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Prognostic Value of Atherogenic Index of Plasma, Cardiac Risk Ratio and hs-CRP in Cardiovascular Risk Assessment among Diabetic Nephropathy Patients

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ABSTRACT
Diabetic Nephropathy (DN) is a significant microvascular complication of type 2 diabetes mellitus (T2DM) that increases cardiovascular morbidity and mortality. The Atherogenic Index of Plasma (AIP), Cardiac Risk Ratio (CRR) and high-sensitivity C-reactive protein (hs-CRP) are potential markers for assessing cardiovascular risk in DN patients. This study aimed to investigate the prognostic value of these markers in predicting cardiovascular risk in DN patients. To evaluate the relationship between lipid profile markers (AIP, CRR) and inflammatory marker (hs-CRP) in predicting cardiovascular risk in DN patients and to compare these markers between DN patients and healthy controls. This cross-sectional observational study was conducted at a tertiary care hospital over one year. A total of 70 DN patients and 70 age-and sex-matched healthy controls were included. Lipid profiles, hs-CRP levels, CRR and AIP were measured in all participants. The relationships between these markers and cardiovascular risk were analysed using appropriate statistical tests. DN patients had significantly higher total cholesterol, triglycerides and hs-CRP levels, along with lower HDL levels compared to healthy controls. AIP and CRR were also significantly elevated in DN patients. Patients with macroalbuminuria had significantly higher hs-CRP, CRR and AIP compared to those with microalbuminuria, indicating greater cardiovascular risk. A majority of DN patients with high LDL levels also had hs-CRP levels above 3 mg/L, compounding cardiovascular risk. Elevated AIP, CRR and hs-CRP are strongly associated with increased cardiovascular risk in DN patients, particularly those with macroalbuminuria. These markers provide a more comprehensive assessment of cardiovascular risk than traditional lipid measures alone, underscoring the importance of combining lipid and inflammatory markers in evaluating and managing cardiovascular risk in DN patients.

INTRODUCTION

Diabetes Mellitus Type 2 has emerged as a prevalent non-communicable disease, with its global prevalence soaring over the past two decades due to urbanization, industrialization, sedentary lifestyles and stress[1]. According to the International Diabetes Federation, by 2040, it is estimated that 642 million individuals worldwide will be affected by Diabetes Mellitus. Within India, the number of cases has significantly increased from 32.6 million in 2000-74.2 million in 2021, solidifying its status as the Diabetes capital of the world[2]. Additionally, there are an estimated 39.3 million undiagnosed cases, alongside substantial prevalence rates of Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)[3].

The chronic nature of Diabetes Mellitus leads to numerous complications, both microvascular and macrovascular. Among the microvascular complications, Diabetic Nephropathy (DN) stands out as a prominent contributor to chronic kidney disease (CKD). DN significantly impacts the quality of life and increases the risk of cardiovascular morbidity and mortality[4]. Early identification and management of diabetic complications are imperative for prognosis., however, current screening methods, primarily reliant on renal function tests, often lag behind the onset of complications, particularly Diabetic Nephropathy[5].

Inflammation is a key mechanism in the pathogenesis of diabetic complications. Recognizing the pro-inflammatory state intrinsic to Diabetes Mellitus and its association with endothelial dysfunction, investigations have highlighted elevated levels of inflammatory markers in diabetic populations[6]. Recent research has initiated the process of identifying the inflammatory causes of Diabetic Nephropathy, indicating that inflammation plays a critical role in its pathogenesis. Low-grade inflammation precedes the manifestation of Diabetic Nephropathy, with elevated levels of inflammatory markers, including IL-6, fibrinogen and high-sensitivity C-reactive protein (hs-CRP), observed in affected individuals[7].

High-sensitivity C-reactive protein (hs-CRP) is a marker of inflammation that has been implicated in various disorders, including diabetes mellitus. Studies indicate a significant correlation between hs-CRP levels and markers of glycemic control, such as glycated haemoglobin A1c (HbA1c)[8]. In the context of Diabetic Nephropathy, elevated hs-CRP levels reflect an increased inflammatory state, which contributes to disease progression and the associated cardiovascular risks. The American Heart Association (AHA) categorizes hs-CRP levels as follows: <1 mg/L indicating low risk, 1-3 mg/L moderate risk and >3 mg/L high risk[9].

In addition to inflammation, lipid abnormalities are common in diabetic nephropathy patients and significantly contribute to cardiovascular risk. Insulin resistance in DN patients leads to poor lipid metabolism, causing diabetic dyslipidemia characterized by low HDL-C levels and elevated VLDL-C and LDL-C levels. The Cardiac Risk Ratio (CRR) and the Atherogenic Index of Plasma (AIP) are two significant lipid-related markers that aid in assessing cardiovascular risk in DN patients[10].

The Cardiac Risk Ratio (CRR) simplifies cardiovascular risk assessment by combining key lipid parameters into a single ratio, facilitating the identification of high-risk patients. The Atherogenic Index of Plasma (AIP), defined as the logarithm of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol, is a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk[11].

AIP correlates with the size of HDL and low-density lipoprotein (LDL) particles and with the fractional esterification rate of cholesterol by lecithin: cholesterol acyltransferase in plasma. This ratio accurately reflects the presence of atherogenic small LDL and HDL particles, serves as a sensitive predictor of coronary atherosclerosis and cardiovascular risk and is a useful surrogate for insulin resistance[12].

This study aims to elucidate the relationship between hs-CRP and diabetic complications, particularly Diabetic Nephropathy and explore the potential of hs-CRP as a prognostic indicator for disease severity. By examining serum hs-CRP levels alongside lipid profiles, including CRR and AIP, in patients with Diabetic Nephropathy, this study seeks to provide insights that could aid clinicians in early detection, assessment of severity, and timely management of diabetic complications, ultimately improving patient care and outcomes.

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional observational study was conducted at Index Medical College and Hospital, Indore, from January 2021-2022, following ethical approval. Informed consent was obtained from all participants.

Participants: Seventy patients with Diabetic Nephropathy (DN), aged 30-70 years, were enrolled. T2DM was defined by fasting plasma glucose (FPG) >126 mg/dl and HbA1c >6.5%. DN was confirmed by a urine albumin/creatinine ratio (UACR) $\geq$30 mg/g and/or eGFR <60 mL/min/1.73m². Age-and sex-matched seventy healthy controls with no history of diabetes or renal impairment were included.

Exclusion Criteria: Participants were excluded if they had active infections, malignancy, smoking, alcoholism, rheumatoid arthritis, BMI >30, or were on medications such as lipid-lowering drugs, anti-inflammatory agents, multivitamins, or aspirin. Patients with type 1 diabetes, gestational diabetes, or diabetic ketoacidosis were also excluded.

Anthropometric and Clinical Assessments: All participants underwent physical examination and had anthropometric measurements (waist circumference, BMI, height and weight) recorded.

Sample Collection and Biochemical Analysis: Venous blood samples (7 mL) were collected after an 8-12-hour fast. Samples were processed for serum and plasma separation. Biochemical analyses included plasma glucose by glucose oxidase-peroxidase method, HbA1c by High-Performance Liquid Chromatography (HPLC) and lipid profiles including total cholesterol, triglycerides, HDL, Serum creatinine and blood urea were measured using a COBAS automated analyser. Levels of LDL, CRR and AIP were calculated. Urinary albumin was measured by immune-turbidometry and urinary creatinine by Jaffe's spectrophotometric method. eGFR was calculated using the Cockcroft-Gault equation. Serum hs-CRP levels were determined using an immunoturbidometric method on a COBAS-501 analyser.

Statistical Analysis: Data were analysed using appropriate statistical tests. Continuous variables were expressed as mean±standard deviation (SD), with comparisons between groups made using Student's t-test or Mann-Whitney U test. Correlations between hs-CRP and lipid profiles were assessed using Pearson or Spearman correlation coefficients. A $p<0.05$ was considered significant.

RESULTS AND DISCUSSIONS

Table 1: Comparison of Demographics, Lipid Profile and Inflammatory Markers Between Patients with Diabetic Nephropathy (DN) and Healthy Controls.

Variable	DN Patients (n=70)	Healthy Controls (n=70)	P-value
Age (years)	47.05±8.62	47.78±7.83	0.762
BMI (kg/m²)	25.56±3.50	23.71±3.72	0.361
Total Cholesterol (mg/dL)	216.21±40.02	168.60±38.24	0.021
Triglycerides (mg/dL)	200.04±56.45	151.77±63.38	<0.001
HDL (mg/dL)	37.03±8.85	47.8±9.91	<0.001
LDL (mg/dL)	139.17±41.21	119.44±33.14	0.312
hs-CRP (mg/L)	4.17±1.57	1.22±0.54	<0.001
Cardiac Risk Ratio	6.20±2.07	3.70±1.47	0.012
Atherogenic Index of Plasma (AIP)	0.065±0.016	0.047±0.013	<0.001

The present study aimed to investigate the prognostic value of the Atherogenic Index of Plasma (AIP), Cardiac Risk Ratio (CRR) and high-sensitivity C-reactive protein (hs-CRP) in assessing cardiovascular risk in patients

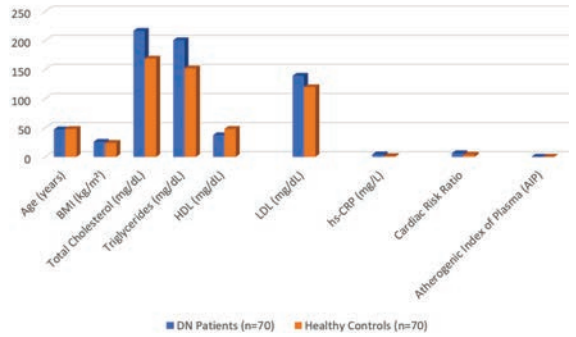

Fig. 1: Comparison of Demographics, Lipid Profile and Inflammatory Markers Between Patients with Diabetic Nephropathy (DN) and Healthy Controls

Table 2: Comparison of Variables Between Patients with Microalbuminuria and Macroalbuminuria.

Variable	Microalbuminuria (n=)	Macroalbuminuria (n=)	P-value
Total Cholesterol (mg/dL)	211.32±32.26	218.93±43.84	0.410
Triglycerides (mg/dL)	187.08±51.64	207.24±58.25	0.141
HDL (mg/dL)	38.07±9.41	36.44±8.57	0.478
LDL (mg/dL)	135.82±33.17	141.03±45.53	0.585
hs-CRP (mg/L)	3.35±1.40	4.63±1.49	0.001
Cardiac Risk Ratio	4.19±0.86	5.98±1.27	0.001
Atherogenic Index of Plasma (AIP)	0.051±0.004	0.063±0.011	0.032

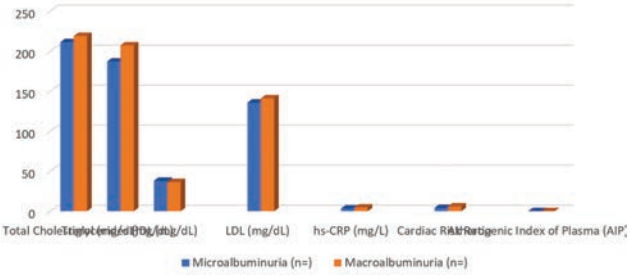

Fig. 2: Comparison of Variables Between Patients with Microalbuminuria and Macroalbuminuria

Table 3: Distribution of Patients with Diabetic Nephropathy (DN) and Healthy Controls According to hs-CRP Levels

hs-CRP Group (mg/L)	DN Patients (n=70)	Healthy Controls (n=70)
<1.0	0	56
1.0-3.0	19	14
>3.0	51	0

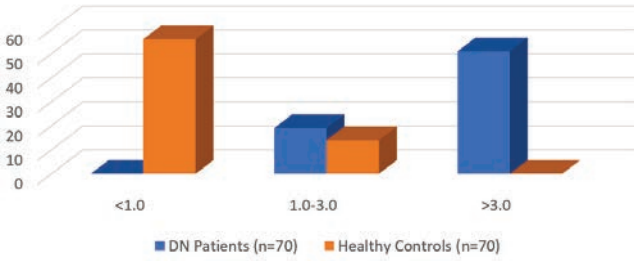

Fig 3: Distribution of Patients with Diabetic Nephropathy (DN) and Healthy Controls According to hs-CRP Levels

Table 4: Distribution of Patients With Diabetic Nephropathy based on their LDL levels in three Groups of hs-CRP

LDL	hs-CRP < 1 mg/L	hs-CRP 1-3 mg/L	hs-CRP > 3 mg/L
LDL < 100 mg/dl	0	5	6
LDL > 100 mg/dl	0	15	44

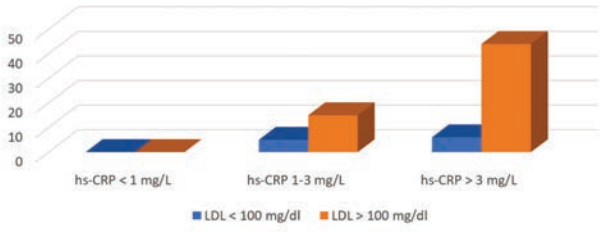

Fig. 4: Distribution of Patients with Diabetic Nephropathy based on their LDL levels in three Groups of hs-CRP

with Diabetic Nephropathy (DN). By analysing the lipid profiles and inflammatory markers in DN patients and comparing them with healthy controls, this study sought to elucidate the relationship between these parameters and the cardiovascular risk associated with DN. The study design was a cross-sectional observational study conducted over one year at a tertiary care hospital. A total of 70 DN patients and 70 age-and sex-matched healthy controls were included. Table 1 highlights the significant differences in lipid profiles and inflammatory markers between DN patients and healthy controls. The mean total cholesterol, triglycerides and LDL levels were higher in DN patients, although the difference in LDL levels was not statistically significant. Conversely, HDL levels were significantly lower in DN patients. Elevated hs-CRP levels were observed in DN patients compared to controls, indicating a higher inflammatory state. Both the Cardiac Risk Ratio (CRR) and Atherogenic Index of Plasma (AIP) were significantly higher in DN patients.

These findings emphasize the complex relationship between lipid abnormalities and inflammation in DN. Elevated CRR and AIP in DN patients suggest these indices, which integrate lipid profile components, are more sensitive markers of cardiovascular risk than traditional lipid measures alone. Elevated hs-CRP further supports the role of chronic inflammation in DN progression and cardiovascular risk. The significant differences in CRR, AIP and hs-CRP between DN patients and healthy controls underscore their potential as prognostic indicators for CVD[13].

The dyslipidaemia in DN can be attributed to insulin resistance, a hallmark of the condition. Normally, insulin inhibits hormone-sensitive lipase (HSL) in adipose tissue, reducing free fatty acids (FFAs) in circulation. However, insulin resistance impairs this inhibition, increasing FFA release. These FFAs are converted into triglycerides and secreted as VLDL by the liver. Insulin resistance also promotes VLDL overproduction, contributing to elevated cholesterol and triglycerides, driving atherosclerosis and cardiovascular risk. Elevated CRR and AIP in this study further highlight dyslipidaemia as a key predictor of cardiovascular events[14].

Additionally, insulin resistance increases hepatic lipase activity, breaking down HDL into smaller, less functional particles. It also reduces apolipoprotein A-I (ApoA-I) production, further lowering HDL levels. This diminished HDL function weakens its protective role against oxidative stress and inflammation, which are central to both atherosclerosis and nephropathy. As a result, reduced HDL in DN patients contributes to their heightened cardiovascular risk[15]. Our findings are similar to the study done by Kannel *et al.* (2000) who demonstrated that elevated total cholesterol and triglyceride levels, coupled with low HDL levels, are strong predictors of cardiovascular disease in diabetic populations[16].

High-sensitive CRP (hs-CRP), produced by the liver in response to inflammatory cytokines like interleukin-6 (IL-6), is a key marker of systemic inflammation. In diabetes, chronic hyperglycemia activates inflammatory pathways such as the nuclear factor-kappa B (NF-κB) pathway, increasing pro-inflammatory cytokine production. The elevated hs-CRP levels seen in DN patients in this study reflect this inflammation. Festa *et al.* (2000) similarly reported higher hs-CRP levels in type 2 diabetes, correlating with cardiovascular morbidity[17], while the Strong Heart Study (Howard *et al.,* 1998) associated elevated hs-CRP with increased cardiovascular risk in diabetic populations[18].

Our findings of increased Cardiac Risk Ratio (CRR) in DN patients suggest a higher proportion of atherogenic lipoproteins relative to HDL, contributing to greater cardiovascular risk. This dyslipidaemia, characterized by elevated total cholesterol and triglycerides alongside reduced HDL, is consistent with the literature. Haffner *et al.* (2002) emphasised the utility of CRR in identifying high-risk patients, noting its superiority over individual lipid measures for cardiovascular risk prediction[19].

The Atherogenic Index of Plasma (AIP), which measures the imbalance between triglycerides and HDL, further underscores the increased cardiovascular risk in DN patients. A higher AIP reflects greater atherogenicity due to the presence of small, dense LDL particles and lower HDL levels, both of which are strongly linked to increased cardiovascular risk. In our study, elevated AIP levels in DN patients point to significant lipid abnormalities, particularly the disproportionate rise in triglycerides relative to HDL[20]. This aligns with findings from Niromound *et.al* (2015),

who identified AIP as a significant predictor of atherogenicity and cardiovascular risk, especially in patients with metabolic disorders like diabetes[11].

Table 2 compares lipid profiles and inflammatory markers between DN patients with microalbuminuria and macroalbuminuria. While traditional lipid levels (total cholesterol, triglycerides, HDL and LDL) showed no significant differences, hs-CRP, CRR and AIP were significantly higher in the macroalbuminuria group, indicating more severe kidney damage and increased cardiovascular risk.

Elevated hs-CRP levels in macroalbuminuria patients suggest increased inflammation as DN progresses, which correlates with greater nephropathy severity and heightened cardiovascular risk. This finding aligns with Gomes *et al.* (2004), who noted hs-CRP as a predictor of nephropathy progression[21]. CRR and AIP were also significantly higher in macroalbuminuria, reflecting a more atherogenic lipid profile and increased cardiovascular risk. This supports the findings of Mannangi *et al.* (2015), who identified CRR and AIP as strong predictors of cardiovascular risk in advanced nephropathy[22].

The role of inflammation in DN is further driven by the accumulation of advanced glycation end-products (AGEs), which activate RAGE receptors and trigger oxidative stress, promoting nephropathy and cardiovascular complications.

Table 3 categorizes DN patients and healthy controls based on hs-CRP levels, showing that a significant number of DN patients had hs-CRP levels above 3 mg/L, while none of the healthy controls were in this high-risk category. Most healthy controls had hs-CRP levels below 1 mg/L, highlighting the stark contrast in inflammation between DN patients and controls. This supports findings by Ridker *et al.* (2000), who reported higher hs-CRP levels associated with increased cardiovascular risk. Oemrawsingh *et al.* (2016) similarly noted that hs-CRP levels above 3 mg/L predicted higher cardiovascular risk in diabetic nephropathy[23,24].

Table 4 further categorizes DN patients by LDL levels within different hs-CRP categories, revealing that most patients with LDL above 100 mg/dL also had hs-CRP levels greater than 3 mg/L, placing them at high cardiovascular risk according to American Heart Association guidelines. This combination of elevated LDL and hs-CRP indicates compounded cardiovascular risk. The chronic hyperglycemia in DN promotes non-enzymatic glycation of LDL particles, enhancing their atherogenic potential and leading to prolonged circulation and arterial deposition.

The present study highlights the importance of integrating lipid profile measures like AIP and CRR with inflammatory markers such as hs-CRP to better predict cardiovascular risk in Diabetic Nephropathy patients. Elevated CRR, AIP and hs-CRP were strongly associated with increased cardiovascular risk, reinforcing the need for early identification and targeted interventions. As DN progresses, lipid abnormalities and inflammation become more pronounced, underscoring the critical role of managing these risk factors to mitigate cardiovascular complications. These findings support the growing evidence that combined assessment of dyslipidemia and inflammation offers a more comprehensive approach to evaluating and managing cardiovascular risk in DN patients.

CONCLUSION

This study highlights the importance of integrating lipid abnormalities and inflammation in assessing cardiovascular risk in Diabetic Nephropathy (DN) patients. Elevated Atherogenic Index of Plasma (AIP), Cardiac Risk Ratio (CRR) and high-sensitivity C-reactive protein (hs-CRP) were strongly associated with increased cardiovascular risk, with hs-CRP reflecting the inflammatory burden in DN progression.

The significant increase in CRR, AIP and hs-CRP in patients with macroalbuminuria underscores the heightened cardiovascular risk as DN advances. Combining these markers offers a more comprehensive risk assessment than traditional lipid measures alone, enabling earlier identification of high-risk patients.

In conclusion, a combined evaluation of dyslipidemia and inflammation is essential for effective cardiovascular risk management in DN patients, providing an opportunity for timely interventions and improved patient outcomes.

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