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ORIGINAL RESEARCH

Aortic Stiffness Index And Carotid Intima-Media Thickness Are Independently Associated With The Presence Of Microalbuminuria In Patients With Type 2 Diabetes Mellitus

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Yaşar Turan [1]
Elif Turan [2]

[1]Department of Cardiology, Medical School of Bozok University, Yozgat, Turkey; [2]Department of Endocrinology and Metabolic Disease, Medical School of Bozok University, Yozgat, Turkey

Purpose: Microalbuminuria is a premature and widely used indicator of diabetic nephropathy and is reported to be related with a higher cardiovascular risk in diabetic patients. We aimed to examine whether the echocardiographic parameters, such as epicardial fat thickness (EFT), carotid intima-media thickness (CIMT) and aortic stiffness index (ASI) are associated with microalbuminuria in patients with diabetes mellitus type 2 (T2DM).

Patients and methods: A total of 272 consecutive patients were enrolled and after the exclusion criteria, the data of 180 patients with T2DM were used in this cross-sectional study. Patients were divided into two groups: 82 patients with microalbuminuria and 98 patients without microalbuminuria (normoalbuminuria). The laboratory results and echocardiographic EFT, CIMT and ASI parameters were noted.

Results: Compared with the normoalbuminuria group, EFT, CIMT and ASI were significantly higher in the microalbuminuria group ($p<0.05$ for all). In logistic regression analysis; CIMT (OR: 3.15, $p=0.024$) and ASI (OR: 4.19, $p=0.016$) were independently associated with microalbuminuria in patients with T2DM.

Conclusion: In addition to CIMT, as a novel finding, ASI which is an indicator for the elastic properties of the aortic root was independently associated with microalbuminuria. CIMT and ASI measurement by echocardiography may be helpful in identifying the accompanying factors in the development of nephropathy.

Keywords: aortic stiffness, carotid intima-media thickness, microalbuminuria

Introduction

Diabetes mellitus (DM) is a major risk factor for cardiovascular disease.[1] Cardiovascular complications and events are more common in patients with diabetic nephropathy (DNP) than in patients without.[2] Microalbuminuria is a premature and widely used indicator of DNP and is reported to be related with cardiovascular risk.[3]

Epicardial fat thickness (EFT) indicates visceral adipose tissue around the heart. This adipose tissue is located between the pericardial and myocardial layer. It has endocrine effects by secreting some cytokines. These cytokines are related with endothelial dysfunction, oxidative stress, inflammation and atherosclerosis.[4,5] Ultrasonographic assessment of carotid intima-media thickness (CIMT) is a marker of subclinical atherosclerosis and may predict future cardiovascular disease.[6] It is

Correspondence: Yaşar Turan
Bozok University, Cardiology, Yozgat 66200, Turkey
Tel +903542127050
Fax +903542126201
Email yasar044@yahoo.com

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widely used in clinical practice because of its advantages such as low cost, reliability and reproducibility.

Distension during systole and elastic recoil during the diastole phase, primarily in elastic arteries such as the aorta and the carotid, is fundamental to maintain optimal blood flow in a cardiac cycle. The elasticity of these major arteries enables the pressure wave to be dampened. A decrease in the elasticity leads to the loss of this compensatory mechanism. Aortic elastic properties may give additional information about the future cardiovascular events.[7] An impaired aortic stiffness is a known cardiovascular risk factor and is related with other cardiovascular risk factors like age, hyperlipidemia, hypertension, diabetes, and smoking.[8,9] Echocardiographic measurement of aortic stiffness index (ASI) is a simple and low-cost method that can provide satisfactory information about the aortic elasticity.[10,11] ASI can be calculated by using the simple parameters such as blood pressure and systolic-diastolic aortic root diameters.[12]

We aimed to examine whether the echocardiographic parameters, such as EFT, CIMT and ASI, are associated with microalbuminuria in patients with diabetes mellitus type 2 (T2DM).

Materials And Methods

In this cross-sectional study, 272 consecutive patients who applied to the endocrinology outpatient clinic with the diagnosis of T2DM, according to the criteria of the American diabetes association,[13] between November 2018 and June 2019 were enrolled. The study was performed to conform to the Declaration of Helsinki and the study protocol was approved by the ethics committee of Bozok University. Written and informed consent was taken from all the participants. Patients with known cardiovascular disease, heart failure, severe valvular disease, inflammatory disease, chronic renal failure with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2, liver insufficiency, acute infections, glucocorticoid therapy, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy and pregnant or nursing women were excluded. After the exclusion criteria, the data of 180 patients were used. Demographic data and anthropometric measurements of the participants were recorded. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Laboratory Analysis

Venous blood samples were taken for biochemical analyses, after at least 12 hrs of fasting. Fasting glucose, HbA1C, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), serum creatinine were studied for all patients. HbA1C was determined using HPLC-UV detector. The other parameters were measured using Abbott Architect c8000 analyzer (Abbott Laboratories, Abbott Park, Illinois) and original measurement kits. Microalbuminuria was determined by a commonly used clinical index (urinary albumin-to-creatinine ratio). Urinary albumin and creatinine were measured in morning spot urine twice with an interval of 3 months for all patients. The diabetic patients with an albumin-to-creatinine ratio ≤30 mg/g were categorized as normoalbuminuria group (*N*=98), whereas the diabetic patients with an albumin-to-creatinine ratio 30–300 mg/g were categorized as microalbuminuria group (*N*=82). Patients with macroalbuminuria (≥300 mg/g) were not included in our study. eGFR was calculated based on Modified Diet in Renal Disease formula which is recommended in patients with diabetes.[14]

Cardiac Evaluation

The participants included in the study were referred to the cardiology department for echocardiography and measurement of CIMT. Blood pressure (BP) was measured by using the standard mercury manometer. The patients underwent transthoracic echocardiography imaging conforming to the American Society of Echocardiography/European Association of Echocardiography recommendations.[15] Echocardiographic examinations were performed using a Philips Affiniti 50 echocardiography device (Philips Healthcare, the Netherlands) and a broadband transducer with simultaneous electrocardiogram follow-up. Echocardiography was done by the same cardiologist who was unaware of the clinical data. Epicardial adipose tissue appears as a relatively echo-free area between the external surface of the myocardium and visceral layer of pericardium.[16] EFT was measured from the long axis and apical four-chamber view, perpendicularly on the free wall of the right ventricle at end-diastole in three cardiac cycles.

Carotid intima-media thickness was measured from the far wall of the right carotid artery within 10 mm proximal to the bifurcation on two-dimensional ultrasound images with a 12–4 MHz linear array transducer (Logic Affiniti 50G; Philips, Amsterdam, Netherlands). Three measurements were obtained per scan and the mean CIMT was calculated from these measurements.

In the parasternal long-axis view, both systolic and diastolic inner diameters of the ascending aorta were

measured via M-mode echocardiography 3 cm above the aortic annulus.[11] Three measurements were obtained from 3 consecutive cardiac cycles and the mean values of aortic systolic diameter (AoSD) and aortic diastolic diameter (AoDD) were calculated.[11] ASI was calculated by following formula:[11,12]

$$\text{Aortic stiffness index (ASI)} = \text{Ln}[(\text{Systolic BP}/\text{Diastolic BP})/(\text{AoSD} - \text{AoDD})/(\text{AoDD})]$$

(Ln : natural logarithm)

Ten patients were selected on a random basis for repeated echocardiographic EFT, CIMT and ASI measurement to assess intraobserver variability. Reproducibility of the measurements was significantly correlated for intraobserver agreement ($p < 0.01$ for all).

Statistical Analysis

Kolmogorov–Smirnov test was used for the distribution analysis. Categorical variables were compared by chi-square test. Comparisons among the groups were performed using independent samples *t*-test for variables distributed normally and Mann–Whitney *U*-test for non-normally distributed variables. Correlation of the ASI with the other study parameters was assessed by Pearson or Spearman correlation analysis, as appropriate.

A multivariate logistic regression analysis was used to identify factors that independently associated with microalbuminuria in the study population. The variables associated with the presence of microalbuminuria in the univariate analysis were included in the multivariable models. All analyses were performed by SPSS version 18.0 (SPSS for Windows, Chicago, IL). P values <0.05 were accepted as significant.

Results

A total of 180 patients participated in this study (112 females, 68 males), patients were divided into two groups; 82 diabetic patients with microalbuminuria and 98 diabetic patients without microalbuminuria (normoalbuminuria). Baseline demographic and clinical characteristics are summarized in Table 1. Compared with the normoalbuminuria group, diabetes duration, HbA1C, fasting glucose and serum creatinine levels were significantly higher, while eGFR and HDL-C were significantly lower in the microalbuminuria group (p<0.05 for all). Analysis of echocardiographic parameters showed that; compared with the normoalbuminuria group, EFT (5.91±1.43 vs. 6.45±1.39; p=0.014), CIMT (0.71±0.12 vs. 0.76±0.11; p=0.001) and ASI (3.16±0.23 vs. 3.28±0.30; p=0.002) were significantly higher in the microalbuminuria group (Figure 1).

A correlation analysis was performed in order to determine the factors associated with the albumin-to-creatinine ratio in patients with T2DM. The albumin-to-creatinine ratio was positively correlated with age (r=0.169, p=0.023), diabetes duration (r=0.160, p=0.032), HbA1C (r=0.198, p=0.008), fasting glucose (r=0.196, p=0.008), serum creatinine (r=0.175, p=0.019), EFT (r=0.179, p=0.016), CIMT (r=0.206, p=0.005) and ASI (r=0.226, p=0.002) (Figure 2) as well as negatively correlated with eGFR (r=−0.181, p=0.015) in patients with T2DM (Table 2).

The results of the logistic regression analysis showed that CIMT [odds ratio (OR): 3.15; 95% confidence interval (CI): 1.5 to 36.3; P=0.024] and ASI (OR: 4.19; 95% CI: 1.3 to 13.4; P=0.016) was independently associated with the presence of microalbuminuria in patients with T2DM.

Discussion

The main findings of the present study were that EFT, CIMT and ASI were significantly higher in diabetic patients with microalbuminuria compared to the diabetic patients without microalbuminuria. Furthermore, logistic regression analysis revealed that CIMT and ASI were independently associated with the presence of microalbuminuria in patients with T2DM.

In diabetic patients, DNP is a major complication, and it is an important cause of end-stage renal disease. Several pathways are activated during the development of DM. Main pathways, considered as responsible for the pathogenesis of DNP are; oxidative stress, inflammation, fibrosis and cell death. These pathways also regulate the progression of DNP. DM is accompanied by chronic inflammation affecting the kidneys and the whole body. DN is traditionally considered as nonimmune disease, but there is an accumulating data indicating a significant role of inflammatory processes in the pathophysiology of DNP.[17,18] Microalbuminuria can be defined as the earliest clinical marker of DNP and it is a well-documented predictor of DNP development in diabetic patients.[19] Detection of microalbuminuria is beneficial because starting the treatment early may be preventive for overt nephropathy.

Epicardial fat is an indicator of visceral adiposity, which has a role in the pathogenesis of inflammation, endothelial dysfunction and cardiovascular diseases.[20–22] Visceral adiposity has been implicated in the pathogenesis of DNP. Hanai K.

Table 1 Demographic And Clinical Data Of The Participants

	Normoalbuminuria *N*=98	Microalbuminuria *N*=82	P
Age (year)	57.65±8.7	59.41±7.6	0.157
Gender (male/female)	35/63	33/49	0.319
Height (cm)	160.9±8.5	160.9±9.6	0.926
Weight (kg)	84.0±12.6	88.2±15.1	0.103
Body mass index (kg/m^2)	32.9±5.5	34.4±6.2	0.218
Hypertension, *n* (%)	54 (55)	48 (58)	0.643
Diabetes duration (year)	10.5±6.8	12.7±6.7	**0.033**
Oral antidiabetic drugs, *n* (%)	70 (71)	53 (64)	0.340
Insulin therapy, *n* (%)	45 (46)	47 (57)	0.137
Heart rate (bpm)	75.5±9.8	76.5±9.9	0.617
Systolic blood pressure (mmHg)	134.2±18.2	135.3±16.0	0.333
Diastolic blood pressure (mmHg)	80.4±11.6	80.5±11.2	0.968
HbA1C (%)	8.4±1.8	8.5±2.0	**0.015**
Fasting glucose (mg/dL)	153 (54–520)	204 (59–495)	**0.001**
Serum creatinine (mg/dL)	0.84±0.2	0.91±0.2	**0.005**
eGFR (mL/min per 1.73 m^2)	86.9±18.0	80.3±20.3	**0.021**
Total cholesterol (mg/dL)	203±36	211±41	0.361
Triglyceride (mg/dL)	188.7±99	211.5±155	0.757
HDL-C (mg/dL)	46.7±9.8	44.0±10.6	**0.045**
LDL-C (mg/dL)	123.6±29.9	122.6±34.7	0.961
Albumin-to-creatinine ratio (mg/g)	16.7±14.2	134.4±83.0	**<0.001**
Ejection fraction	61.3±5.2	61.1±3.5	0.178
Epicardial fat thickness (mm)	5.9±1.4	6.5±1.4	**0.014**
CIMT (mm)	0.71±0.1	0.76±0.1	**0.001**
Aortic stiffness index	3.16±0.2	3.28±0.3	**0.002**

Notes: The p-values are bold where they are <0.05. Continuous variables are presented as mean ± SD or median (Min-Max), and the categorical variables as *n* (%).
Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CIMT, carotid intima-media thickness.

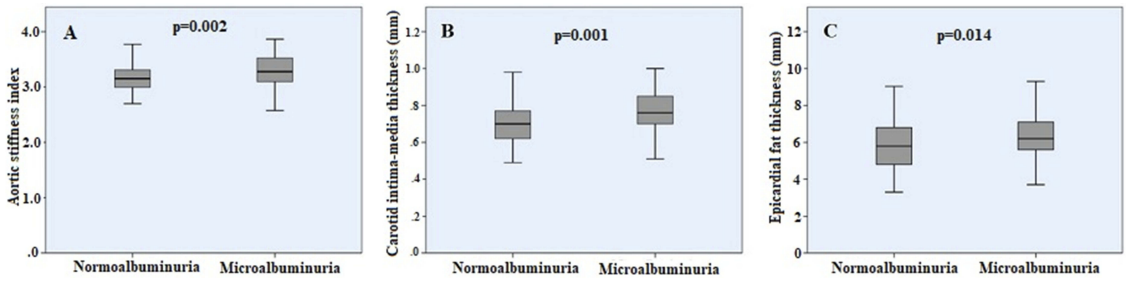

Figure 1 Comparison of aortic stiffness index (**A**), carotid intima-media thickness (**B**) and epicardial fat thickness (**C**) among the normoalbuminuria and microalbuminuria groups.

reported that visceral adiposity was independently associated with microalbuminuria in Japanese adult patients with T2DM.[23] Data regarding the relationship between microalbuminuria and EFT are very limited. Akbaş et al have reported that EFT was independently associated with microalbuminuria in diabetic patients.[24] EFT was higher in the microalbuminuria group in our study. However, possibly because the other parameters related to atherosclerosis were also involved in regression analysis, the independent relationship was not detected.

Albuminuria is reported to be associated with endothelial dysfunction and subclinical atherosclerosis.[25,26] Atherosclerosis has a long asymptomatic period and CIMT measurement is a useful method for the assessment of atherosclerosis in the asymptomatic period.[27] In this context, we aimed to investigate the relationship between CIMT and microalbuminuria. CIMT measurements were significantly higher in the microalbuminuria group in the present study. Additionally, CIMT was independently

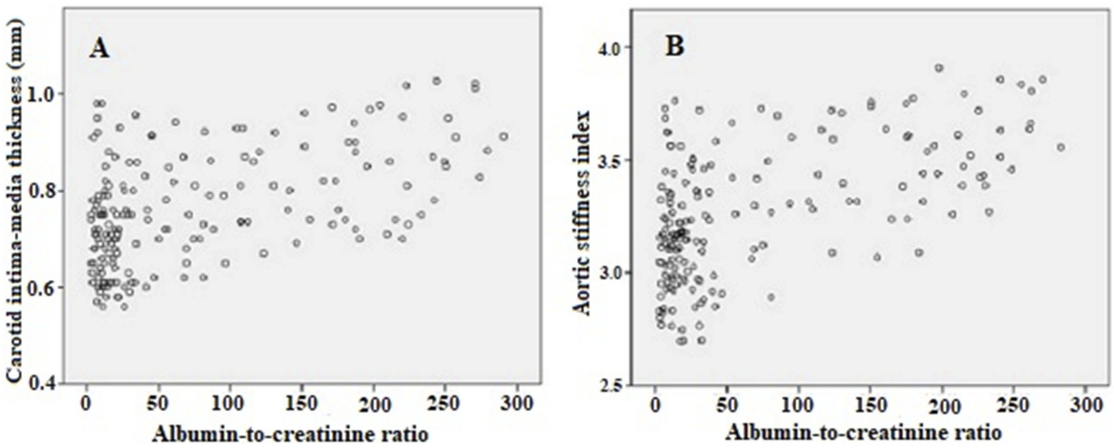

Figure 2 Scatter plot showing correlation of albumin-to-creatinine ratio with carotid intima-media thickness (**A**) and aortic stiffness index (**B**).

Table 2 The Correlation Between Albumin-To-Creatinine Ratio And Clinical/demographic Variables In T2DM Patients

Variables	Albumin-To-Creatinine Ratio	
	r	P
Age	0.169	**0.023**
Body mass index	0.124	0.098
Diabetes duration	0.160	**0.032**
Systolic blood pressure	0.125	0.094
Diastolic blood pressure	0.088	0.239
HbA1C	0.198	**0.008**
Fasting glucose	0.196	**0.008**
Serum creatinine	0.175	**0.019**
eGFR	−0.181	**0.015**
Total cholesterol	0.124	0.097
Triglyceride	0.119	0.113
HDL-C	−0.022	0.766
LDL-C	0.059	0.429
Ejection fraction	−0.109	0.184
Epicardial fat thickness	0.179	**0.016**
CIMT	0.206	**0.005**
Aortic stiffness index	0.226	**0.002**

Note: The p-values are bold where they are <0.05.
Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CIMT, carotid intima-media thickness.

associated with microalbuminuria in patients with T2DM. Our results were consistent with the previous data probing the relationship between CIMT and microalbuminuria.[25,28] However, the possible mechanism of this relation in patients with T2DM remains unclear. With these results, we cannot conclude whether this is a cause or a common result of diabetes complications.

The usefulness of CIMT measurement in cardiovascular risk stratification is a current issue and it is still controversial whether CIMT measurement could add predictive value to the Framingham risk score and associate with subsequent cardiovascular events.[29–32] In this manner, considering the relation of microalbuminuria and cardiovascular risk,[6] the current results may provide a proof for the relationship between CIMT and risk of cardiovascular events. We can conclude that CIMT measurement may be useful for predicting future cardiovascular events.

Noninvasive detection of premature vascular changes related to the cardiovascular risk is becoming increasingly important in daily clinical practice. Subclinical atherosclerosis may alter vascular functions by causing arterial stiffness. Arterial stiffness can be evaluated in various sections of the vascular system by using different methods. Pulse wave velocity may be simply described as the speed of an arterial pulsation when it is propagating through the arterial tree and the current-recognized gold standard for the assessment of arterial stiffness is the carotid-femoral pulse wave velocity (cfPWV).[33] However, the availability of appropriate equipment and experienced operators is essential to assess cfPWV. In addition, considering the required exposure of the inguinal area and the extended examination time, this method is mostly used in research settings rather than daily clinical practice.[34] Echocardiography-based analysis of aortic deformation may be a widely available and relatively low-cost option to investigate the biomechanical properties of the ascending aorta. The image quality is the most important factor for capturing a sufficient sequence of digital images over a cardiac cycle and may vary depending on the patient, operator and device. A good parasternal view clearly depicting the ascending aorta may be considered pivotal and insufficient image quality may adversely affect the results of this analysis.[34]

When the groups were compared in terms of aortic elastic properties, the microalbuminuria group was found to have a stiffer aorta. The ASI was significantly higher in the microalbuminuria group. As a novel finding, ASI was independently associated with the presence of microalbuminuria. There is an accumulated data concerning the relation of microalbuminuria and arterial stiffness assessed by cfPWV method.[35,36] However, there is no data probing the relation of microalbuminuria and elastic properties of the aortic root. Proximal aorta with a normal elasticity has a protective function and may store 50% of the systolic left ventricular stroke volume.[37] An impaired aortic elasticity may be associated with the progression of microvascular and macrovascular complications of diabetes. Echocardiography, which has a widespread availability compared to above-mentioned methods, may be quite helpful in determining aortic stiffness and the risk of microalbuminuria and DNP in diabetic patients. It is doubtful whether aortic elasticity causes microalbuminuria or *vice versa*. An unknown mechanism may underlie the association between microalbuminuria and aortic elasticity, but clear evidence for this is lacking.

Echocardiographic measurements of ASI and CIMT were independently associated with the presence of microalbuminuria in the present study. Diabetes is associated with chronic low-grade inflammation and subclinical atherosclerosis. Compared with other study parameters, both CIMT and ASI may be interpreted as the indicators of long-term cardiovascular impact of diabetes. In this context, echocardiography-based evaluation of CIMT and ASI in patients with T2DM may help us to detect the patients who are more exposed to the harmful effects of diabetes, likewise, in identifying patients with a greater risk of developing diabetic nephropathy. We can conclude that our results may be a proof for the importance of multidisciplinary approach to diabetes and its complications.

There are some limitations in the present study. First, it is a cross-sectional study. Therefore, we could make assumptions about only possible etiological relationships. Longitudinal studies may be designed to determine the long-term influence of these parameters. Second, the sample size of this study population was relatively small. Third, it reflects a single-center experience. Fourth, the exclusion criteria were applied for many situations and patients with macroalbuminuria and established cardiovascular disease were also excluded; therefore, the validity of the results for different populations and settings is potentially limited.

Conclusion

In addition to CIMT, as a novel finding, ASI which is an indicator for the elastic properties of the aortic root was independently associated with the presence of microalbuminuria. Our results may be evidence of a complex mechanism between subclinical atherosclerosis, aortic elasticity and nephropathy, and may constitute proof for the importance of multidisciplinary approach to diabetes and its complications. Our findings need to be confirmed by prospective studies with larger populations and long-term follow-up. The causal effect of these parameters can be demonstrated with longitudinal studies evaluating them in diabetic patients without microalbuminuria.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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