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The relationship with disease severity of ischemia-modified albumin levels in diabetic nephropathy

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Abstract

Aim: While type 2 diabetes (T2DM) is increasing rapidly, developing diabetic complications are the leading cause of morbidity and mortality. Biochemical markers are important for early diagnosis and treatment of nephropathy, which is a common complication. The aim of this study is to evaluate serum ischemia-modified albumin (IMA) levels in the development of diabetic nephropathy in T2DM patients and to determine the effectiveness of this parameter in predicting the presence and severity of nephropathy.

Materials and Methods: 68 adult patients diagnosed with T2DM and 30 healthy controls were included in this study. The T2DM group consisted of 34 patients without microalbuminuria (<30 mg/g) and 34 patients with microalbuminuria (30–300 mg/g) according to albumin/creatinine ratio (UACR). Biochemical data and serum IMA levels of the patient and control groups were measured and compared.

Results: In terms of IMA levels, the difference between T2DM patients with microalbuminuria (0.55 ± 0.08 ABSU) and without microalbuminuria (0.42 ± 0.05 ABSU) and control (0.37 ± 0.08 ABSU) groups was significant ($p<0.0001$). The T2DM group with microalbuminuria had the highest glucose, HbA1c, UACR, and IMA levels. There was a positive correlation between IMA levels and UACR ($r = 0.541$, $p < 0.001$). IMA had a weak correlation with HbA1c ($r = 0.345$, $p = 0.002$). ROC analysis was performed and the IMA test had a high diagnostic value in the diagnostic differentiation of T2DM patients with microalbuminuria. According to multiple logistic regression analysis, IMA levels were an independent risk factor for DN ($p = 0.003$).

Conclusion: Our data showed that IMA values increased significantly in diabetic patients, especially in those with microalbuminuria, and this increase was correlated with UACR levels. This study has shown that increased IMA levels are an important marker for the presence and severity of microalbuminuria in diabetic patients and therefore may be important in the early detection of renal dysfunction in T2DM. We even think that it can be used as an important marker in the follow-up of diabetic patients, even before the development of microalbuminuria.

Introduction

Type 2 diabetes (T2DM) cases are increasing rapidly all over the world and diabetic nephropathy (DN) develops in 20-40% of these patients [1]. Inflammation, which is accepted as an early marker of DN, which is a complex process, causes increased urinary albumin excretion. Increased albumin excretion develops with decreased glomerular filtration as a result of hyperglycemia, ischemia, oxidative stress, and increased renal endothelial damage [2]. It is also characterized by increased cardiovascular mortality and morbidity [3 However, although microalbuminuria develops as a result of severe damage to glomerular function, DN was found in 29%-61% of T2DM patients with normal urine albumin concentrations [4,5]. Thus, this precludes the use of microalbuminuria alone as an adequate predictive marker in DN, and additional biomarkers are needed for the early detection of DN.

Chronic hyperglycemia in diabetic patients causes endothelial dysfunction as a result of increased oxidative stress. Decreased antioxidant levels and increased reactive oxygen species (ROS) in diabetes, structural changes occur in the N-terminal region with the effect of hydroxyl radical in albümin [6]. This altered form of albumin, which has been found to be related to oxidative stress and ischemia, is called ischemia-modified albumin (IMA) [7].

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Unlike normal serum albumin, IMA with an altered N-terminal region has a very low capacity to bind free metals [8]. FDA approved that IMA can be used in the emergency department for the diagnosis of acute coronary syndrome and myocardial ischemia [8,9]. IMA, whose role in cardiac and noncardiac diseases, has been reported, has also been shown to be associated with diabetic complications [10,11]. Piwowar et al examined the relationship between diabetes and IMA, and it was determined that IMA values increased by 75% in diabetic patients [11].

Since early detection of the microalbuminuria stage is very important in the diagnosis and prevention of diabetic nephropathy, biomarkers with high sensitivity and specificity are needed. In addition to the UACR, which is used as a routine laboratory parameter, these markers will contribute to the diagnosis, follow-up, and early determination of the possible response to treatment, and will be useful in the prevention of the development of renal failure, in the evaluation of oxidative damage, and will guide the treatment. The aim of this study was to evaluate serum IMA levels and the relationship between IMA levels and metabolic parameters in T2DM patients with diabetic nephropathy, which is known to be closely related to oxidative stress, and to determine the effectiveness of this parameter in predicting the presence, development, and severity of nephropathy.

Materials and Methods

Our study complies with the principles of the Declaration of Helsinki. Approval was obtained from the ethics committee of Istanbul Başakşehir Çam and Sakura City Hospital (No: 2023.06.264). Consent was obtained from the patients who were informed before the study. Our prospective study was carried out with 68 adult patients diagnosed with T2DM and 30 healthy controls who were examined in the Internal Medicine outpatient clinic from January 2023 to May 2023. People with T2DM over the age of 18 without chronic disease were included. Patients with cardiovascular disease, cerebrovascular disease, pulmonary embolism, renal failure, infection, and malignancy were not included. T2DM patients were divided into 2 groups according to the UACR ratio 34 patients without microalbuminuria (UACR <30 mg/g) and 34 patients with microalbuminuria (UACR 30-300 mg/g).

Data collection

The data of the patients were obtained from the hospital information system and compared. The tests were analyzed in Istanbul Başakşehir Çam and Sakura City Hospital Central Laboratory. To investigate albuminuria, UACR was studied in morning spot urine samples. Fasting venous blood samples were centrifuged at 3000 rpm at 4 °C for 10 min and stored at -80 °C for IMA analysis. Glucose (enzymatic reference with hexokinase method), urea level (kinetic test with urease and glutamate dehydrogenase), serum and urine creatinine level (Jaffé method), urine albumin (Immunoturbidimetric method), serum cholesterol, triglyceride and HDL (enzymatic colorimetric method) were measured on Roche Diagnostics Cobas 8000 (Roche Indianapolis/America) analyzer in the hospital central laboratory. Intraassay and interassay CV values were for glucose 0.63%, 0.75%; for urea 0.87%, 1%; for serum creatinine1.36%, 1.3%; for urinary creatinine 2.05%, 1.8%; for urinary albümin 2.55%, 1.45%; for cholesterol 1.5%, 1.6%; for triglyceride 1.85%,1.8%; for HDL 1.46%, 1.5% respectively. HbA1c was measured with the multicapillary zone electrophoresis method in the Sebia Capillarys 3 Tera (Sebia/France) device. Intraassay CV values were 0.85% and interassay CV values were 0.96%. In the measurement of IMA levels, Bar-Or et al. a method developed by have been used [12]. The structural change in albumin due to ischemia is measured by the colorimetric test. It is based on the addition of cobalt and the spectrophotometric measurement of unbound cobalt and measured at 470 nm using a spectrophotometer. Since IMA concentrations are not standard, they are reported in absorbance units (ABSU).

Statistical analysis

Categorical variables were given as numbers and percentages, and continuous variables as mean±SD and median (min–max) values. Analysis of variance was used for comparison between groups. Tukey test was used as a post hoc test. Pearson correlation coefficient was used for correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to determine IMA activity in the development of diabetic nephropathy. Statistical significance in the study was accepted as $p<0.05$ for all analyses. IBM SPSS 21 program was used in the analysis of all data.

Results

This study consisted of 3 groups, 34 with normoalbuminuria, 34 with microalbuminuria T2DM patients, and 30 healthy controls. There was no significant difference between the groups in terms of age, gender, BMI, urea, creatinine, cholesterol, HDL, and LDL ($p>0.05$) (Table 1). In patients with microalbuminuria and normoalbuminuria, glucose, HbA1c, UACR, triglyceride, and IMA levels were higher than in the control group ($p<0.05$). In addition, glucose, HbA1c, UACR, triglyceride, and IMA levels increased more in T2DM groups with microalbuminuria than in the normoalbuminuria patient group ($p<0.05$). The

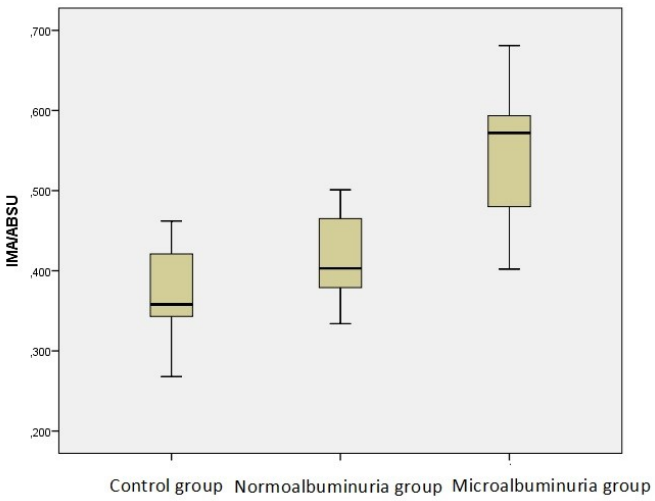

Figure 1. IMA averages of the groups.

Table 1. Comparison of the basic parameters and IMA levels of the groups.

	Control group (n=30)	T2DM group with normoalbuminuria (n=34)	T2DM group with microalbuminuria (n=34)	P value
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)	
Age, years	45.24 ± 9.60 45 (28 – 67)	51.24 ± 12.60 51 (21 -74)	50.63 ± 13.50 53 (20- 73)	0.328
Gender, F/M	14/16	17/17	18/16	0.237
BMI, kg/m^2	27.50 ± 4.48 27.76 (18.22 – 33.30)	31.27 ± 4.74 30.48 (22.86 – 41.02)	30.56 ± 8.38 30.42 (17.36 – 46.88)	0.255
Glucose, mg/dL	91.71 ± 8.38 93 (74-104)	128.90 ± 53.31 114 (81-314)	154.53 ± 76.173 133 (76-382)	<0.0001*
Hba1c, %	5.39 ± 0.40 5.5 (4.1-5.9)	7.35 ± 1.36 7 (5.6-11.5)	8.5 ± 2.22 8.3 (5.6-13.2)	<0.0001*
UACR, mg/g dL	4.76 ± 2.97 4 (1-13)	7.76 ± 7.09 6 (0 – 25)	95.95 ± 62.10 81 (33 – 281)	<0.0001*
Urea, mg/	26.78 ± 7.29 26.8 (17-41)	29.03 ± 8.55 28.30 (15-48)	27.24 ±7.54 24.80 (18-49)	0.176
Creatinine, mg/dL	0.82 ± 0.09 0.82 (0.7-1.0)	0.77 ± 0.20 0.72 (0.5-1.2)	0.72 ± 0.16 0.72 (0.3-1.0)	0.382
Cholesterol, mg/dL	176.06 ± 44.32 176 (99-256)	179.95 ± 33.54 184 (97-222)	199.16 ± 61.07 200 (81-390)	0.199
Triglyceride, mg/dL	102 ± 37.07 105 (25-162)	141.29 ± 92.27 117 (60-454)	190.32 ± 169.06 134 (69-757)	0.008*
HDL, mg/dL	47.24 ± 11.32 48 (25-76)	45.52 ± 11.37 41 (31-77)	45.21 ± 20.51 40 (13-106)	0.543
LDL, mg/dL	108.41 ± 34.91 108 (38-175)	106.62 ± 27.15 105 (43-160)	108.42 ± 37.18 117 (32-170)	0.924
IMA, ABSU	0.37 ± 0.05 0.36 (0.27-0.46)	0.42 ± 0.05 0.40 (0.33-0.50)	0.55 ± 0.08 0.57 (0.40-0.68)	<0.0001*

BMI, body mass index; UACR, urine albumin to creatinine ratio; IMA, ischemia-modified albumin; * p<0.05.

Table 2. Diagnostic efficacy of IMA level to differentiate T2DM patients with normoalbuminuria and microalbuminuria.

	AUC	Cut off	Sensitivity	Specificity	PPV	NPV	+LR	–LR	DOR
IMA(microalbuminuria)	0.966	0.456	84.4	96.7	97	85	25.31	0.16	156.6
IMA(normoalbuminuria)	0.710	0.374	79.4	60	69	72	1.99	0.34	5.786

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; –LR, negative likelihood ratio; DOR, diagnostic odd ratio.

group with microalbuminuria had the highest concentrations of HbA1c and IMA (Figure 1, 2).

IMA levels were significantly positively correlated with UACR ($r = 0.541$, $p < 0.001$). There was a weak correlation between IMA and HbA1c ($r = 0.345$, $p = 0.002$). No significant correlation was found between IMA concentrations and other parameters.

ROC analysis was performed to distinguish T2DM patients with normalbuminuria and microalbuminuria from the control group (Figure 3, 4). The IMA test had a high diagnostic value, especially in the diagnosis of T2DM patients with microalbuminuria (Table 2).

Multiple logistic regression analysis was performed to evaluate risk factors leading to microalbuminuria. We found that IMA levels were an independent factor for DN ($p = 0.003$).

Discussion

An increase is observed in the incidence of diabetes all over the world, and DN develops in 20-40% of these patients [1]. Increased albumin excretion in the urine, which is accepted as an early marker of DN, which has a complex process, develops with decreased glomerular filtration as a result of renal endothelial damage [2]. However, the development of microalbuminuria as a result of severe damage to glomerular function prevents its use as an adequate predictive marker in DN. Therefore, additional biomark-

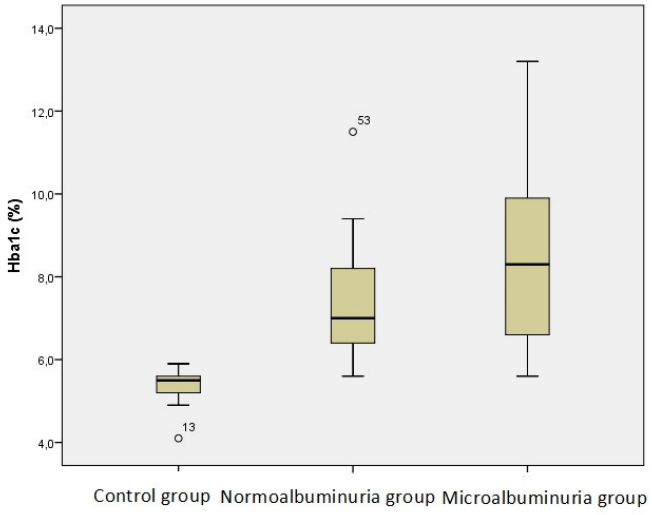

Figure 2. HbA1c averages of the groups.

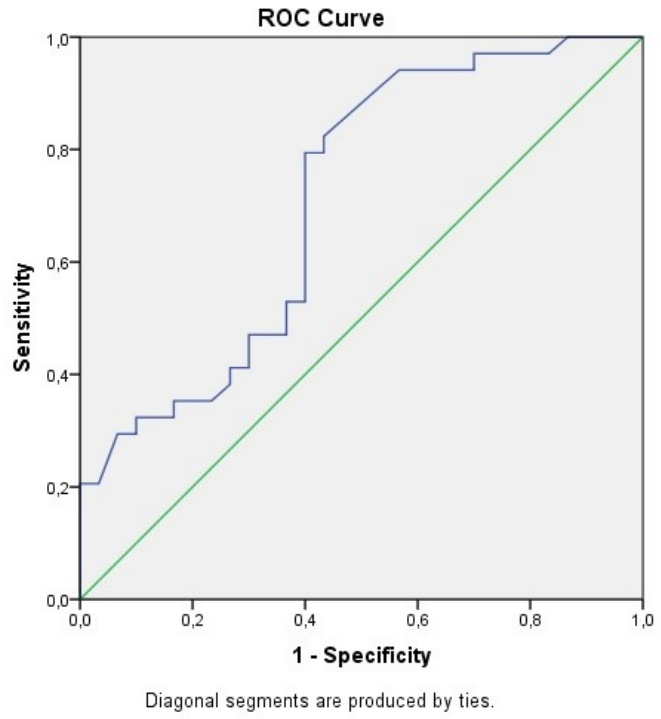

Figure 3. ROC analysis of IMA level to differentiate between control and normoalbuminuria T2DM patients according to UACR.

ers are required to detect DN before it progresses. In our study, we found higher serum IMA concentrations in patients with T2DM compared to the control group. IMA levels were higher in those with microalbuminuria than in those without microalbuminuria. In addition, IMA levels increased in correlation with UACR. Measurement of IMA together with routine parameters may be useful in monitoring the prognosis and early detection of DN in T2DM.

Various research has shown an increase in oxidative stress related to an increase in free radicals and a decrease in antioxidant capacity in diabetes [13]. Oxidative stress and excessive production of free radicals contribute to diabetes prognosis, progression, and development of several complications [14]. Hyperglycemia; leads to an increase in IMA levels through hypoxia, ischemia, oxidative stress, and inflammatory processes [15]. It has been shown that IMA increases renal failure, cardiovascular diseases, cerebrovascular diseases, infections, some malignancies, and traumas [12].

Menteşe et al. examined the relationship between deep vein thrombosis and IMA, the level of IMA was detected to be significantly increased when compared to the control group [16]. In a study, 290 diabetic patients were examined, It was determined that IMA was significantly increased in diabetics with peripheral artery disease compared to those without peripheral artery disease, and it was emphasized that it could be used as a risk marker in follow-up of the disease [17]. Türk et al. in their study examining the relationship between Diabetic Retinopathy and IMA, found the highest average of IMA in the retinopathy group and suggested the use of IMA as a marker for the early detection of microvascular hypoxia in order to prevent retinal complications in diabetes [18]. C29 or T(173).

For the first time, Piwowar et al. showed increased IMA values in patients with T2DM compared to controls [19]. Kaefer et al. stated that the high IMA concentrations they detected in T2DM patients were caused by hyperglycemia and inflammation [20]. In our study, similar to other studies, we detected that T2DM groups had higher IMA levels than the healthy control group [21,22]. This shows that IMA occurs in the early stages before the development of DN and is effective in the development of diabetic complications [22].

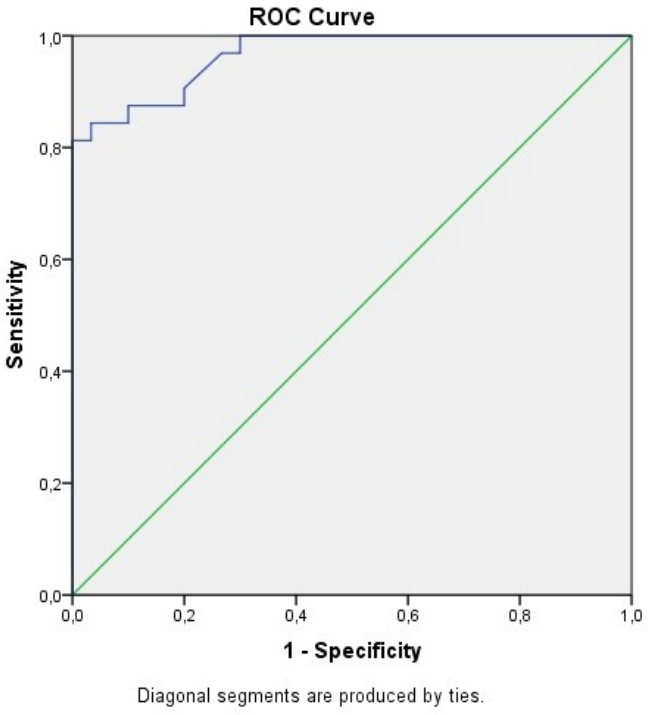

Figure 4. ROC analysis of IMA level to distinguish between control and microalbuminuria T2DM patients according to UACR.

A study showed that IMA concentrations increased more in patients with T2DM than in the healthy group, and in patients with nephropathy than in those without nephropathy [23]. In this study, it is stated that increased IMA concentrations in T2DM patients may signify subclinical vascular damage [23]. Similar to other studies, the fact that IMA concentrations were increased in the group with microalbuminuria than in the normoalbuminuric group in our study shows that IMA concentrations are associated with the severity of DN [22]. Piwowar et al. emphasized that the measurement of IMA may contribute to the diagnosis of DN and monitoring the course of the disease in diabetes mellitus patients [3]. Genetic predisposition, hyperglycemia, metabolic and hemodynamic changes are held responsible for the etiopathogenesis of DN. Studies have reported that IMA may indicate vascular dysfunction and subclinical disease in the DN [24,25]. Chronic hyperglycemia triggers excessive production of ROS that causes molecular damage and leads to the development of DN [26]. The ischemia, oxidant activity, and inflammation due to hyperglycemia cause a rise in IMA concentrations and consequently podocyte damage [22]. Our data showed a significant correlation between IMA levels and UACR in the T2DM groups, similar to some studies [21,22]. Therefore, the measurement of IMA is an extremely useful biomarker in addition to the measurement of HbA1c and UACR in the detection of deterioration in kidney functions in the early period.

It is stated that increased HbA1c levels in T2DM are associated with the presence and severity of various diabetes complications, including DN [27]. Aging, diabetes duration, advanced hemoglobin glycosylation, and dyslipidemia are known as risk factors for diabetes complications [17]. Ma et al established a positive relationship between IMA and HbA1c in diabetic patients, and it was emphasized that IMA is an independent risk factor for DM complications [17]. In our study, we detected that IMA with HbA1c was weakly positively correlated and that IMA was an important risk factor for DN.

The fact that our patient groups did not include patients with macroalbuminuria is one of the limitations of our study. Our primary aim was purpose was to establish whether IMA is an important biomarker for the early detection of diabetic nephropathy. Our data should be supported by large-scale and multicenter prospective studies by measuring IMA levels, an important marker of DN, in diabetic patients. Our results will contribute to the literature as a study showing the effectiveness of IMA levels in the detection of the early period when DN detection is difficult.

Increased oxidative stress is effective in the development of nephropathy in diabetes. In our research, UACR and IMA concentrations were increased in T2DM patients and showed a positive correlation. Our results showed that IMA levels as well as markers such as HbA1c and UACR are useful markers for early detection of DN. In fact, we can say that IMA will be useful as a prognostic diagnostic biomarker in the monitoring of diabetic patients who have a high risk of developing DN and who have not yet developed microalbuminuria, and in the early detection of DN.

Conflict of interest

The authors declare that there is no conflict of interest in the study.

Financial disclosure

The authors declared that this study received no financial support.

Disclaimers

The views expressed in the article are my own. The institution or funder does not have an official opinion.

Authorship contributions

Concept: GŞ, BC, Design: GŞ, BE, Data Collection or Processing: GŞ, EK, BC Analysis or interpretation: GŞ, CC Literature Review: GŞ, EK Wrote the Paper: GŞ, CC, EK, BC, BE.

Ethical approval

This study was approved by the ethics committee of Istanbul Başakşehir Çam and Sakura City Hospital (No:2023.06.264).

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