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Coronary calcium score, albuminuria and inflammatory markers in type 2 diabetic patients: Associations and prognostic implications

Akın Dayan [a], *Burcu Narin* [b], *Murat Biteker* [c], *Sukru Aksoy* [d], *Hakan Fotbolcu* [e], *Dursun Duman* [f,*]

[a] *Haydarpaşa Numune Education and Research Hospital, Department of Internal Medicine, Istanbul, Turkey*
[b] *Haydarpaşa Numune Education and Research Hospital, Department of Radiology, Istanbul, Turkey*
[c] *Haydarpaşa Numune Education and Research Hospital, Department of Cardiology, Istanbul, Turkey*
[d] *Siyami Ersek Thoracic and Cardiovascular Surgery Center, Training and Research Hospital, Department of Cardiology, Istanbul, Turkey*
[e] *Central Hospital, Department of Cardiology, Istanbul, Turkey*
[f] *Medipol University School of Medicine, Department of Cardiology, Istanbul, Turkey*

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ABSTRACT

Aims: To investigate the relationship of coronary artery calcium (CAC) scores with common carotid artery intima media thickness (CCA-IMT), albuminuria and inflammatory factors in type 2 diabetes.

Methods and results: 128 asymptomatic type 2 diabetic patients, with at least one cardiovascular risk factor in addition to diabetes, were included in the study. CAC scores, carotid arteries plaque formation and CCA-IMT were assessed. The patients were followed for a mean period of 36.6 ± 3.3 months. Linear regression analysis identified the logarithmically transformed (Ln) albuminuria ($\beta = 0.32$, $P = 0.007$), age ($\beta = 0.04$, $P = 0.001$) and the uric acid ($\beta = 0.13$, $P = 0.04$) as independent determinants of the CAC score. During follow-up period, cardiovascular events occurred in 18 out of 46 patients with CAC score ≥100 compared with 5 out of 82 patients with CAC score <100 (log rank, $P < 0.0001$). Multivariate Cox proportional hazards analysis identified LnCAC score ($P < 0.0001$), LnAlbuminuria ($P = 0.01$) and uric acid ($P = 0.03$) as independent predictors for cardiovascular events.

Conclusions: There was a significant relationship between CAC score, albuminuria and inflammation in patients with type 2 diabetes. LnCAC score together with LnAlbuminuria and uric acid were identified as independent predictors of cardiovascular events in these patients.

1. Introduction

Cardiovascular disease is the major cause of death in 65–70% of patients with diabetes [1]. Diabetes nephropathy occurs in 20–40% of people with diabetes and is one of the leading causes of end-stage renal disease [2]. Microalbuminuria and proteinuria were independently associated with risk of cardiovascular disease and death [3]. Albuminuria reflects generalized vascular damage and it is closely associated with inflammation which underlies all stages of atherosclerotic lesion formation, including early atherogenesis [4].

It is known that diabetic patients are less symptomatic in terms of coronary artery disease (CAD), and when CAD

* *Corresponding author*. Tel.: +90 5324234190; fax: +90 2165452006.
E-mail address: drduman@excite.com (D. Duman).
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appears clinically, diabetes results in a worse prognosis [1]. It is important to investigate new risk factors in addition to known factors to aid in early diagnosis of patients, especially asymptomatic ones. Common carotid artery intima media thickness (CCA-IMT) is a surrogate marker of atherosclerosis and associated with cardiovascular events [5]. CCA plaque is easily detected and may be more closely related to systemic atherosclerosis. There is a relation between albuminuria, CCA-IMT, CCA plaque and atherosclerosis [6]. Recently, coronary artery calcium (CAC) imaging, a simple, fast, and non-invasive method for detecting subclinical coronary artery disease, has become a popular method [7]. CAC score was demonstrated to be a predictor of CAD in numerous studies on general population [3]. Furthermore, there are studies demonstrating that elevated levels of inflammatory markers such as IL-6, TNF-α appear to be associated with a greater number of diseased arteries and, consequently, the severity of CAD [8].

In this study, we investigated the relationship of CAC scores with excreted urinary albumin, CCA-IMT, plaque formation and inflammatory factors in high risk type 2 DM patients with no previous history of heart disease.

2. Methods

Type 2 diabetes mellitus patients (40–80 years of age) followed in our hospital between 2008 and 2009, with no previous history of cardiovascular disease and no complaints, but at least one cardiovascular risk factor addition to diabetes were included in the study. Patients were diagnosed with type 2 diabetes mellitus according to the American Diabetes Association criteria revised in 2009 [9]. Exclusion criteria were use of drugs that impair metabolic control (such as cortisol or immunosuppressive treatment), chronic liver disease, any infectious disease, malignancy, hyperthyroidism, hypothyroidism, familial hypercholesterolemia, diagnosis of diabetes before the age of 35 years, and presence of connective tissue diseases and planned or actual pregnancy, glomerular filtration rate <30 mL/min/1.73 m^2 according to KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification [10]. Contraindications to electron beam computed tomography included known allergy to iodine contrast media (supra)ventricular arrhythmias and renal insufficiency (serum creatinine >140 μmol/l).

Approval was obtained from the Ethical Advisory Committee of clinical researches and informed consents were obtained from each patient.

Medical history was taken, including presence of cardiovascular risk factors and duration of diabetes. Physical examination was performed. Height, weight, body mass index (BMI) and blood pressure data were recorded. Fasting blood and urine samples were obtained. Glucose, glycosylated hemoglobin (HbA1c), creatinine, fibrinogen, uric acid, blood albumin, urinary albumin were included in the analysis. TNF-α and interleukin-6 levels were measured (Immulite 1000 Immunoassay Analyzer, Siemens Medical Solutions Diagnostics, New Jersey, USA).

Multislice computed tomography (MSCT) examinations were performed with a 64-slice Toshiba multislice Aquilion 64 system (Toshiba Medical Systems, Tokyo, Japan). In all patients, a noncontrast enhanced scan was performed before MSCT angiography to assess the total coronary calcium burden. Collimation was 4 mm × 3.0 mm and rotation time was 500 ms. Tube current and voltage were 200 mA and 120 kV. For the contrast-enhanced scan, collimation was 64 mm× 0.5 mm and rotation time was 400 or 450 ms, depending on heart rate. Tube current and voltage were 300 mA (range 250–400 mA) and 120 kV (range 100–135 kV), respectively. Total amount of contrast (Iomeron 400, Altana, Konstanz, Germany) was 85–105 mL, followed by a saline flush of 45 mL, both injected at 5 mL/s. Automated detection of peak enhancement in the aortic root was used to time the scan. Forty-four 3 mm-thick slices of the coronary arteries were obtained during a single breath hold (15–20 s) synchronized to 40% of the R–R interval. In patients with a heart rate >65 beats/min, intravenous metoprolol (5–20 mg) was administered immediately before MSCT imaging if contraindications for beta-blockade were absent. No additional nitroglycerin was given for MSCT imaging. Quantitative CAC score were calculated according to the method described by Agatston et al. [11].

Bilateral CCA-IMT measurement was performed using a B mode ultrasound Toshiba Aplio (Toshiba Medical Systems, Tokyo, Japan) linear array probe (7.5 MHz). Subjects were studied in the supine position with their head turned 45° from the side being scanned. Each common carotid artery was evaluated with the subject's head turned slightly to the contralateral side. The field depth, gain, and near and far field gain controls were optimized to enable visualization of the far wall of the common carotid artery. Carotid arteries were screened for presence of plaques bilaterally in the transverse and longitudinal planes, and CCA-IMT was studied in the right and left carotid arteries. Carotid artery plaque was defined as a focal area of arterial wall thickening >1.5 times that of the surrounding arterial wall. CCA-IMT measurements were made in both carotid arteries at about 3 cm after the bifurcation, at the widest point of a segment devoid of plaques. CCA-IMT was defined as the distance between the leading edge of the lumen–intima interface and the leading edge of the media–adventitia interface of the far wall. In each longitudinal projection, three sites, at the greatest thickness and at 1 cm distal and proximal, were averaged and expressed as mean-CCA-IMT. The right and left mean and maximum values were determined. All measurements were performed by a single trained sonographer who was unaware of the clinical profile of the study subjects.

Albuminuria was measured as the amount of albumin excretion in 24-h urine collection (urinary albumin excretion, UAE). UAE <30 mg/24 h was considered as normoalbuminuria; 30–299 mg/24 h, microalbuminuria and $\geq$300 mg/24 h, macroalbuminuria.

Patients were categorized as having coronary heart disease on the basis of clinical and electrocardiographic evidence of coronary artery disease or myocardial infarction.

Cardiovascular events were defined as acute myocardial infarction, hospital admission because of heart failure, intracerebral hemorrhage, occlusion or stenosis of the precerebral or cerebral arteries, documented significant coronary, peripheral artery stenosis (more than 50% in angiography), coronary artery bypass grafting or percutaneous transluminal

angioplasty/stenting, and other vascular interventions such as percutaneous transluminal angioplasty/stenting or bypass grafting of aorta and peripheral vessels.

3. Statistical analysis

SPSS 15.0 for Windows was used in statistical analysis. Categorical variables were expressed as number and percentage in tables, while descriptive statistics were used for numerical variables (mean, standard deviation, median, minimum, maximum). Cross-tabulated statistics were provided in the categorical comparison between the groups, and the level of significance was determined using the Chi-Square test. Mann Whitney and Kruskal Wallis tests were used in numerical comparisons of independent groups not fulfilling the condition of normal distribution. In pairwise comparisons, Bonferroni correction was applied before Mann Whitney test. Skewed data were logarithmically transformed (Ln), and the Ln values were then used in correlation and regression analyses. Pearson rho test was used in correlation analysis. Multiple linear regression analysis was used for prediction of LnCAC score. Survival curves were estimated by the Kaplan–Meier method and evaluated using a Log-rank test. Predictive variables for outcomes were first examined using univariate Cox proportional hazards analysis, and variables with a significant association ($P < 0.10$) were used in a multivariate Cox proportional hazards model. $P < 0.05$ was considered significant

4. Results

4.1. Clinical and laboratory characteristics of the study population

One hundred and twenty eight patients (68.8% female, mean age, 57.5 ± 8.3 (40–80) years) were included in the study. Median duration of diabetes was 10 (1–39) years, and mean BMI was 32.8 ± 5.4 kg/m^2. In terms of urinary albumin excretion, 35 (27.3%) patients were normoalbuminuric, 62 (48.4%) microalbuminuric, and 31 (24.2%) were macroalbuminuric.

When parameters were compared in between normo-, micro-and macro-albuminuria groups, statistically significant differences were found in serum albumin, glucose, HbA1c, HDL, BUN, creatinine, TNF-α, IL-6, CAC scores and CCA plaque formation, as well as use of insulin and oral antidiabetic drugs (OAD). The use of statins, acetylsalicylic acid, beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and calcium channel blocker were similar in three groups. CAC score and formation of CCA plaques increased with increasing levels of albuminuria. Plaque formation was seen in 80% of the patients in the macroalbuminuria group, which is a considerably high rate. These results are summarized in Table 1.

Total CAC score was statistically significantly higher in patients with plaque formation ($P < 0.001$). CAC score was <10

Table 1 – Patients's parameters in total and normo-, micro-, macroalbuminuria groups.

	Normoalbuminuria ($n = 35$)	Microalbuminuria ($n = 62$)	Macroalbuminuria ($n = 31$)	P	Total ($n = 128$)
Age[a] (years)	57.77 ± 8.85	58.58 ± 8.67	55.16 ± 6.72	0.271	57.5 ± 8.3
Diabetes duration[b] (years)	10 (1–30)	10 (2–33)	14 (2–39)	0.170	10 (1–39)
BMI[b] (kg/m^2)	33.75 ± 5.94	32.57 ± 5.09	32.33 ± 5.52	0.558	32.8 ± 5.4
Waist circumference[b] (cm)	106.53 ± 13.51	105.49 ± 12.10	105.84 ± 11.06	0.827	105.8 ± 12.1
Systolic BP[b] (mmHg)	138.4 ± 23.9	141.4 ± 21.9	149.9 ± 25.4	0.164	142.6 ± 23.5
Albuminuria[a] (mg/24 h)	19.2 (4.9–29.5)	73.9 (30.6–294.0)	342.8 (317.8–487.6)	**<0.001**	71.2 (4.9–487.6)
Creatinine clearance[b] (mL/min)	93.05 ± 28.59	99.01 ± 33.62	84.77 ± 35.61	0.543	93.93 ± 33.09
HbA1c[b] (%)	7.5 ± 1.3	8.7 ± 1.8	9.1 ± 1.7	**<0.001**	8.4 ± 1.8
HDL cholesterol[b] (mg/dL)	52.06 ± 12.91	51.37 ± 13.09	45.10 ± 13.76	**0.039**	50.0 ± 13.4
LDL cholesterol[b] (mg/dL)	115.94 ± 32.74	108.36 ± 34.82	122.56 ± 37.12	0.170	113.6 ± 34.9
Triglyceride[a] (mg/dL)	152 (63–340)	162 (50–614)	188 (77–602)	0.372	165 (50–614)
Uric acid[b] (mg/dL)	4.99 ± 1.25	4.89 ± 1.27	5.52 ± 1.51	0.089	5.0 ± 1.3
Creatinine[b] (mg/dL)	0.84 ± 0.20	0.86 ± 0.20	1.10 ± 0.36	**0.001**	0.91 ± 0.27
Fibrinogen[b] (mg/dL)	390.0 ± 81.4	406.8 ± 74.0	441.5 ± 106.1	0.110	410.6 ± 86.1
hsCRP[a] (mg/dL)	0.46 (0.5–1.62)	0.42 (0.06–1.99)	0.62 (0.04–1.87)	0.522	0.44 (0.04–1.99)
TNF-α[a] (pg/mL)	10.30 (6.69–27.6)	10.55 (4.09–31.90)	13.70 (7.89–32.90)	**0.015**	11.00 (4.09–32.9)
IL-6[a] (pg/mL)	3.01 (2.00–8.07)	3.41 (2.00–10.50)	4.41 (2.00–8.60)	**0.020**	3.46 (2.00–10.50)
CAC score[a] (AU)	15.9 (0.0–1962.8)	40.6 (0.0–2344.0)	160.5 (0.0–2916.0)	**0.011**	46.4 (0.0–2916.0)
CCA-IMT[b] mean (mm)	1.016 ± 0.261	0.990 ± 0.293	1.082 ± 0.249	0.268	1.074 ± 0.317
CCA-IMT[b] max (mm)	1.063 ± 0.278	1.041 ± 0.334	1.155 ± 0.318	0.307	1.019 ± 0.276
CCA plaque formation[c]	17 (50.0)	32 (53.3)	24 (80.0)	**0.025**	73 (57)
Smoking[c]	4 (11.4)	11 (17.7)	4 (12.9)	0.241	19 (14.8)
Antidiabetic drugs					
Insulin[c]	20 (57.1)	51 (82.3)	29 (93.5)	**0.001**	100 (78.1)
OAD[c]	32 (91.4)	54 (87.1)	18 (58.1)	**0.001**	104 (81.3)

The values were shown as [a]mean (SD), [b]median (interquartile range), or [c]n (%). BMI, body mass index; BP, blood pressure; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; CAC, coronary artery calcium; CCA-IMT, common carotid arteries intima medial thickness; CCA, common carotid arteries; OAD, oral antidiabetic drugs.

Table 2 – Correlation between LnCAC scores and other parameters.

	rho	P
Age (years)	0.339	<0.001
LnDuration of diabetes (years)	0.308	<0.001
Systolic blood pressure (mmHg)	0.249	0.005
LnAlbuminuria (mg/24 h)	0.260	0.003
Creatinine clearance (mL/min)	−0.271	0.002
BUN (mg/dL)	0.333	<0.001
Albumin-blood (g/dL)	−0.186	0.036
Creatinine (mg/dL)	0.426	<0.001
Uric acid (mg/dL)	0.327	<0.001
LnTNF-α (pg/mL)	0.236	0.012
LnIL-6 (pg/mL)	0.236	0.012
CCA-IMT mean (mm)	0.212	0.020
CCA-IMT max (mm)	0.188	0.039

LnCAC, logarithmically transformed coronary artery calcification; BUN, blood urea nitrogen; LnTNF-α, logarithmically transformed tumor necrosis factor alpha; LnIL-6, logarithmically transformed interleukin-6; CCA-IMT, common carotid arteries intima medial thickness.

in 25.0%, 11–100 in 39.1%, 101–400 in 16.4%, 401–1000 in 10.9% and >1000 AU in 8.6%.

4.2. *Determinants of coronary calcuim score*

LnCAC score showed a statistically positive correlation with age, LnDuration of diabetes, systolic blood pressure, LnAlbuminuria, BUN, creatinine, uric acid, LnTNF-α, LnIL-6, mean CCA-IMT and a negative correlation with creatinine clearance, blood albumin. The results are presented in Table 2.

In order to determine the factors affecting the LnCAC score, a model was created with age, LnDuration of diabetes, systolic blood pressure, LnAlbuminuria, creatinine clearance, uric acid, LnTNF-α, LnIL-6 and mean CCA-IMT, multiple linear regression analysis was performed. Backward regression analysis predicted age, LnAlbuminuria and uric acid as statistically significant factors affecting the LnCAC score (Table 3).

4.3. *Fatal and non-fatal cardiovascular events and the parameters*

The mean follow-up duration was 36.6 ± 3.3 months. The small number of deaths during this period did not permit evaluation of overall or cardiovascular mortality. Therefore, we assessed the incidence of cardiovascular events. Cardiovascular events occurred in 23 patients ($n = 18$ and $n = 5$ for patients with CAC score ≥100 and CAC score <100 respectively). The 23 cardiovascular events included ischemic heart disease ($n = 14$; 5 coronary artery by-pass graft operation, 3 myocardial infarction, 4 significant coronary stenosis, 2 coronary artery stenting), heart failure ($n = 4$), peripheral vascular disease ($n = 2$) stroke ($n = 2$), and sudden death ($n = 1$). To analyze the relationship between CAC score and the cardiovascular events, the patient population were divided into those with CAC score ≥100 ($n = 46$) and CAC score <100 ($n = 82$). Patients with CAC score ≥100 had more cardiovascular events compared to those with CAC score <100 (39% vs. 6%, $P < 0.0001$). Unadjusted cardiovascular event-free survival curves for patients with CAC score ≥100 and CAC score <100 are represented in Fig. 1 ($P < 0.0001$ by Log-rank test). In univariate Cox proportional hazards analysis, LnCAC score, LnAlbuminuria, uric acid and creatinine clearance were significantly associated with cardiovascular events, whereas factors including age, mean CCA, LnTNF-alpha and LnDiabetes duration were not (Table 4). In a multivariate Cox proportional hazards model using significant variables ($P < 0.10$) from the univariate analysis, LnCAC score, LnAlbuminuria and uric acid were identified as independent predictors of cardiovascular events (Table 4).

Table 3 – Significant predictors of LnCAC score identified by multiple linear regression analysis.

	B	P	95% confidence interval
Constant coefficient	−2.931	<0.001	−4.542/−1.319
Age (years)	0.042	<0.001	0.024/0.061
LnAlbuminuria (mg/24 h)	0.323	0.007	0.089/0.558
Uric acid (mg/dL)	0.129	0.036	0.008/0.250
LnTNF-α (pg/mL)	0.896	0.093	0.152/1.944

LnCAC, logarithmically transformed coronary artery calcification; LnTNF-α, logarithmically transformed tumor necrosis factor alpha.

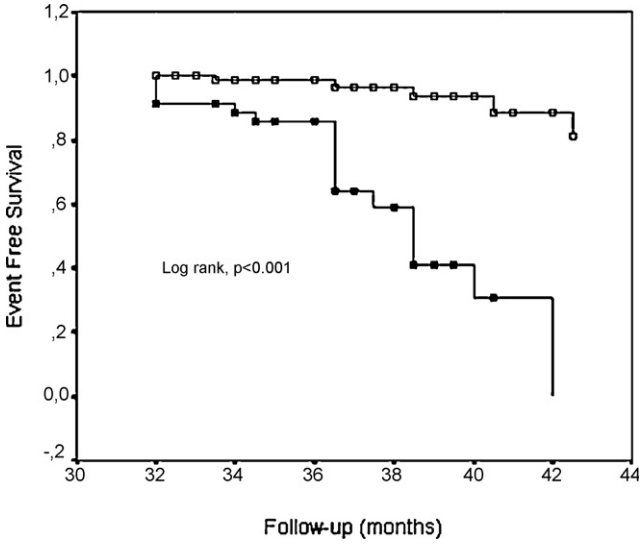

Fig. 1 – Cardiovascular event-free survival curves of type 2 diabetic patients during a 44 month period according coronary calcium score ≥ 100 (closed square) and < 100 (open circle). There were 46 patients in the coronary calcium score ≥ 100 group and 82 patients in the coronary calcium score < 100 group.

5. Discussion

Type 2 DM is a highly prevalent disease associated with several complications such as retinopathy, neuropathy, nephropathy, cardiovascular disease, and increased morbidity and mortality [12]. In this study, we investigated the relationship between albuminuria and cardiovascular event predictors, CAC and inflammatory markers, in type 2 DM patients.

Table 4 – Factors associated with the cardiovascular events in univariate and multivariate Cox proportional hazards regression analysis.

	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
LnCAC score	6.48 (2.7–15.5)	0.000	6.82 (3.42–13.58)	<0.0001
LnAlbuminuria (mg/24 h)	2.86 (1.29–6.34)	0.01	2.30 (1.22–4.35)	0.01
Uric acid	0.62 (0.41–1.00)	0.03	0.62 (0.42–0.91)	0.02
Creatinine clearance	0.98 (0.96–1.00)	0.04	0.98 (0.97–1.00)	0.02
Age (years)	1.02 (0.95–1.09)	0.64	1.03 (0.97–1.09)	0.36
LnDiabetes duration	0.97 (0.23–4.16)	0.97	–	–
Mean CCA (mm)	1.59 (0.30–8.44)	0.58	(1.62 0.31–8.54)	0.57
LnTNF-α	0.54 (0.02–13.17)	0.70	(0.55 0.02–13.18)	0.71

LnCAC, logarithmically transformed coronary artery calcification; LnAlbuminuria, logarithmically transformed albuminuria; LnDiabetes, logarithmically transformed diabetes; LnTNF-α, logarithmically transformed tumor necrosis factor alpha.

CAC score has been shown to be proportional with atherosclerotic disease severity and extent, and presence of coronary calcium was shown to be predictive of future coronary events [13,14]. Studies investigating CAC scores in various risk groups and different populations were reported and discussed [15–18]. Blaha et al. [19] compared coronary heart disease and cardiovascular disease event rates, multivariable-adjusted hazard ratios after stratifying by burden of CAC (scores of 0, 1–100, or >100) on 444 patients in the MESA JUPITER population. They found 74% of all coronary events were in the 239 (25%) of participants with CAC scores of more than 100. Malik et al. [20] evaluated CAC, carotid IMT which could improve CVD risk stratification over traditional risk factors on 6603 people with metabolic syndrome and diabetes. CAC increased the concordance indexes (C-statistic) for events ($P < 0.001$) over risk factors. They concluded that individuals with MetS or diabetes have low risks for CHD when CAC or CIMT was not increased and prediction of CHD and CVD events was improved by CAC.

In our study, LnCAC score, LnAlbuminuria and uric acid were identified as independent predictors of cardiovascular events. Urine albumin excretion rate was found to be >30 mg/24 h in 72.6% of 128 DM patients with no previous history of heart disease. There was a positive correlation between urinary albumin levels and CAC score ($r = 0.260$, $P = 0.003$). CAC score increased with increasing level of albuminuria, and a statistically significant difference was determined between albuminuria groups ($P = 0.011$). In pairwise comparisons, CAC score was significantly higher in macroalbuminuric group compared with normoalbuminuric group (160.5 vs. 15.9, $P = 0.006$).

Elevated serum uric acid levels is a risk factor for cardiovascular and cerebrovascular disease [21–23]. In NHANES I epidemiologic studies showed that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality [24]. Serum uric acid levels are an independent predictor of death in patients at high risk of cardiovascular disease [25]. In present study, we showed a significant positive correlation between uric acid and LnCAC score ($r = 0.36$, $P < 0.001$), which has not been reported before in diabetic population.

In a study performed by Freedman et al. [6] on 588 type 2 DM patients, a strong relationship was demonstrated between albuminuria and calcified plaques in the coronary and carotid arteries. Similarly, in our study we determined that CCA plaque formation increased significantly with increasing level of albuminuria. While the presence of CCA plaque was 50% in the normoalbuminuric group, this rate was as high as 80% in the macroalbuminuric group.

The mean CAC scores in patients with CCA plaque formation were also found to be significantly higher than those with no plaque formation (424.18 vs. 56.08, $P < 0.001$). No significant difference was determined in terms of mean and maximum CCA-IMT values in the albuminuria groups. However, CAC score had a weak positive correlation with mean and maximum CCA-IMT values. Folsom et al. [13], demonstrated that CAC was better than carotid IMT in predicting cardiovascular events. In our study, age, albuminuria and uric acid were found to be statistically significant predictors of CAC score.

Correlation between microalbuminuria and cardiovascular events is well established [26]. In a study by Bruno et al. [27], where type 2 DM patients were followed over a period of 11 years, albumin excretion rate was the main independent predictor of cardiovascular mortality, and this effect was more pronounced at the upper limits of microalbuminuria and in macroalbuminuria. In agreement these studies, our study show that albuminuria was an independent predictor of cardiovascular events.The levels of acute inflammatory phase reactants fibrinogen, IL-6 and TNF-α were found to correlate with urinary albumin excretion in DM patients. The levels of IL-6 and TNF -α were shown to be higher in DM patients than in controls, and these levels were shown to increase with an increase in excretion of albumin [28]. A marked relationship was also found between IL-6 and the CAC score [29]. We determined that higher albuminuria levels were correlated with increasing IL-6 and TNF-α levels. In pairwise comparisons, TNF-α levels were shown to be significantly higher in the macroalbuminuric group than in the normoalbuminuric group. (13.70 vs. 10.30, $P = 0.004$). IL-6 levels were also found to be significantly higher in the macroalbuminuric group than in the normoalbuminuric group (4.41 vs. 3.01, $P = 0.005$). In present study, we also demonstrated that LnCAC score showed a statistically significant positive correlation with LnTNF-α and LnIL-6. The relationship between the CAC and cytokine levels in diabetic patients was also assessed by Saremi at al. A marked association between IL-6 and the CAC score was reported in this study [30]. However, they did not investigate the interrelationship between urinary albumin excretion, cardiovascular outcome in addition to CAC score and cytokines. In present study, we showed for the first time, the strong relationship between cytokines, CAC score,

albuminuria and cardiovascular events in the same diabetic population.

In conclusion, CAC score which reflects subclinical coronary artery disease were significantly associated with albuminuria levels, the presence of CCA plaque and inflammatory markers in DM patients. Furthermore, CAC score, albuminuria and uric acid were identified as independent predictors of cardiovascular events.

Conflict of interest

The authors declare that they have no conflict of interest

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