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*Research Article*

# Association between Monocyte to High-Density Lipoprotein Ratio and Diabetic Nephropathy

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## ABSTRACT

Diabetes mellitus (DM) is a chronic disease affecting carbohydrate metabolism, contributing significantly to global morbidity and mortality. Among its complications, diabetic nephropathy (DN) stands out as the most prevalent, traditionally diagnosed through serum creatinine levels, urine protein creatinine ratio (UPCR), and estimated glomerular filtration rate (eGFR). However, the complexity and cost associated with these methods have spurred the search for a more accessible parameter.This study delves into the assessment of the Monocyte-High Density Lipoprotein ratio (MHR) as a potential predictor for DN development. One hundred participants were meticulously chosen and sorted into four groups based on plasma glucose, HbA1c, serum creatinine, UPCR, and eGFR. The calculation of MHR for each group revealed a statistically significant difference between controls and cases. Furthermore, a noteworthy negative correlation between eGFR and MHR was observed across the study groups. The findings suggest that MHR could serve as a straightforward and cost-effective tool in predicting both the onset and progression of Diabetic Nephropathy.

## INTRODUCTION

Diabetes mellitus is a widespread chronic ailment that affects the metabolism of carbohydrates, characterized by persistent high levels of blood sugar, or chronic hyperglycemia. This condition arises from either a partial or complete deficiency of insulin and/or the body's resistance to insulin, resulting in disruptions in the metabolism of carbohydrates, proteins, and lipids[1-3]. The prolonged elevation of blood glucose levels associated with diabetes can lead to damage in crucial organ systems, including the eyes, kidneys, heart, and blood vessels. Among these complications, Diabetic Nephropathy (DN) stands out as the most prevalent, holding a prominent position as a leading contributor to end-stage renal disease (ESRD) on a global scale[4, 5 ].

The progression of Diabetic Nephropathy is linked to microvascular complications triggered by high blood sugar levels, combined with the local and systemic release of various cytokines, chemokines, and growth factors.

It is deemed essential to screen for microproteinuria in individuals with Type-2 diabetes from the time of diagnosis, while those with Type-1 diabetes may undergo assessment after an average of five years. Physiological changes, such as an increase in renal plasma flow, intraglomerular hydrostatic pressure, and glomerular filtration rate, become evident in the early stages of diabetes before morphological alterations occur[6, 7].

In the initial stages, high blood glucose levels induce the loss of sulfated proteoglycans and anionic regions in the basal membrane of the glomerulus and mesangial matrix. This leads to the accumulation of proteoglycans and alterations in renal selectivity, setting the stage for the development and progression of Diabetic Nephropathy. The intricate interplay of biochemical processes involved in the pathogenesis of DN underscores the multifaceted nature of this complication within the broader spectrum of diabetes[8, 9].The pathophysiology underlying potential and innovative biomarkers for

diabetic kidney disease shown in **Figure 1.**

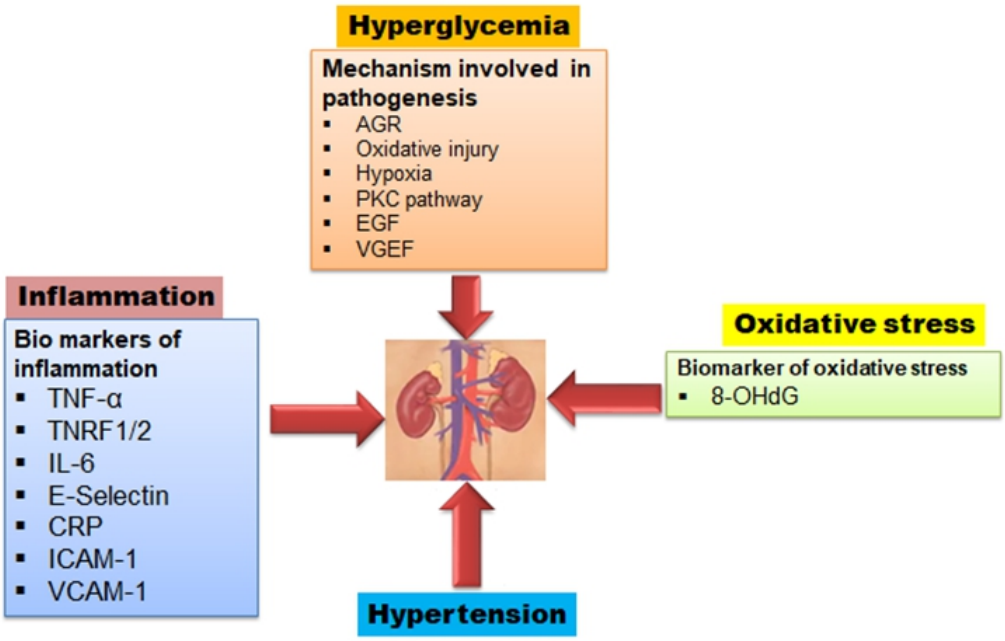


**Figure 1:** The pathophysiology underlying potential and innovative biomarkers for diabetic kidney disease.

Diabetic Nephropathy, being a significant contributor to end-stage renal disease, imposes a substantial burden on global healthcare systems. The economic and social implications of managing this complication necessitate a comprehensive understanding of its underlying mechanisms and risk factors. The identification of early markers, such as microproteinuria, in Type-2 diabetes patients and timely assessment in Type-1 diabetics, can play a pivotal role in implementing preventive measures and interventions to mitigate the progression of Diabetic Nephropathy[10, 11].Furthermore, the intricate physiological changes occurring in the renal system during the early stages of diabetes highlight the importance of addressing not only the symptomatic aspects but also the underlying molecular and cellular processes. This holistic approach is essential for developing targeted therapies that can effectively manage and potentially prevent the onset of Diabetic Nephropathy, thereby improving the overall prognosis and quality of life for individuals affected by diabetes[7, 12, 13].

Monocytes, the largest type of leukocytes, play a pivotal role in inflammatory responses and possess the ability to differentiate into macrophages and monocyte-derived dendritic cells. Recently, there has been a growing interest in the Monocyte-High Density Lipoprotein ratio (MHR) as a potential indicator for the early detection of Diabetic Nephropathy (DN). The MHR serves as a reflection of inflammation and oxidative stress, leveraging the anti-inflammatory and antioxidant effects of high-density lipoprotein cholesterol (HDL-C) and juxtaposing them against the proinflammatory effect of monocytes[14-16].

While numerous studies have delved into the significance of these measurements in understanding the role of inflammation and atherosclerosis in cerebrovascular and cardiovascular diseases, there exists a notable gap in research when it comes to exploring the association between MHR and DN. This study endeavors to bridge this void in the existing literature by delving into the intricate relationship between the Monocyte to High-Density Lipoprotein Cholesterol ratio (MHR) and the decline in renal function observed in patients grappling with diabetic nephropathy[17, 18].

The rationale behind investigating MHR in the context of diabetic nephropathy lies in its potential to serve as a biomarker that encapsulates the dynamic interplay between inflammatory processes and lipid metabolism. As monocytes contribute significantly to inflammatory responses, their interaction with high-density lipoprotein cholesterol provides a nuanced perspective on the delicate balance between anti-inflammatory and proinflammatory forces within the body. Understanding how these components converge in the context of diabetic nephropathy is paramount for elucidating the underlying mechanisms and identifying novel avenues for early detection and intervention[20, 21].

Diabetic Nephropathy (DN) manifests as a decline in renal function, often discerned by elevated serum urea and creatinine levels. If left unchecked, DN can advance to proteinuria, a condition diagnosed through various means, including urine routine examination, urine spot/24-hour protein/creatinine ratio (PCR), and Glomerular Filtration Rate (GFR). Unfortunately, both PCR and GFR estimations are not only time-consuming but also pose a financial burden, underscoring the urgent necessity for a simpler and more cost-effective diagnostic tool to facilitate early detection and management of DN. This study seeks to explore the potential correlation between the Monocyte to High-Density Lipoprotein (HDL) ratio (MHR) and the progression of Diabetic Nephropathy[22-24].

In the context of DN, the escalation of serum urea and creatinine levels serves as a crucial indicator of compromised renal function. The subsequent development of proteinuria, a hallmark of advanced DN,

necessitates meticulous examination through urine routine analysis and more sophisticated assessments such as PCR and GFR[25]. However, the inherent drawbacks of these methods, including their time and cost implications, have spurred the quest for a more streamlined and economically viable diagnostic approach[26].

The focus on MHR as a potential diagnostic marker is grounded in its capacity to encapsulate the intricate interplay between monocytes and high-density lipoprotein cholesterol. By investigating the association between MHR and the progression of DN, this study aims to unravel a simpler and more accessible avenue for clinicians to identify early signs of renal compromise in diabetic patients. The exploration of MHR as a potential biomarker not only holds promise for its diagnostic utility but also sheds light on the underlying inflammatory and oxidative stress mechanisms that contribute to the pathogenesis of DN[27, 28].

The significance of this research lies in its potential to introduce a paradigm shift in the diagnostic landscape of DN. A simplified and cost-effective diagnostic tool like MHR could not only streamline the early identification of diabetic nephropathy but also facilitate timely intervention and management. By providing clinicians with a readily accessible marker, this study aspires to contribute to more efficient healthcare practices, particularly in the context of a prevalent and impactful complication[29].

## MATERIALS AND METHODS

This case-control investigation took place at the Clinical Biochemistry Laboratory within the Department of Biochemistry at the Saveetha Institute of Medical and Technical Sciences. The study, titled "Association Between Monocyte to High-Density Lipoprotein Ratio and Diabetic Nephropathy," was conducted prospectively and received approval from the Institutional Review Board (SCAHS/IRB/2022/DECEMBER/439). The research involved a total of 100 participants, aged between 20 and 80 years, encompassing both genders. Exclusion criteria ensured the exclusion of individuals with a history of Coronary Artery Disease (CAD), malignancy, inflammatory disorders, or those on medications that could impact the study parameters.

Study participants were selected from both outpatient and inpatient departments of General Medicine and Nephrology at Saveetha Medical College Hospital (SMCH). Additionally, healthy individuals visiting the hospital for Master Health Checkup, SMCH, were included after meeting the specified inclusion and exclusion criteria. Informed consent was obtained from all participants before the study commenced. Participants were divided into four groups based on age, gender, and specific health parameters:

- **Group I:** 50 participants with normal levels of fasting blood sugar (FBS), postprandial blood sugar (PPBS), HbA1c, and serum creatinine.
- **Group II:** 29 patients with elevated levels of FBS, PPBS, HbA1c, serum creatinine, urine protein creatinine ratio, and Glomerular Filtration Rate (GFR).
- **Group III:** 12 patients with elevated levels similar to Group II but with a GFR ranging from 60 to 90 ml/min.
- **Group IV:** 9 patients with elevated levels similar to Group II but with a GFR below 60 ml/min. Non-diabetic healthy individuals served as controls, while participants with diabetic nephropathy were categorized as cases.

Peripheral venous blood samples and spot urine samples were collected from all study participants. Blood samples were centrifuged, and plasma/serum was separated on the same day, then stored at -20ºC until analysis. Serum samples underwent processing for the estimation of fasting blood glucose, postprandial blood glucose, serum creatinine, and urine samples for protein and creatinine using a VITROS 5600 fully automated dry chemistry analyzer. Protein Creatinine Ratio (PCR) was calculated from urine protein and creatinine values, and GFR was determined using the Modification of Diet in Renal Disease (MDRD) formula. A complete hemogram was analyzed using EDTA plasma in an XN1000 analyzer, providing monocyte counts. Additionally, EDTA plasma was utilized to estimate Glycated Hemoglobin (HbA1c) in a Biorad D10 HPLC analyzer.

## RESULTS

Our study encompassed a nearly equal representation of both men and women in both the case and control groups, as illustrated in **Figures 2 and 3.** The majority of cases fell within the 41-50 age range, while a predominant portion of controls belonged to the 21-30 age group, as depicted in **Figures 4 and 5.** The distribution of study participants across the three groups is visually presented in **Figure 6.**


**Figure2:** Gender distribution among cases


**Figure 3:** Gender distribution among controls

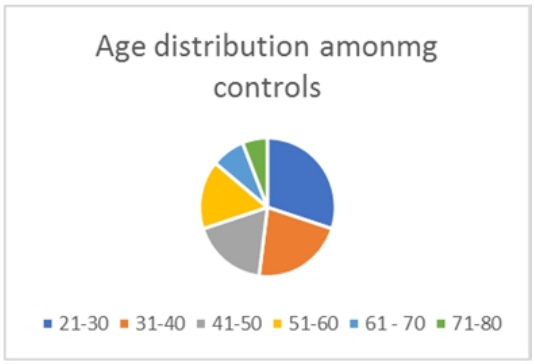


**Figure 4:** Age distribution among controls

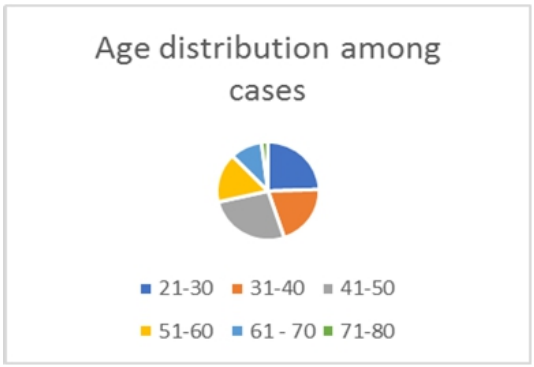


**Figure 5:** Age distribution among cases

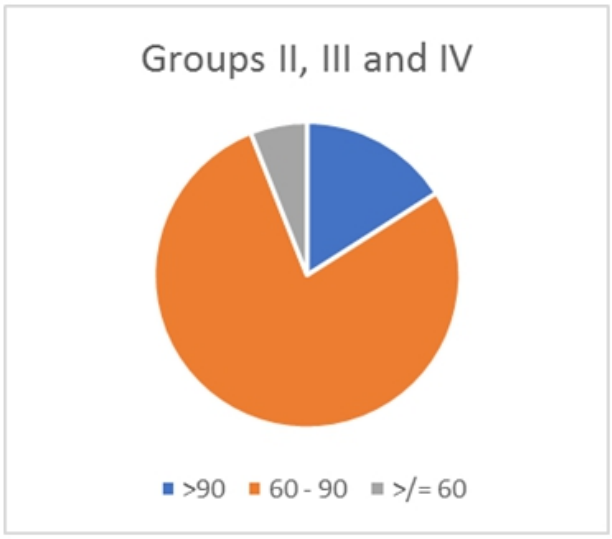


**Figure 6:** Distribution of study participants across the three groups

An analysis of the data revealed a statistically significant difference between the study groups concerning all the study parameters, except for age, as summarized in **Table 1.** Furthm-ore, when the groups were stratified based on Glomerular Filtration Rate (GFR), a statistically significant difference in Monocyte to High-Density Lipoprotein Ratio (MHR) levels was observed, as detailed in **Table 2.**

**Table 1:** Demographic and Laboratory Data of the Study Participants

| | Cases(diabetic nephropathy patients) | | Controls(non-diabetic healthy individuals) | | p value |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | |
| **Age(years)** | 42.2 | 13.09 | 44.2 | 12.61 | 0.48 |
| **FBS(mg/dl)** | 140.84 | 24.22 | 101.24 | 15.43 | <0.0001* |
| **PPBS(mg/dl)** | 235.3 | 35.31 | 138.55 | 10.23 | <0.0001* |
| **HbA1c(%)** | 7.08 | 2.65 | 4.33 | 1.71 | <0.0001* |
| **Creatinine (mg/dl)** | 3.46 | 1.34 | 1.12 | 0.25 | <0.0001* |
| **HDL(mg/dl)** | 36.32 | 6.38 | 40.72 | 5.86 | 0.0005* |
| **Monocytes ($x10^9$/L)** | 408.51 | 120.3 | 334.12 | 116.32 | 0.002* |
| **PCR(mg/mmol)** | 33.62 | 9.23 | 10.33 | 3.45 | <0.0001* |
| **eGFR(ml/min)** | 77.42 | 10.29 | 108.21 | 9.34 | <0.0001* |
| **MHR** | 14.62 | 7.4 | 10.24 | 5.12 | 0.0009* |

*p-value of <0.05 is considered to be statistically significant.

**Table 2:** Correlation between eGFR and MHR between the study groups

| | eGFR(ml/min) | | MHR | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| GroupI | 108.21 | 9.34 | 10.24 | 5.12 | <0.0001* |
| Group II | 93.62 | 2.87 | 13.63 | 8.05 | <0.0001* |
| GroupIII | 75.56 | 6.94 | 14.48 | 7.32 | <0.0001* |
| Group IV | 58.33 | 2.35 | 15.92 | 7.43 | <0.0001* |

*pvalueof<0.05 is considered to be statistically significant.

The relationship between estimated Glomerular Filtration Rate (eGFR) levels and MHR across the various study groups is visually represented in **Figure 7.** These findings underscore the nuanced variations in MHR levels across different GFR categories, providing valuable insights into the association between Monocyte to High-Density Lipoprotein Ratio and Diabetic Nephropathy in our study population.

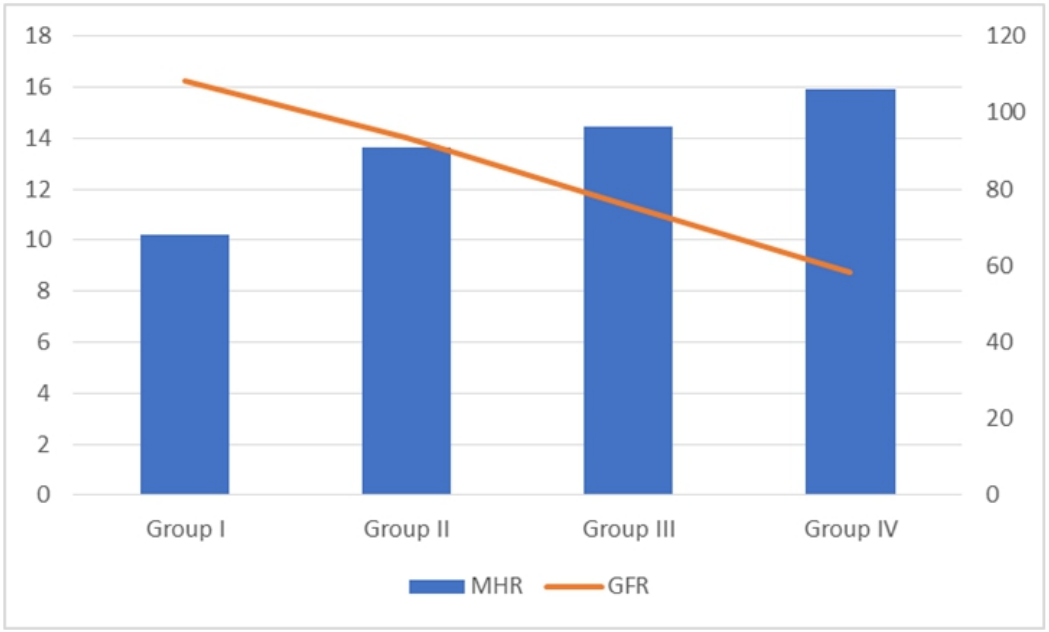


**Figure 7:** Comparison between GFR and MHR across the study groups

## DISCUSSION

The findings of this study reveal a noteworthy correlation between the increase in Monocyte to High-Density Lipoprotein Ratio (MHR) in patients with diabetic nephropathy (DN) and a concurrent decrease in estimated glomerular filtration rate (eGFR). Notably, the comparison of individuals with Type-2 diabetes, diabetic patients with and without nephropathy, and healthy controls highlighted that those with diabetic nephropathy exhibited higher MHR values than other diabetic patients without nephropathy and healthy controls. This study stands out as the first to demonstrate such a distinction[30, 31].

A statistically significant negative correlation was identified between eGFR and MHR across the study groups, suggesting that MHR increases with the progression of DN. Diabetes mellitus, characterized by disturbances in carbohydrate, protein, and lipid metabolism due to insulin deficiency or resistance, is a chronic global health concern[32]. The prevalence of diabetes is on the rise, driven by sedentary lifestyles, unhealthy dietary habits, and obesity. Complications associated with diabetes can be categorized as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, peripheral vascular disease, cerebrovascular diseases)[33].

Despite advances in disease management leading to increased life spans for diabetics, the prevalence of diabetic nephropathy (DN) and end-stage renal disease (ESRD) has increased. The risk of developing DN has particularly risen due to the extended survival times of Type-2 diabetes patients[34]. Studies such as the United Kingdom ProspectiveDiabetes Study (UKPDS) have reported rates of micropro-

teinuria at 25%, macroproteinuria at 5%, and the need for renal replacement therapy at 0.8% in Type-2 diabetes patients at the 10th year after diagnosis[35, 36].High-density lipoprotein (HDL) plays a crucial role as an anti-inflammatory and antioxidant agent. It inhibits endothelial expression of adhesion proteins and monocyte passage in response to oxidized substances, providing protection against the harmful effects of low-density lipoprotein (LDL)[37, 38]. Notably, a study by Adler et al reported an annual progression rate of 2% for the transition from normoproteinuria to microproteinuria. Monocytes and macrophages, key players in the synthesis and release of proinflammatory and prooxidant cytokines, contribute to the inflammatory milieu associated with diabetes[39, 40].

In the context of diabetic nephropathy, the study highlights the significance of MHR as a potential indicator of disease progression. While previous research has shown higher MHR in type 2 diabetics with coronary artery disease (CAD), this study establishes a unique correlation between MHR and eGFR in the context of diabetic nephropathy[41]. Unlike some studies that found no correlation between the severity of DN, in terms of albuminuria, and MHR, this investigation establishes a significant negative correlation between MHR and eGFR, providing a valuable tool for the easy and early prediction of DN progression[42, 43].

## CONCLUSION

Our study establishes a significant and distinctive difference in Monocyte to High-Density Lipoprotein Ratio (MHR) between patients with diabetic nephropathy and their healthy counterparts. The observed correlation between MHR and Glomerular Filtration Rate (GFR) across the study groups suggests a consistent increase in MHR as the disease progresses. This underscores the potential of MHR as a valuable biomarker for diabetic nephropathy, offering a means of detection through simple and cost-effective investigations.

## FUTURE PROSPECTIVE

Looking ahead, the future scope of this study holds promising avenues for further exploration and understanding. The study can be extended to a larger population, providing a more comprehensive perspective on the correlation between MHR and diabetic nephropathy. Additionally, exploring correlations with other parameters and comorbidities could contribute to a more holistic understanding of the role of MHR in the context of diabetes-related complications. This ongoing research could pave the way for improved diagnostic and prognostic tools, enhancing our ability to detect and manage diabetic nephropathy in its early stages.

## FUNDING

Nil.

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## CONFLICTS OF INTEREST

There are no conflicts of interest.

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