoprotein and it leads to dyslipidemia and atherogenic lipoprotein accumulation. The dyslipidemia spectrum in CKD will differs from normal population.[18] The lipoproteins alteration is also depended upon on CKD stage. With these viewpoints the current study was designed with the main objectives to find the association between dyslipidemia and atherogenic index of plasma with severity of CKD.

Methodology

Study Design And Patients

This is a cross-sectional study conducted with total of 90 patients diagnosed with CKD at Department of General Medicine, Bapuji hospital attached to J. J. M. Medical College, Davangere, Karnataka. The ethical committee approval was obtained before the conduct of study.

Inclusion Criteria

1. **Age:** ≥18 years
2. Diagnosed as CKD
3. Sonological findings suggestive of CKD
4. Who are willing to give consent

Exclusion Criteria

1. **Age:** <18 years old
2. On treatment with lipid lowering drugs, corticosteroids, androgens and oral contraceptive pills, highly active antiretroviral therapy
3. Medication with immune-suppressive drugs
4. Diagnosed as hypothyroid
5. With liver disease, nephrotic syndrome, ischemic heart disease
6. Who are not willing to give consent

Data Collection And Assessment Parameters

After obtaining informed consent, the demographic details, such as age, gender, nature of underlying renal disease, treatment history if any, duration and frequency of haemodialysis (if applicable), family history of non-communicable disease and kidney disease were recorded in a structured proforma.

A thorough history taking coupled with a meticulous physical examination wase done for all the patients included in the study. 5 ml of venous blood was drawn aseptically from the ante-cubital fossa of the patient after an overnight fast for lipid profile determination. Estimated glomerular filtration rate (eGFR) was calculated using following Cockroft–Gault equation.

CCr={((140–age) x weight)/(72xSCr)}x 0.85 (if female)

Abbreviations/Units
CCr (creatinine clearance) = mL/minute
Age = years
Weight = kg
SCr (serum creatinine) = mg/dL

Based on the eGFR rate, chronic kidney disease patients are grouped into five stages as shown in Figure 1.

Adapted From: Valdivielso et al., (2019)[19]

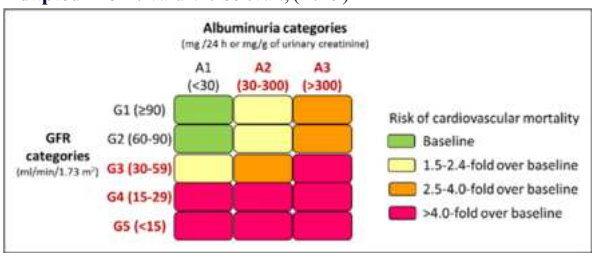

Figure 1: CKD categories according to KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease and heat map of cardiovascular mortality risk.

Atherogenic Index Of Plasma (AIP)
AIP is a good predictor for assessing the risk factor of cardiovascular disease viz. atherosclerosis and coronary heart disease.[16] AIP reveals the association between atherogenic and protective lipoprotein, and it is also related to size of pre-atherogenic and anti-atherogenic lipoprotein particle. Based on the AIP value cardiovascular risk was assessed viz. AIP value <0.11 is considered as low risk, If AIP value ranges between 0.11-0.21 is considered as intermediate risk and AIP value >0.21 is considered as high risk.[17] AIP value was calculated as logarithmic ratio of triglycerides to high density lipoprotein cholesterol [log (TG/HDL-C)].[20]

Statistical Analysis
Data were entered in Microsoft Excel 2021 and statistical analysis was done using IBM Statistical Software for Social Sciences (SPSS) version 22. Categorical variables were represented in the form of percentages and frequencies.

Continuous variables were presented as descriptive statistics (Mean and Standard deviation). Continuous data were compared by independent student t-tests and One-way ANOVA and the correlation assessed by Pearson correlation test. p≤0.05 was considered statistically significant.

RESULTS

The mean age of the study subjects was found to be 55.20 ± 14.40 years. Male predominance was observed (61.11%) as compared to female (38.89%). Majority of the study subjects i.e., 66.67% were with diabetes as comorbid condition followed by 33.33% with hypertension as comorbid condition (Table 1).

Table 1. Distribution Of Study Subjects Based On Demographic And Comorbidities

Variables	Frequency	Percentage
Age (years)	55.20 ± 14.40	
Gender		
Male	55	61.11
Female	35	38.89
Comorbidities		
Diabetes	60	66.67
Hypertension	30	33.33

A total of 40 out of 50 study subjects (44%) underwent hemodialysis; while 56% (50/90) study subjects did not required hemodialysis (Figure 2).

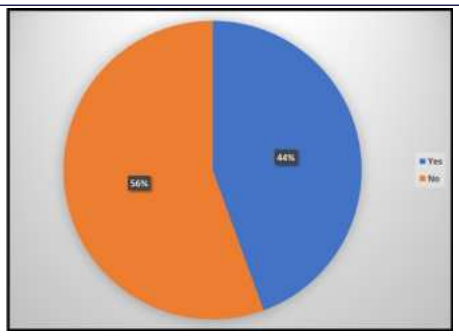

Figure 2. Distribution of study subjects based on hemodialysis status

The distribution of study subjects based on severity of CKD stage was illustrated in Figure 3. Results depicted that majority of the study i.e., 43.33% were diagnosed as CKD stage 5 followed by CKD stage 4 (34.44%) and CKD stage 3 (22.22%).

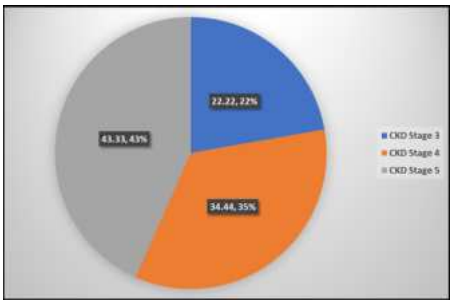

Figure 3. Distribution of study subjects based on severity of CKD

The distribution of study subjects based on AIP value and CKD stage was represented in Table 2. Results revealed that majority of the study i.e., 47.78% (43/90) of study subjects in stage 5 CKD having eGFR of <15 ml/min/1.73 m^2) followed by stage 4 CKD with eGFR of 15-29 ml/min/1.73 m^2 (35/90; 38.89%) and 13.33% (12/90) study subjects in stage 3 CKD having eGFR of 30-59 ml/min/1.73 m^2. These findings implied that mean AIP values increased with increased stages of CKD.

Table 2. Distribution Of Study Subjects Based On Aip Value And Ckd Stage

CKD Stage	Frequency	AIP Value
3	12	0.67 ± 0.12
4	35	0.81 ± 0.09
5	43	0.86 ± 0.15

Values were expressed as mean ± standard deviation (SD)

There was a statistically significant (p<0.001) negative correlation exists between eGFR and AIP values (r = -0.518). These findings inferred that with decreasing eGFR values there is an increase in the AIP (Table 3).

Table 3. Assessment Of Correlation Between eGFRAnd AIP

Variables	Correlation coefficient (r)	p-value
eGFR vs. AIP	-0.518	<0.001

There was a significant correlation exists between lipid profile of study subjects and CKD stages. The lipid parameters viz. total cholesterol (p=0.001), TGL (p<0.0001), HDL (p<0.0001), VLDL (p<0.0001), and AIP (p<0.0001) were significantly correlated with CKD stages. However, LDL was non-significantly (p=0.277) correlated with CKD stages (Table 4). These findings delineated that all the lipid profile parameters increased with increasing CKD stages except HDL which in decreased with increasing CKD stages.

Table 4. Assessment Of Correlation Of Lipid Profile With Stages Of CKD

Lipid profile parameters	CKD Stage	Mean ± SD	p- value
Total cholesterols	3	193.27 ± 16.58	0.001
	4	215.77 ± 20.84	
	5	221.55 ± 26.51	
TGL	3	192.93 ± 47.09	<0.0001
	4	232.48 ± 55.04	

	5	270.18 ± 46.51	
LDL	3	95.60 ± 6.57	0.277
	4	95.55 ± 12.78	
	5	106.13 ± 25.14	
HDL	3	43.07 ± 5.74	<0.0001
	4	39.66 ± 6.20	
	5	40.66 ± 6.62	
VLDL	3	37.40 ± 8.20	<0.0001
	4	44.61 ± 9.92	
	5	53.05 ± 9.16	
AIP	3	0.67 ± 0.12	<0.0001
	4	0.81 ± 0.09	
	5	0.86 ± 0.15	

TGL, Triglycerides; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein; AIP, Atherogenic index of plasma

DISCUSSION

The leading etiology of hospital admissions and death in CKD patients is cardiovascular disease.[21] The spectrum of cardiovascular disease likely begins in the early stages of CKD to reach critical level at the initiation of renal replacement therapy.[21,22] Dyslipidemia, one of the traditional risk factors for coronary artery disease occurs frequently in CKD.[23] However, the pattern of dyslipidemia in CKD patients differs from the general population. Furthermore, AIP will be good predictor for assessing the peril factor of cardiovascular disease.[16] Atherogenic index of plasma revels the association between atherogenic and protective lipoprotein and it is also related to dimension of pre atherogenic and antiatherogenic lipoprotein level.[17] With this context in the current cross-sectional study we aimed to determine the association between dyslipidemia and atherogenic index of plasma with severity of CKD.

Results of our study revealed that, the mean age of the study subjects was found to be 55 years with male predominance. Majority of the study i.e., 43.33% were diagnosed as CKD stage 5 followed by CKD stage 4 (34.44%) and CKD stage 3 (22.22%). AIP values increased with increased stages of CKD. There was statistically significant ($p<0.001$) negative correlation exists between eGFR and AIP values ($r = -0.518$). These findings were comparable with the literature findings reported by various other research investigators.

In a study conducted by Magar et al., showed that CKD patients exhibited dyslipidemia pattern irrespective of the hemodialysis status.[24] These findings were consistent with our study wherein 44% underwent hemodialysis; while 56% study subjects did not required hemodialysis.

Phukan et al, reported that TGL and VLDL of the CKD group was elevated and the HDL-C was decreased when compared with the control group.[25] Raju et al., reported similar findings where in TGL and VLDL of the CKD group was elevated and the HDL-C was decreased when compared with the control group. However, there was no significant difference in serum total cholesterol and LDL-C in both the groups.[26]

Chijioke et al., reported that TC, TGL, HDL-C, LDL-C, and VLDL levels of the CKD patients were significantly ($p<0.05$) different in both sexes on comparing with the control group. The cardiovascular risk indices such as TC/HDL-C, and LDL-C/HDL-C of the study group were higher than that of the control group.[27] In concurrence with literature findings, in our study the lipid parameters viz. total cholesterol ($p=0.001$), TGL ($p<0.0001$), HDL ($p<0.0001$), VLDL ($p<0.0001$), and AIP ($p<0.0001$) were significantly correlated with CKD stages. However, LDL was non-significantly ($p=0.277$) correlated with CKD stages.

Ekonoyan reported that reduced catabolism of the lipoprotein rich triglyceride is one of the basic disturbances of lipoprotein metabolism in kidney disease.[28] High triglyceride levels can be explained by significant increases in the levels of apolipoprotein C-III, which is a potent inhibitor of Lipoprotein lipase.[29,30] In CKD, plasma Lp(a) levels are greatly influenced by the GFR values, and are elevated in the earlier stages of renal impairment.[31]

There are certain limitations of this cross-sectionals study. Firstly, the study was conducted in a small sample size and hence further studies with higher sample size are needed. Secondly, the study lacked a non-CKD control group, and hence randomized studies with case-control groups are warranted.

CONCLUSION

In conclusion, lipid metabolism significantly varies in most patients with renal failure. The results of our current study unequivocally demonstrated that dyslipidemia in CKD tends to worsen as the disease (or stage of CKD) advances. In CKD stages 3 to 5, dyslipidemia may result in an elevated atherogenic index. It is clear that stage 5 of CKD carries a higher risk for atherogenic index, as evidenced by the increased AIP and decreased eGFR. A new understanding of early diagnosis and prognosis of atherogenic risk will be provided by the stage-wise atherogenic index.

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