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RELATIONSHIP BETWEEN HbA1c LEVELS AND ATHEROGENIC INDEX OF PLASMA IN DIABETIC NEPHROPATHY PATIENTS

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ABSTRACT

Diabetic nephropathy is the leading cause of kidney failure worldwide. Its incidence is comparable to that of cardiovascular disease (CVD), with macrovascular complications remaining the main cause of death among diabetic patients. The Atherogenic Index of Plasma (AIP) is an independent marker and predictor of CVD. AIP indicates risk even when other atherogenic risk factors are normal, categorized as low risk (AIP < 0.11), intermediate risk (AIP 0.11–0.21), and high risk (AIP > 0.21). This study aims to explore the relationship between Glycated Hemoglobin (HbA1c) levels and AIP in patients with diabetic nephropathy to identify the risk of CVD complications. It used a prospective analytical design with a cross-sectional approach, conducted at Adam Malik Hospital, Medan, from February to May 2025. Forty-three outpatients with diabetic nephropathy who met the inclusion criteria were selected using a consecutive sampling technique. Patients were assessed for HbA1c, triglycerides, HDL, and urinary albumin-to-creatinine ratios. AIP was calculated by taking the logarithm of (triglycerides/HDL). Data analysis involved Pearson and Spearman correlation tests. A significant positive correlation was found between HbA1c and AIP ($r = 0.670$, $p = 0.000$), as well as between HbA1c and triglycerides ($r = 0.398$, $p = 0.008$). A significant negative correlation was observed between HbA1c and HDL ($r = -0.648$, $p = 0.000$). However, there was no significant correlation between HbA1c and ACR, nor between ACR and AIP ($p > 0.05$). In conclusion, higher HbA1c levels are associated with increased AIP levels, which elevate the risk of CVD, characterized by rising triglycerides and decreasing HDL.

Keywords: ACR; AIP; CVD; HbA1c

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INTRODUCTION

Diabetes is the leading cause of blindness, end-stage renal disease, cardiovascular disease, and stroke. Diabetic nephropathy, a microvascular complication of type 2 diabetes, causes decreased kidney function and is the main cause of global kidney failure in 25-40% of patients. Early detection is crucial due to the risk of worsening kidney function and potential need for renal replacement therapy. Clinically, diabetic nephropathy shows as persistent albuminuria with an ACR above 30 mg/g and a gradual decline in kidney function. Macrovascular CVD complications remain the leading cause of death among diabetic patients, with a 1.8% higher risk of heart attack in U.S. adults with diabetes. Insulin resistance, common in early type 2 diabetes and CVD, is linked to increased cardiovascular risk. Elevated blood glucose and excess lipid accumulation enhance the risk of macrovascular and microvascular complications.(Jung & Yoo, 2022; Lee et al., 2021; Ma et al., 2022; Putri et al., 2020; Sharma et al., 2020; Vujicic et al., 2012)

According to WHO, in 2014, 422 million adults had diabetes, with prevalence rising from 4.7% in 1980 to 8.5%, especially in low- and middle-income countries. Indonesia's 2018 data shows a DM prevalence of 14.7% in urban areas and 7.2% in rural areas among 133 million adults. By 2030, cases are expected to reach 194 million—28 million urban and 13.9 million rural. WHO projects type 2 DM cases in Indonesia will rise from 8.4 million in 2000 to 21.3 million in 2030.(Alam et al., 2021; PB. PERKENI, 2021; World Health Organization, 2019, 2021).

The diagnosis of diabetes relies on plasma glucose or glycated hemoglobin (HbA1c) levels. HbA1c was initially used to monitor glucose levels because it correlates with extracellular glucose and gives an average over approximately 120 days. Standardizing HbA1c measurements has made it both a diagnostic tool and a way to monitor glycemic control and prevent complications. An international committee appointed by the ADA, the European Association, and the International Diabetes Federation concluded that an HbA1c level of 6.5% or higher can be used to diagnose diabetes. In 2011, the WHO approved the use of an HbA1c level greater than 6.5% for diagnosing diabetes. The target HbA1c for managing diabetes is less than 7% in adults.(Campbell et al., 2019; CS & TC, 2020; World Health Organization, 2020).

According to the 2007 European Society of Cardiology and European Atherosclerosis Society guidelines, the incidence of diabetic nephropathy is considered equivalent to CVD risk. Abnormal urinary albumin excretion and decreased eGFR are strong predictors of CVD, especially in patients with diabetes. A Japanese study found that the risk of CVD is more closely associated with the development of albuminuria than with eGFR in DM, with a relatively low risk. Patients with ACR ≥ 35.0 mg/mmol and eGFR < 89 have an increased risk of CVD compared to those without, while those with eGFR ≥ 90 do not. Patients with ACR < 3.5 mg/mmol and eGFR < 60 do not have an increased risk of CVD. (Chen & Tseng, 2019; Swamy et al., 2023).

Insulin resistance and decreased beta-cell function are the main causes of diabetes. Their interaction leads to Type 2 DM development and worsens lipid metabolism, increasing triglycerides (TG) and decreasing HDL by inhibiting ApoA-I. These changes, known as dyslipidemia, are common in DM and raise CVD risk. AIP, calculated as log (TG/HDL), measures dyslipidemia and CVD risk, with categories: low risk (<0.11), intermediate (0.11-0.21), and high (>0.21). (Kim et al., 2022) found AIP significantly linked to CVD risk, with hazard ratios rising across AIP quartiles. (Fawwad et al., 2023) also reported a significant relationship between AIP and CVD risk factors, with a mean AIP of 0.38 ± 0.31. (Abdissa & Hirpa, 2022; Tang et al., 2022). This study aims to determine the relationship between Glycated Hemoglobin (HbA1c) levels and the Atherogenic Index of Plasma (AIP) in patients with Diabetic Nephropathy at H. Adam Malik General Hospital, Medan.

METHOD

The study used a prospective analytical design with a cross-sectional approach, conducted at Adam Malik Hospital in Medan from February to May 2025. The population included patients diagnosed with Diabetic Nephropathy by the Department of Internal Medicine at Adam Malik Hospital who visited the Internal Medicine Endocrine Clinic. Sampling was conducted using a consecutive sampling technique, where all eligible patients who met the inclusion criteria and visited during the study period were included. A correlation test sample size formula was applied, and the minimum required sample size was calculated to be 35 people. A total of 43 samples meeting the inclusion criteria were collected. The inclusion criteria were patients aged 18 or older with complete medical records, including patient identity, characteristics, diagnosis, and recent laboratory data such as HbA1c, ACR, Triglycerides, and HDL tests. Exclusion criteria included patients with hematological disorders (acute or chronic anemia, hemoglobinopathy), those taking triglyceride-lowering medications, individuals with chronic liver disorders, Chronic Kidney Disease, thyroid disorders, or those who were pregnant.

Sampling was performed and analyzed at the Clinical Pathology Laboratory of Adam Malik Hospital. The collected specimens included blood without an anticoagulant and random urine samples. Urine albumin-to-creatinine ratio was measured using the Sysmex UC 3500 device with a reflectance photometry method. HbA1c levels were determined using the Cobas C503 device with a turbidimetric inhibition immunoassay (TINIA) method. Triglyceride levels were measured using the Cobas C503 device with an enzymatic colorimetric test. HDL levels were also measured using the Cobas C503 device with a homogeneous enzymatic colorimetric test. AIP was then calculated by taking the logarithm of triglycerides divided by HDL.

Quality control for HbA1c, triglycerides, and high-density lipoprotein (HDL) tests on the Cobas C503 uses ready-to-use control materials with known values, such as PreciControl HbA1c norm and PreciControl HbA1c path for HbA1c, as well as PreciControl ClinChem Multi 1 and PreciControl ClinChem Multi 2 for triglycerides and HDL. Meanwhile, quality control for Albumin Creatinine Ratio (ACR) testing on the Sysmex Urine Chemistry Analyzer UC-3500 is performed using control reagents from available providers, specifically UC-Control-L (low value) and UC-Control-H (high value). Data were analyzed using standard statistical software. Data are presented in descriptive tables showing patient demographics and laboratory results. To assess normality, the Shapiro-Wilk test was used because the sample size in this study was ≤ 50. The analysis included Pearson and Spearman correlation tests for numerical variables, as well as the Chi-square test to evaluate the relationship between categorical variables.

RESULT

A total of 43 patients with diabetic nephropathy were included, consisting of 22 men (51.2%) and 21 women (48.8%). The most common age group was 46–59 years (48.8%), with an overall mean age of 58 years (range 34–73 years). Most patients (83.7%) had HbA1c levels ≥ 7%, indicating poor glycemic control. The mean HbA1c level was 9.4 ± 2.2%, the mean AIP was 0.71 ± 0.27, triglycerides were 159 (66–421) mg/dL, and HDL levels averaged 34.47 ± 10.46 mg/dL. Microalbuminuria was found in 67.4% and macroalbuminuria in 32.6% of participants (Table 1).

Table 1.
Characteristics of Patients with Diabetic Nephropathy

Characteristics	Total (n=43)
Age (years)	58 (34-73)
18 – 45	5 (11.6%)
46 – 59	21 (48.8%)
≥ 60	17 (39.5%)
Gender (%)	
Male	22 (51.2%)
Female	21 (48.8%)
Hb (g/dL)	12.1 (10.0 – 16.2)
HbA1c (%)	9.4 ± 2.2
< 7%	7 (16.3%)
≥ 7%	36 (83.7%)
Triglycerides (mg/dL)	159 (66-421)
HDL (mg/dL)	34.47 ± 10.46
Creatinine (mg/dL)	1.03 (0.09 – 3.37)
Albumin Creatinin Ratio (ACR) (%)	
Microalbuminuria	29 (67.4%)
Macroalbuminuria	14 (32.6%)
Atherogenic index of plasma	0.71 ± 0.27

Data presented with an average±SD, median (min-max)

A significant positive correlation was observed between HbA1c and AIP ($r = 0.670$, $p = 0.000$) as well as between HbA1c and triglycerides ($r = 0.398$, $p = 0.008$). Conversely, HbA1c and HDL showed a significant negative correlation ($r = -0.648$, $p = 0.000$) (Table 2, Figures 1 and 2).

However, there was no significant correlation between HbA1c and ACR ($p = 0.806$) nor between AIP and ACR ($p = 0.482$) (Tables 3 and 4). These findings indicate that poor glycemic control is associated with a more atherogenic lipid profile, though not significantly with albuminuria severity.

Table 2.
Correlation of HbA1c levels with AIP, Triglycerides, and HDL

Variable	HbA1c levels		
	Total (n)	r	*p value*
AIP	43	0.670	0.000*
Triglycerides	43	0.398	0.008*
HDL	43	- 0.648	0.000*

* statistically significant at $p < 0.05$

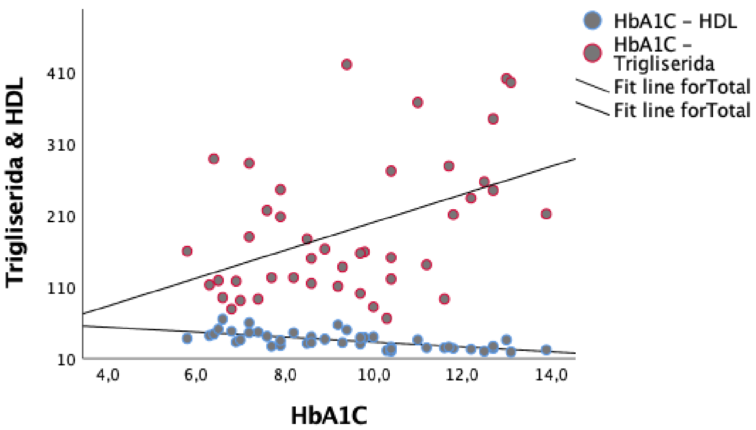

Figure 1. Scatter plot showing the relationship between HbA1c levels with triglycerides (red) and HDL (blue), indicating a positive correlation between HbA1c and triglyceride levels and a negative correlation with HDL levels.

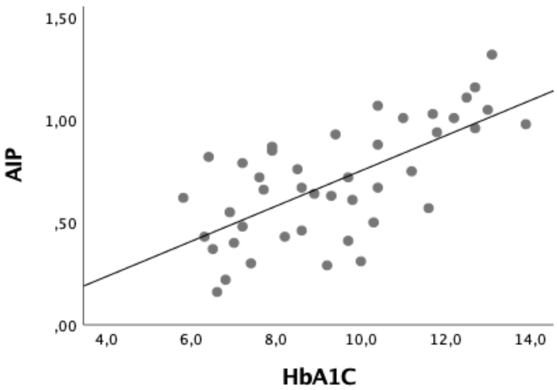

Figure 2. Scatter plot showing the relationship between HbA1c levels and AIP, indicating a positive correlation between them.

Table 3.
Relationship between HbA1c levels and ACR

ACR	HbA1c		Total	*p value*
	Controlled (< 7%)	Uncontrolled (≥ 7%)		
Microalbuminuria	5	24	29	
Macroalbuminuria	2	12	14	0.806
Total	7	36	43	

* statistically significant at $p <0.05$

Table 4.
Relationship between AIP score and ACR score

ACR	AIP		Total	*p value*
	Medium Risk	High Risk		
Microalbuminuria	1	28	29	
Macroalbuminuria	0	14	14	0.482
Total	1	42	43	

* statistically significant at p <0.05

DISCUSSION

Based on data from the 2024 Indonesian Health Survey, the number of people with diabetes mellitus was 877,531, including 434,270 women (49.49%) and 443,261 men (50.51%). The highest age group was 35-75 years old, with 519,793 individuals (59.2%), where 2.3% of men suffered from chronic kidney failure, indicating that male diabetics have a higher risk of developing chronic kidney failure compared to women.(Badan Kebijakan Pembangunan Kesehatan, 2024). (Giandalia et al., 2021) found in their research that the sex hormone testosterone in men influences the development of diabetic nephropathy. Testosterone has been shown to significantly increase fasting blood glucose, HbA1c, triglycerides, cholesterol, LDL cholesterol, and reduce insulin sensitivity. Therefore, sex hormones play an essential role in the pathophysiology of diabetes mellitus and its complication.

The HbA1c test is the gold standard for assessing long-term glucose control, as it reflects the average plasma glucose levels over the past 8–12 weeks. However, the validity of HbA1c results can be affected by non-glycemic factors, one of which is hemoglobin (Hb) levels and anemia conditions.81 In this study, the Hb value was within normal limits, so the potential distortion of HbA1c results due to anemia or hemoglobin abnormalities can be ignored. (Aydın et al., 2022) The results of the HbA1c level examination showed an average of 9.4 ± 2.2%, with HbA1c ≥ 7% in 36 people (83.7%). This suggests that most participants in this study had poor glycemic control. In the study by (Abera et al., 2022), it was shown that nearly three-quarters (73.8%) of the study subjects had inadequate and poor glycemic control, which was similar to previous studies conducted in Saudi Arabia (74.9%), Ghana (70%), Uganda (73.52%), and Ethiopia (70.8%). This is related to factors such as older age, a diabetes duration of more than 10 years, insulin therapy, and adherence to a diet less than 3 days a week.

Triglyceride and HDL levels were measured, revealing elevated triglycerides and decreased HDL levels. Lipoprotein abnormalities, marked by high triglycerides, low HDL cholesterol, and increased LDL particles, are very common in diabetes, affecting approximately 72% to 85% of patients. The mechanism behind these lipoprotein issues in diabetes involves insulin resistance and hyperglycemia, which can lead to increases in triglycerides (TG), higher LDL particle levels, and lower HDL levels, as observed in patients with insulin resistance, fasting glucose, and impaired glucose tolerance. (Abdissa & Hirpa, 2022; Jialal & Singh, 2019).

In the study by (Prabandari et al., 2021), which compared triglyceride and HDL values in individuals with good and poor glycemic control, it was found that patients with poor glycemic control had higher triglyceride levels (211.92 ± 146.09) (p = 0.00) and lower HDL levels (40.08 ± 18.12) (p = 0.001) compared to those with good glycemic control. This finding aligns with the study by (Liu et al., 2021), which stated that triglyceride levels increased in patients with diabetic nephropathy compared to non-diabetic nephropathy (2.05 ± 0.15 vs. 1.40 ± 0.04) (mmol/L), while HDL levels decreased (1.14 ± 0.03 vs. 1.29 ± 0.15) (mmol/L), indicating that dyslipidemia plays an essential role in the development of kidney disease in type 2 diabetes diabetes.

Creatinine tests indicated that most study participants still had relatively good kidney function, although some had higher creatinine levels. Several recent studies highlight the importance of creatinine as a marker of nephropathy. A study by (Cao et al., 2025) found a significant and nonlinear relationship between creatinine and the risk of diabetic nephropathy, measured through both serum and urinary creatinine levels. These results support the role of creatinine as a crucial biomarker for early detection of diabetic nephropathy. (Butt et al., 2024).

The results of this study revealed a significant positive correlation between HbA1c and triglycerides ($r = 0.398$, $p = 0.008$), suggesting that patients with higher HbA1c levels may be at a greater risk of elevated triglyceride levels compared to those with lower levels (Figure 1). Conversely, the study also found a significant negative relationship between HbA1c and HDL ($r = -0.648$, $p = 0.000$), which suggests that as HbA1c increases, HDL levels tend to decrease. This is because, in states of increased glycemic index, insulin becomes less effective, leading to excessive production and release of fatty acids into the bloodstream. In the liver, these free fatty acids are converted into triglycerides, thereby raising triglyceride levels. Hypertriglyceridemia can then accelerate HDL catabolism, resulting in lower HDL concentrations in plasma. (Esfandiari et al., 2023; Parcero-Valdés, 2021).

The results of this study showed a significant correlation between HbA1c levels and the Atherogenic Index of Plasma ($r = 0.670$, $p = 0.000$), indicating that higher HbA1c levels are associated with higher AIP levels (Figure 2). This aligns with the findings of (Nosrati et al., 2021), who suggest that an increased ratio offers a simple and valuable way to identify patients with poor glycemic control who may be at high risk of cardiovascular disease. Other studies, such as those by (Prabandari et al., 2021) and (Anjankar et al., 2018), also found a positive correlation between AIP and HbA1c levels ($r = 0.411$, $p = 0.000$; $r = 0.335$, $p = 0.009$), indicates that increasing HbA1c levels are in line with increasing AIP levels and increase the risk of cardiovascular disease.

According to the DISCOVER cohort study by (Soeatmadji et al., 2023) in Indonesia, 26.2% of T2DM patients experienced macrovascular complications, with coronary artery disease and heart failure being the most common conditions. The most frequent comorbidities were hypertension and hyperlipidemia. Studies in diabetic subjects have shown that atherogenic risk factor patterns can increase the likelihood of macrovascular outcomes. Therefore, to reduce cardiovascular risk in diabetic individuals, interventions may be needed before the development of cardiovascular issues symptoms. (Šebeková et al., 2023; Yuvaraj et al., 2022).

In this study, a chi-square analysis was performed to examine the relationship between HbA1c levels and ACR values.24 microalbuminuria patients with uncontrolled HbA1c and 12 macroalbuminuria patients with uncontrolled HbA1c were identified. However, no significant relationship was observed between ACR values and HbA1c ($p = 0.806$). Measuring the albumin-to-creatinine ratio (ACR) in urine is a common method used to detect and monitor kidney dysfunction. The accumulation of glucose and glycosylated proteins in endothelial cells leads to disruption of the glomerular filtration barrier and changes in glomerular capillary permeability in patients with diabetic nephropathy. (Lian et al., 2021).

However, the results of this study did not show a significant relationship, which could be due to several reasons, including the fact that albuminuria is influenced not only by glycemic control but also by other factors such as hypertension, duration of diabetes, obesity, dyslipidemia, and genetic factors.(Thomas et al., 2015) (Sindi et al., 2023) in their study also explained that, besides glycemic control, factors such as hypertension, obesity, dyslipidemia, and a family history of nephropathy can contribute to albuminuria. In children, these factors can be even more prominent than HbA1c.

(Zhu et al., 2025) found that higher AIP values were significantly associated with the occurrence of albuminuria in diabetics (OR 7.69, 95% CI: 2.90–20.40). Additionally, AIP also showed a significant positive relationship with albuminuria ($p < 0.05$). (Deepesh Makhijani et al., 2024) also identified a significant positive correlation between AIP and microalbuminuria ($r = 0.70$, $p = 0.000$), concluding that AIP values are an independent risk factor for CVD. In relation to microalbuminuria, AIP can help predict the occurrence of coronary vascular risk in newly diagnosed diabetic patients.98 The presence of microalbuminuria may reflect a process of general vascular damage affecting the glomerulus, retina, and the intima of large blood vessels simultaneously.(Ragab et al., 2020). In this study, no correlation was found between AIP and ACR values ($p = 0.482$), which could be due to several factors, such as the relatively small sample size in this study, differences in data analysis measurement methods where the data is ordinal, and the lack of modifications to eliminate confounding factors. Additionally, the data were collected only at one point in time, which precludes the establishment of a longitudinal relationship.

CONCLUSION

In this study, 43 patients with diabetic nephropathy were identified, with the majority being male (51.2%) and the most common age range between 46 and 59 years (48.8%). Blood glucose tests showed that 36 individuals (83.7%) had HbA1c levels of 7% or higher. The ACR tests revealed microalbuminuria in 29 patients (67.4%) and macroalbuminuria in 14 patients (32.6%). Results showed increased triglyceride levels and a decrease in both the levels and the calculation results of the Atherogenic Index of Plasma, which averaged 0.71 ± 0.27. In conclusion, higher HbA1c levels (indicating poor glycemic control) are associated with increased AIP levels, raising the risk of CVD, characterized by elevated triglycerides and a subsequent decrease in HDL.

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