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Diagnostic Value of Plasma Atherogenicity Index for Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Biochemical markers play a crucial role in the early diagnosis of diabetic nephropathy (DN), a common complication of type 2 diabetes mellitus (T2DM). This study aims to assess the plasma atherogenic index (AIP) in patients with T2DM who have DN, and evaluate the relationship between this parameter and other metabolic parameters, to determine its effectiveness in predicting the development and severity of DN.

This retrospective study included 1,902 adult patients diagnosed with T2DM and 455 healthy controls. The T2DM group was further classified based on the albumin/creatinine ratio (UACR) into 770 patients without microalbuminuria, 701 patients with microalbuminuria, and 431 patients with macroalbuminuria.

In the T2DM group, levels of creatinine, uric acid, HbA1c, cholesterol, triglycerides, UACR, and AIP increased in the microalbuminuria group compared to the normoalbuminuria group, with the highest levels observed in the macroalbuminuria group ($p = 0.000$ for each). AIP showed a significant positive correlation with HbA1c and triglycerides. Binary logistic regression analysis indicated that AIP and triglyceride levels had a significant impact on the likelihood of having T2DM with microalbuminuria.

According to our findings, AIP is associated with the presence and severity of DN in patients with T2DM and serves as an independent risk factor for DN. Therefore, we believe that AIP is a reliable biomarker that can be used additionally to assess risk, determine severity, monitor progression, and guide DN treatment in patients with T2DM.

Keywords: Diabetic nephropathy, microalbuminuria, macroalbuminuria, atherogenic index of plasma

Introduction

Type 2 diabetes mellitus (T2DM) causes serious macrovascular and microvascular complications such as diabetic nephropathy (DN), neuropathy, retinopathy, and coronary heart disease (1). The increasing prevalence of T2DM worldwide is becoming increasingly important, particularly because it raises the number of patients with DN, a common cause of end-stage renal failure (2). This situation leads to higher morbidity, mortality, and significant healthcare costs for patients (3).

Patients with T2DM are at higher risk for cardiovascular disease (CVD) (4). Dyslipidemia, a frequently observed complication in diabetic patients, contributes to the increased risk of CVD as an independent risk factor (3). Dyslipidemia also plays an important role in the development and progression of DN (5). It causes apoptosis of podocytes, infiltration of macrophages, and overproduction of extracellular matrix, leading to the development of DN (5). Additionally, studies have shown that DN creates a vicious cycle by causing dyslipidemia (6). Since cardiovascular disease is the most common cause of death in DN, more attention should be paid to dyslipidemia in patients with nephropathy (7)

Dyslipidemia, defined as changes in triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations, as well as abnormal glucose metabolism, which contribute to poor prognosis, is frequently observed in diabetic patients (8). However, when dyslipidemia is defined in this way, sufficient information about particle sizes and lipoprotein subclasses cannot be obtained (3). The Plasma Atherogenic Index (AIP), calculated as log (TG/HDL-C), provides information about the size of lipoprotein particles reflecting abnormal lipid metabolism in diabetic patients and can measure the degree of lipid metabolism abnormalities. AIP reflects

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the balance between proatherogenic and antiatherogenic factors in detail (9). It has been suggested that AIP can be used as an independent, beneficial index in the assessment of atherosclerosis and CVD risk (3). AIP has also been reported to be associated with the incidence of T2DM (10). Furthermore, AIP has been reported to predict the risk of developing T2DM better than other lipid parameters (8). AIP has also been reported as an independent risk factor for coronary heart disease in patients with T2DM (11). However, while studies have been conducted on the relationship between diabetic macroangiopathy and AIP in patients with T2DM, its relationship with microvascular complications has not been sufficiently analyzed (12).

As a result of advancements in medicine, although the prevalence of complications in patients with T2DM has decreased, effective markers for the prevention, early detection, and timely intervention of DN remain crucial. This study aimed to determine AIP in T2DM patients with normoalbuminuria, microalbuminuria, or macroalbuminuria, evaluate the relationship between AIP and other metabolic parameters, and assess the effectiveness of this parameter in predicting the development and severity of nephropathy.

Material and Method

This study, conducted by the Helsinki Declaration, was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital (No: 2023.06.264). Due to the retrospective nature of the study, informed consent was not obtained from the participants.

This study included 455 healthy controls and 1902 T2DM patients aged between 18-70 years who applied to the Internal Medicine outpatient clinic of Başakşehir Çam and Sakura City Hospital between May 2023 and January 2024. The Type 2 DM group consisted of 770 patients without microalbuminuria, 701 patients with microalbuminuria, and 431 patients with macroalbuminuria, classified according to their albumin/creatinine ratio (UACR). Patients with type 1 DM, gestational DM, CVD, cerebrovascular disease, renal failure, malignancy, hypertension, and those using medications for dyslipidemia were excluded from the study. Demographic, clinical, and laboratory data of the patients were collected from electronic records. AIP was calculated using the formula AIP =log (TG/HDL-C) (13).

Glucose, creatinine, uric acid, cholesterol, triglyceride, HDL, urine albumin, urine creatinine were measured on the Roche Cobas 8000 (Roche Diagnostics, Indianapolis, USA) analyzer. HbA1c was measured by the multicapillary zone electrophoresis method using original reagents in the Sebia Capillarys 3 Tera (Sebia/France) instrument.

Statistics Analysis: G power 3.1.9 software was used to determine the sample size for the study. Cohen's criteria were applied to obtain an effect size of 0.12, a margin of error of 5%, and a power of 95%, leading to a planned minimum sample size of 1,220 patients. The data was found to be parametrically distributed based on kurtosis and skewness values. A one-way analysis of variance (ANOVA) was used to examine whether the measurements obtained in the study showed significant differences between the groups. The relationship between the measurements was analyzed using correlation analysis. Binary logistic regression was performed to determine the variables affecting the T2DM group with microalbuminuria. The significance of AIP in the diagnosis of T2DM group with microalbuminuria and macroalbuminuria was examined by ROC analysis. Analyses were performed with SPSS 20.0 software at a 95% confidence level.

Results

Our study consisted of 4 groups; 455 healthy controls, 770 without microalbuminuria, 701 with microalbuminuria, and 431 T2DM cases with macroalbuminuria. When the relationship between gender and groups was examined; 55.4% of the control group were female and 44.6% were male. In the T2DM group with normoalbuminuria, 56.9% were female and 43.1% were male; in the T2DM group with microalbuminuria, 55.6% were female and 44.4% were male; and of the T2DM group with macroalbuminuria group, 54.1% were female and 45.9% were male. There was no significant relationship between the groups in terms of age, gender, and LDL levels ($p = 0.105$, $p = 0.819$, $p = 0.446$ respectively) (Table 1).

The mean values of biochemical parameters across the groups and the statistical significance of the differences between these means were analyzed using an independent samples t-test. Accordingly, glucose, creatinine, uric acid, HbA1c, cholesterol, triglycerides, HDL, UACR, and AIP measurements differed significantly between groups ($p = 0.000$ for each) (Table 1). According to the results of the Tukey test, the levels of glucose, creatinine, uric acid, HbA1c, cholesterol, triglycerides, UACR, and AIP were significantly higher in the T2DM groups compared to the control group average. In comparison, HDL levels

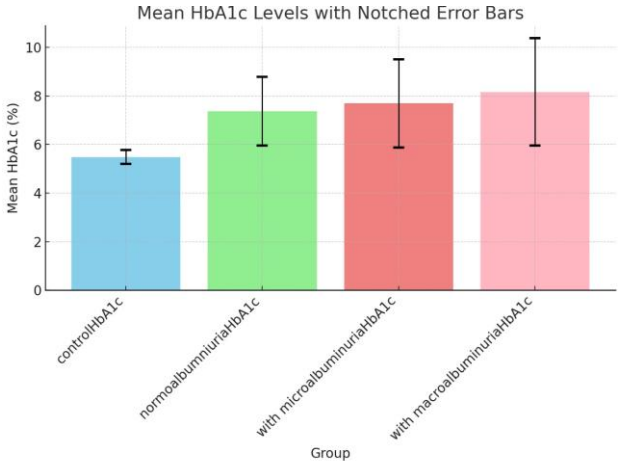

Fig. 1. HbA1c levels of groups

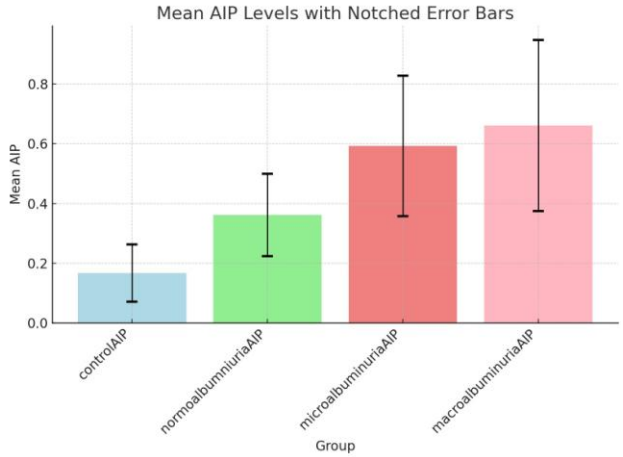

Fig. 2. AIP levels of groups

were significantly lower (p =0.000 for each). In the T2DM groups with microalbuminuria, glucose, creatinine, uric acid, HbA1c, cholesterol, triglycerides, UACR, and AIP levels increased more than in the normoalbuminuria patient group, and HDL levels decreased (p =0.000 for each). In the group with macroalbuminuria, glucose, creatinine, uric acid, HbA1c, cholesterol, triglycerides, UACR, and AIP levels were the highest, while HDL concentrations were the lowest. The distribution of HbA1c and AIP levels in the groups is shown in Figures 1 and 2.

The levels of UACR showed a significant positive correlation with creatinine (r = 0.263, p <0.001), uric acid (r = 0.224, p <0.001), triglycerides (r = 0.272, p <0.001), and AIP (r = 0.283, p <0.001). AIP showed a significant positive correlation with glucose (r = 0.380, p <0.001), HbA1c (r = 0.414, p <0.001), and cholesterol (r = 0.232, p <0.001), and a significant negative correlation with HDL (r = -0.627, p < 0.001).

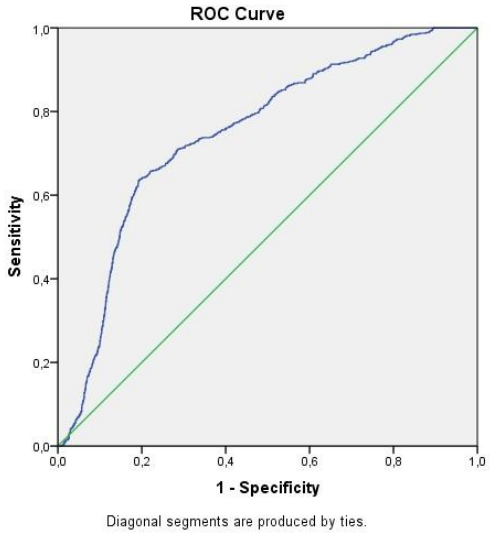

Fig. 3. ROC analysis of the diagnostic value of AIP in T2DM with microalbuminuria

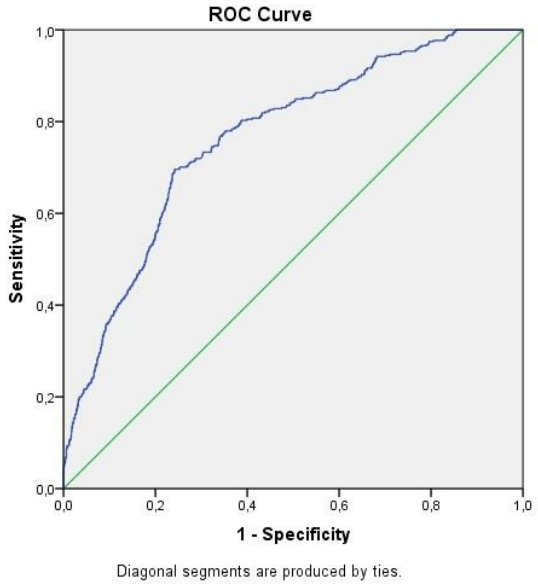

Fig. 4. ROC analysis of the diagnostic value of AIP in T2DM with macroalbuminuria

Binary logistic regression analysis was performed for the microalbuminuria status of the patients (Table 2). When examined with binary logistic regression, AIP and triglyceride measurements were independent risk factors for the T2DM group with microalbuminuria. No significant association was found between other parameters and the risk of microalbuminuria.

ROC curve was constructed to analyze the efficacy of AIP in T2DM patients with microalbuminuria and macroalbuminuria (Figure 3, 4). According to the results of ROC analysis, AIP diagnostic values were statistically significant

Table 1: Mean, SD, and p-values of the Biochemical Parameters of The T2DM Group with Normoalbuminuria, Microalbuminuria, and Macroalbuminuria, As Well As the Control Group

	Control n=455	T2DM group with normoalbuminuria n=770	T2DM group with microalbuminuria n=701	T2DM group with macroalbuminuria n=7431	p
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	
Male, n (%)	44.6	43.1[a]	44.4	45.9	0.819
Age, years	54.2 ± 13.71	55.04 ± 10.55	55.4 ± 11.17	56.2 ± 13.27	0.105
Glucose, mg/dL	91.74 ± 7.69	140.86 ± 51.51	154.14 ± 64.56	171.14[b] ± 85.44	0.000
Creatinin, mg/dL	0.77 ± 0.14	0.79 ± 0.15	0.78 ± 0.17	0.91[b] ± 0.22	0.000
Uricacid, mg/dL	4.68 ± 1.25	4.71 ± 1.25	4.79 ± 1.22	5.67[b] ± 1.55	0.000
HbA1c, %	5.48 ± 0.29	7.37 ± 1.41	7.69 ± 1.81	8.16[b] ± 2.21	0.000
Cholesterol, mg/dL	179.91 ± 35.72	181.18 ± 38.44	188.56 ± 39.66	198.59[b] ± 52.24	0.000
Triglyceride, mg/dL	82.05 ± 19.25	117.64 ± 41.55	182.54 ± 84	217.23[b] ± 136.21	0.000
HDL, mg/dL	55.55 ± 11.69	49.83 ± 9.82	43.57 ± 10.09	41.65[b] ± 10.08	0.000
LDL, mg/dL	107.95 ± 29.83	107.88 ± 33.25	108.93 ± 34.44	111.1[b] ± 35.98	0.446
UACR, mg/g	7.62 ± 5.4	9.38 ± 6.41	70.02 ± 48.43	1477.14[b] ± 1389.59	0.000
AIP	0.17 ± 0.1	0.36 ± 0.14	0.59 ± 0.24	0.66[b] ± 0.29	0.000

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UACR, urine albumin to creatinine ratio; AIP, atherogenic index of plasma
a: chi square test ; b: One way Anova

Table 2: Independent Risk Factors for Detecting the T2DM Group With Microalbuminuria, According to Binary Logistic Regression Analysis (Table 2)

	B	S.E.	Wald	df	p	Exp(B)
Glucose, mg/dL	0.002	0.002	0.666	1	0.414	1.002
Creatinin, mg/dL	-1.163	0.630	3.404	1	0.065	0.313
Uric acid, mg/dL	0.024	0.077	0.095	1	0.758	1.024
HbA1c, %	0.054	0.080	0.455	1	0.500	1.056
Cholesterol, mg/dL	0.042	0.035	1.453	1	0.228	1.043
Triglyceride, mg/dL	-0.019	0.009	4.462	1	0.035	0.982
HDL, mg/dL	-0.020	0.039	0.251	1	0.616	0.980
LDL, mg/dL	-0.040	0.035	1.312	1	0.252	0.961
UACR, mg/g	-0.005	0.001	45.720	1	0.000	0.995
AIP	9.434	1.867	25.542	1	0.000	12512.205
Gender	-0.104	0.197	0.278	1	0.598	0.902
Constant	-4.172	1.141	13.373	1	0.000	0.015

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UACR, urine albumin to creatinine ratio; UACR, urine albumin to creatinine ratio; AIP, atherogenic index of plasma

(p =0.000) (Table 3). When evaluating the effectiveness of AIP in predicting microalbuminuria in the T2DM group, the ROC analysis revealed that the AUC for AIP was 0.747 (95% confidence interval: 0.726-0.768; p =0.000) (Table 3) (Figure 3). The cut-off can be determined as 0.5042 (sensitivity=0.638; specificity=0.805). When evaluating the effectiveness of AIP in predicting macroalbuminuria in the T2DM group, the ROC analysis revealed that the AUC for AIP was 0.764 (95% confidence interval: 0.740-0.788; p=0.000) (Table 3) (Figure 4). The cut-off can be determined as 0.5055 (sensitivity=0.694; specificity=0.758).

Table 3: Effectiveness of AIP in Predicting T2DM Patients with Microalbuminuria and Macroalbuminuria

	AUC	Std. Errora	Cut Off Point	Sensitivity	Specifity	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
AIP (Microalbumina)	0.747	0.011	0.506	63.5	80.8	0.000	0.726	0.768
AIP (Macroalbumina)	0.764	0.012	0.505	69.6	75.8	0.000	0.740	0.788

AUC, area under the curve.

Discussion

DN, one of the common microvascular complications of diabetes, is also a significant indicator of poor prognosis in diabetic patients (14). Studies have shown that DN is detected at diagnosis in approximately 3% of patients newly diagnosed with T2DM worldwide, while 20-30% develop it in the following years (15). Therefore, early detection and treatment of DN formation is significant for a better prognosis of T2DM and to reduce mortality. The 24-hour urinary microalbumin is considered one of the most sensitive markers reflecting early glomerular damage. However, quantitative analysis of 24-hour urine albumin can be influenced by various factors, potentially leading to inaccurate results. Therefore, simple and economical biochemical markers are necessary for the screening, early diagnosis, and treatment of DN in patients with diabetes.

T2DM patients are predisposed to lipid metabolism disorders, characterized by elevated triglyceride levels and low HDL-C levels, which are typical indicators of lipid metabolism abnormalities (14). Hirano et al. have found that in chronic kidney disease (CKD), as the stage of the disease progresses, TG levels increase while HDL levels decrease (16). Impaired HDL-C-mediated cellular cholesterol efflux has been reported to play a role in the development of DN (17). One study found no significant difference in LDL-C levels between diabetic and non-diabetic patients (18). In a study conducted in the prognostic analysis of the diabetes subgroup, it was shown that LDL-C levels did not increase in patients with poor prognosis (9). Therefore, it has been stated that LDL-C cannot explain the poor prognosis and severe lesions in diabetic patients (13). Impaired lipid metabolism in diabetic patients is usually manifested by increased TG and decreased HDL-C, similar to our results, while LDL-C is often normal or slightly elevated (19).

Diabetic dyslipidemia, characterized by increased TG, decreased HDL-C concentrations, and a predominance of small, dense LDL (sdLDL), has been recognized as an important complication of T2DM in recent years (20). Research indicates that smaller LDL particles penetrate and accumulate in the arterial wall, contributing to arteriosclerosis and cardiovascular disease (8). Studies have shown that LDL-C particle diameter is closely associated with the severity of atherosclerosis (14). However, complex techniques and high costs make the detection of sdLDL difficult (20). AIP, which has been reported to have a negative relationship with LDL particle size, is a sensitive index proposed to evaluate potential plasma atherogenicity that can indirectly reflect the size of sLDL-C particles (21).

One study confirmed that AIP is more significant than LDL-C in atherosclerosis (22). Therefore, AIP is useful in predicting the degree of atherosclerosis in diabetic patients with normal LDL-C (13). Additionally, it has been shown that AIP is associated with T2DM because it reflects dyslipidemia well and that high AIP values significantly increase the risk of T2DM (20). Studies have also demonstrated a negative correlation between AIP and insulin sensitivity in diabetic patients (23). Thus, AIP not only provides a comprehensive assessment of blood lipid status but also reflects the severity of insulin resistance. Various studies have found AIP to be a good marker for diabetes and macroangiopathy complications (13). Furthermore, recent epidemiological studies highlight the value of AIP in predicting the risk of future atherosclerosis and cardiovascular complications (20).

Baliarsingh et al. reported that the positive association between serum UA and AIP in middle-aged, healthy men could be explained by hypertriglyceridemia and decreased HDL-C levels (24). A study conducted in Malaysia found a correlation between AIP and various cardiovascular risk factors, including glucose, TG, HDL-C, and visceral fat (25). Notably, AIP has been identified as a better marker than LDL-C for detecting atherosclerosis, and its use alongside

traditional risk factors has been recommended (9). Zhou et al. examined 3,278 patients with T2DM and found that those with CAD had higher AIP levels than those without. They concluded that AIP is an independent risk factor for CAD in diabetic patients (20). Additionally, one study found that AIP was highly correlated with BMI, TG, TC, LDL-C, and physical activity (10). Consistent with previous studies, our findings also showed a positive correlation between AIP and glucose, cholesterol, and HbA1c, as well as a negative correlation with HDL.

Hyperglycemia stimulates intracellular pathways, leading to the development of vascular and microvascular complications such as DN in patients with T2DM (26,27). Additionally, lipid metabolism disorders have been shown to play a crucial role in the progression of DN (28). Dyslipidemia can cause lipotoxicity-related kidney damage through inflammation, endoplasmic reticulum stress, mitochondrial dysfunction, and activation of cell death pathways (29). One study has shown that hypertriglyceridemia is associated with the risk of microalbuminuria in patients with T2DM (30).

Studies indicate that lipid parameters can reflect the risk of T2DM, but AIP may be more strongly associated with T2DM risk. AIP has been recognized as a simple, easily calculated parameter for assessing T2DM risk (8). It has also been reported as an effective marker for prognosis monitoring and complication risk assessment in T2DM (12). In a study following 2.356 T2DM patients for four years, Qin et al. suggested that AIP was associated with prognosis and identified it as an independent risk factor for T2DM prognosis based on regression analysis (13). In DN associated with lipid metabolism disorders, AIP may serve as a sensitive indicator of lipid metabolism abnormalities (14). Qi et al. reported that albuminuria increased in correlation with AIP (3). Similarly, Akbaş et al. found that in diabetic patients, elevated serum UA levels were associated with increased AIP and albuminuria. Notably, patients with hyperuricemia, albuminuria, and high AIP have a heightened risk of developing CVD (31). A study by Adejumo et al. examined AIP across CKD stages in Nigeria and found a significant increase in AIP among CKD patients with declining renal function. Their findings emphasize the need to assess atherogenic risk in CKD patients using lipid ratios such as AIP rather than evaluating individual lipid components separately (32).

In our study, we analyzed biochemical parameters in T2DM patients with DN. In a study examining 335 newly diagnosed T2DM patients, it was found that the AIP index of T2DM patients with microalbuminuria was significantly higher compared to T2DM patients without microalbuminuria, that AIP was an independent risk factor for microalbuminuria in logistic regression analysis, and that AIP had a better predictive value for the formation of microalbuminuria in T2DM patients in ROC analysis (14). Similarly, in our study, AIP levels increased in the T2DM group with microalbuminuria and were at the highest level in the macroalbuminuria group. We found that AIP and triglyceride had high diagnostic values for microalbuminuria and macroalbuminuria. According to the ROC analysis results, the diagnostic value of AIP was significant. The cut-off value of AIP for microalbuminuria was 0.5042, with a sensitivity of 63.8% and a specificity of 80.5%. The cut-off value of AIP for macroalbuminuria was 0.5055, with a sensitivity of 69.4% and a specificity of 75.8%. These threshold values can serve as a guide in diagnosing DN. An AIP of 0.5042 indicates a significantly increased likelihood of microalbuminuria, while an AIP of 0.5055 suggests a high risk of macroalbuminuria. Therefore, AIP is a valuable biomarker that can be used alongside other markers to assess the presence and severity of DN in diabetic patients.

This study had some limitations. First, since it is a single-center study, it may not fully reflect the general population. Some variables may be left out due to the retrospective data collection process. However, our study has a large diabetic patient population and our data show the importance of monitoring lipid profile and glucose levels in developing DN in T2DM patients. However, since our study is retrospective, it is not sufficient to establish a cause-effect relationship. Therefore, multicenter, prospective studies are needed to determine the mechanisms explaining the relationship between albuminuria and AIP that contribute to the development of DN in T2DM patients.

According to the results of our study, AIP is associated with the presence and severity of T2DM. Our data also suggest that AIP is an independent risk factor for DN in patients with T2DM. AIP is an effective marker for predicting the risk of microalbuminuria and macroalbuminuria in T2DM. We believe that AIP, which is easily calculated with routine blood lipid parameters and is simple and low-cost, can be used as a simple, cheap, strong, and reliable biomarker in the assessment, early diagnosis, follow-up, and treatment of DN risk in patients with T2DM. Thus, it could be useful in preventing the development of renal failure, evaluating damage, and guiding treatment.

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