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Evaluation of Subclinical Vascular Disease in Diabetic Kidney Disease: A Tool for Personalization of Management of a High-Risk Population

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Abstract: Background: Patients with diabetic kidney disease (DKD) are at increased risk for cardiovascular events but traditional risk factors do not fully explain this association. Evaluation of subclinical vascular disease might improve risk stratification and management of these patients. The aim of the study was to compare the prevalence of markers of arterial stiffness, carotid atherosclerosis and peripheral arterial disease between patients with DKD and patients with type 2 diabetes mellitus (T2DM) and preserved kidney function. Methods: We prospectively enrolled patients with DKD and age- and gender-matched patients with T2DM but without DKD (estimated glomerular filtration rate < and ≥ 60 mL/min/1.73 m², respectively). The presence of arterial stiffness was evaluated by measuring pulse wave velocity (PWV), augmentation index (AIx), AIx adjusted to a heart rate of 75 beats/min (AIx@75) and central systolic, diastolic, pulse and mean blood pressure. The presence of carotid atherosclerosis was evaluated by measuring carotid stenosis, carotid intima-media thickness and maximal plaque thickness. The presence of PAD was evaluated with the measurement of ankle-brachial index (ABI). Results: Forty patients with T2DM were included in the study (mean age 71.6 ± 8.9 years). The prevalence of cardiovascular risk factors was similar in patients with and without DKD. PWV was higher in the former (9.8 ± 5.5 and 6.6 ± 4.4 m/s, respectively; $p < 0.05$) and carotid stenosis of the left carotid artery was also greater in patients with DKD (36.5 ± 12.6 and $22.1 \pm 17.2\%$, respectively; $p < 0.05$). Other markers of arterial stiffness and carotid atherosclerosis and ABI did not differ between patients with DKD and those without DKD. Conclusions: Patients with DKD appear to have more pronounced arterial stiffness and carotid atherosclerosis than patients with T2DM and preserved kidney function despite the similar prevalence of traditional cardiovascular risk factors in the two groups. Therefore, evaluating the presence of subclinical vascular disease in these patients could be a useful tool for the personalization of their management.

Keywords: type 2 diabetes mellitus; diabetic kidney disease; diabetic nephropathy; arterial stiffness; pulse wave velocity; carotid atherosclerosis; peripheral arterial disease; ankle-brachial index; cardiovascular disease; personalization

1. Introduction

Diabetic kidney disease (DKD) is observed in approximately 40% of patients with type 2 diabetes mellitus (T2DM) and is the leading cause of end-stage renal disease (ESRD) in Western countries [1,2]. Patients with DKD are at increased risk for cardiovascular events, which is similar to those with a history of myocardial infarction [3,4]. In T2DM, excess mortality is largely limited to patients with DKD [4,5].

Given the substantial cardiovascular morbidity associated with DKD, identification of patients with DKD who are at the highest risk for cardiovascular events is pivotal for prevention of such events. However, traditional risk factors, including hypertension, dyslipidemia and obesity, do not fully explain the increased cardiovascular risk of patients with DKD [6,7]. Accordingly, additional markers are needed for accurate risk stratification in this population [6,8]. In this context, several studies showed that the presence of subclinical vascular disease is strongly related to the incidence of cardiovascular events in patients with T2DM [9–11]. However, only few studies compared the prevalence of multiple markers of subclinical vascular disease between patients with DKD and those with T2DM and preserved kidney function [12,13].

The aim of the present study was to compare the prevalence of markers of arterial stiffness, carotid atherosclerosis and peripheral arterial disease (PAD) between patients with DKD and patients with T2DM and preserved kidney function.

2. Patients and Methods

We performed a cross-sectional study in which we enrolled all adult patients with DKD who visited the Internal Medicine Outpatients Clinic of the First Propedeutic Department of Internal Medicine between August 2021 and April 2022. Age- and gender-matched patients with T2DM but without DKD who visited the same outpatient clinic during this period were enrolled as controls. Patients with acute kidney injury were excluded from the study.

Demographic data (age, sex), history of cardiovascular risk factors (hypertension, atrial fibrillation, smoking, alcohol intake, family history of cardiovascular disease (CVD)) and history of concomitant CVD (coronary heart disease, ischemic stroke, heart failure) were recorded. Anthropometric parameters (weight, height, waist circumference), heart rate and systolic and diastolic blood pressure (BP) were also measured.

In all patients, serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, HbA_{1c} and creatinine were determined in fasting blood samples and the urinary albumin/creatinine ratio was determined in a morning spot urine sample. Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation [14]. According to the estimated GFR (eGFR), the study population was divided into: (a) patients with DKD (eGFR < 60 mL/min/1.73 m²) and (b) patients without DKD (eGFR ≥ 60 mL/min/1.73 m²).

The presence of arterial stiffness was evaluated by measuring pulse wave velocity (PWV), augmentation index (AIx), AIx adjusted to a heart rate of 75 beats/min (AIx@75), central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), central pulse pressure (cPP) and central mean pressure (cMP) using a Sphygmocor device (Atcor Medical, Sydney, Australia) [11]. Measurements were performed in the morning, in the supine position, after at least 10 min of rest and after fasting for at least 4 h [11]. Two measurements were performed, and the mean was recorded. If the two measurements differed by >0.5 m/s in PWV or by >5% in AIx, a third measurement was performed, and the median was recorded [11].

The presence of carotid atherosclerosis was evaluated by measuring carotid stenosis, carotid intima-media thickness (cIMT) and maximal plaque thickness (MPT) using a Logiq S8 ultrasound device (GE Healthcare, Milwaukee, Wisconsin). Carotid stenosis was measured according to the European Carotid Surgery Trial (ECST) method [15]. The cIMT was measured between the intimal-luminal and the medial-adventitial interfaces of the

carotid artery wall [16]. The MPT was measured as the height of the largest plaque from any segment of the right and left common carotid arteries [17].

The presence of PAD was evaluated with the measurement of the ankle-brachial index (ABI) in both legs [18].

All data were analyzed using IBM SPSS Statistics for Windows (version 27: Armonk, NY, USA: IBM Corp). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Differences in categorical and continuous variables between groups were assessed using the Chi-square test and the independent samples t-test, respectively. Correlations between continuous variables were evaluated using Pearson’s correlations. In all cases, a two-tailed $p < 0.05$ was considered significant.

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical School of the Aristotle University of Thessaloniki. All patients provided written informed consent.

3. Results

Patients’ characteristics are shown in Table 1. A total of 40 patients with T2DM were included in the study. Eighteen patients had DKD (66.7% males, age 77.4 ± 6.5 years) and 22 patients did not have DKD (72.7% males, age 76.9 ± 7.9 years). The urinary albumin/creatinine ratio was higher in patients with DKD than in patients without DKD (280.6 ± 473.9 and 41.4 ± 50.3 mg/g, respectively; $p < 0.05$). In contrast, demographic, anthropometric and laboratory characteristics did not differ between the two groups. The prevalence of cardiovascular risk factors, including hypertension, smoking, established CVD and lipid and HbA_{1c} levels, were also similar in patients with and without DKD.

Table 1. Characteristics of patients with diabetic nephropathy and of patients without diabetic nephropathy (data shown are percentages or mean \pm SD).

	Patients with Diabetic Nephropathy (n = 18)	Patients without Diabetic Nephropathy (n = 22)	p
Age (years)	77.4 \pm 6.5	76.9 \pm 7.9	0.873
Males (%)	66.7	72.7	0.945
Systolic blood pressure (mmHg)	139.8 \pm 17.3	141.9 \pm 12.0	0.650
Diastolic blood pressure (mmHg)	81.6 \pm 13.9	81.9 \pm 12.8	0.936
Heart rate	71.3 \pm 9.1	74.7 \pm 10.9	0.293
Hypertension (%)	100.0	77.3	0.093
Type 2 diabetes mellitus duration (years)	15.1 \pm 8.8	11.4 \pm 6.6	0.133
Smoking (current/past, %)	5.6/44.4	22.7/36.4	0.318
Package-years	36.2 \pm 19.2	52.5 \pm 35.2	0.223
Alcohol intake (units/week)	0.50 \pm 1.3	0.91 \pm 1.6	0.398
Atrial fibrillation (%)	38.9	13.6	0.142
Family history of cardiovascular disease (%)	27.8	18.2	0.732
Coronary heart disease (%)	44.4	36.4	0.846
Ischemic stroke (%)	22.3	4.5	0.220
Heart failure (%)	27.8	9.1	0.259
Weight (kg)	81.2 \pm 19.4	84.7 \pm 13.9	0.515
Body mass index (kg/m ²)	28.4 \pm 6.1	29.4 \pm 3.9	0.558
Waist circumference (cm)	104.8 \pm 13.8	106.4 \pm 9.9	0.680
Total cholesterol (mg/dL)	129.9 \pm 37.3	123.1 \pm 53.8	0.655
Low-density lipoprotein cholesterol (mg/dL)	59.7 \pm 23.8	57.5 \pm 50.7	0.868
High-density lipoprotein cholesterol (mg/dL)	45.1 \pm 20.4	39.5 \pm 12.4	0.295
Triglycerides (mg/dL)	153.8 \pm 83.4	135.1 \pm 51.8	0.390
HbA _{1c} (%)	6.9 \pm 1.2	7.5 \pm 1.3	0.221
Estimated glomerular filtration rate (mL/min/1.73 m ²)	36.8 \pm 11.3	87.0 \pm 11.9	<0.001
Urinary albumin/creatinine ratio (mg/g)	280.6 \pm 473.9	41.4 \pm 50.3	0.024
Treatment with statins (%)	100.0	100.0	(-)
Treatment with antiplatelet agents (%)	55.6	36.4	0.371
Treatment with antihypertensive agents (%)	100.0	77.3	0.093

Markers of subclinical vascular disease in patients with DKD and in patients without DKD are shown in Table 2. PWV was higher in the former (9.8 ± 5.5 and 6.6 ± 4.4 m/s,

respectively; $p < 0.05$). Other markers of arterial stiffness (AIx, AIx@75, cSBP, cDBP, cPP and cMP) did not differ between patients with DKD and patients without DKD. Carotid stenosis of the left carotid artery was greater in the former (36.5 ± 12.6 and $22.1 \pm 17.2\%$, respectively; $p < 0.05$). Other markers of carotid atherosclerosis did not differ between patients with DKD and patients without DKD. The ABI in both legs was similar in the two groups (Table 2).

Table 2. Markers of subclinical vascular disease in patients with diabetic nephropathy and in patients without diabetic nephropathy (data shown are mean \pm SD).

	Patients with Diabetic Nephropathy (<i>n</i> = 18)	Patients without Diabetic Nephropathy (<i>n</i> = 22)	<i>p</i>
Ankle-brachial index (left)	1.07 \pm 0.23	1.09 \pm 0.22	0.806
Ankle-brachial index (right)	1.08 \pm 0.21	1.06 \pm 0.27	0.791
Pulse wave velocity (m/sec)	9.8 \pm 5.5	6.6 \pm 4.4	0.039
Augmentation index (%)	29.6 \pm 12.3	24.5 \pm 11.9	0.201
Augmentation index adjusted to a heart rate of 75 beats/min (%)	29.7 \pm 11.2	27.3 \pm 13.3	0.556
Central systolic blood pressure (mmHg)	127.1 \pm 11.8	128.3 \pm 10.2	0.741
Central diastolic blood pressure (mmHg)	76.2 \pm 10.7	81.4 \pm 13.5	0.198
Central mean blood pressure (mmHg)	97.2 \pm 10.8	103.3 \pm 11.8	0.097
Central pulse pressure (mmHg)	48.9 \pm 15.4	46.9 \pm 11.8	0.639
Carotid stenosis (left)(%)	36.5 \pm 12.6	22.1 \pm 17.2	0.024
Carotid intima-media thickness (left)	0.82 \pm 0.17	0.79 \pm 0.30	0.779
Maximal plaque thickness (left)	0.25 \pm 0.11	0.17 \pm 0.12	0.087
Carotid stenosis (right) (%)	31.3 \pm 17.8	21.8 \pm 18.6	0.177
Carotid intima-media thickness (right)	0.93 \pm 0.26	0.89 \pm 0.32	0.718
Maximal plaque thickness (right)	0.22 \pm 0.11	0.25 \pm 0.29	0.756

In the total study population, the eGFR correlated with carotid stenosis of the left carotid artery ($r = -0.397$, $p < 0.05$) and did not correlate with other markers of subclinical vascular disease.

4. Discussion

In the present study, PWV was higher in patients with DKD than in patients with T2DM and preserved kidney function. Given that risk factors for arterial stiffness, particularly age and BP, did not differ between the two groups, it appears that DKD is independently associated with arterial stiffness. Even though other markers of arterial stiffness did not differ between patients with and without DKD, it is widely accepted that PWV is the gold standard for the evaluation of this marker of target organ damage [11]. Similar to our findings, a previous study reported that diabetic patients with ESRD have higher PWV than patients with T2DM but without DKD [19]. Our study expands these results in patients with less advanced DKD. In contrast, another study in T2DM patients reported no difference in PWV between patients with eGFR \geq and <60 mL/min/1.73 m² [12]. However, in the latter study, eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation [12]. In contrast, we used the CKD-EPI equation to measure eGFR since the latter equation has less bias, improved precision and greater accuracy than the MDRD Study equation, especially in patients with GFR ≥ 60 mL/min/1.73 m² [20,21]. Notably, PWV not only predicts cardiovascular events but two prospective studies reported that it is also independently associated with the development and progression of albuminuria in patients with T2DM [22,23]. It has been suggested that increased arterial stiffness results in higher systolic pressure and greater pressure fluctuations in renal arteries, leading to renal microvascular damage and renal dysfunction [24]. More studies are needed to evaluate whether the measurement of PWV in patients with T2DM has prognostic implications for either cardiovascular events or the progression of DKD. On the other hand, it should be

noted that measurement of PWV is time-consuming and needs better standardization and that our study possibly lacked power to firmly establish an association between arterial stiffness and DKD. Moreover, there was a trend for higher prevalence of hypertension in patients with DKD, which is a major risk factor for arterial stiffness and might have contributed to the higher PWV in these patients.

In our study, patients with DKD had more advanced carotid atherosclerosis than patients without DKD even though cardiovascular risk factors did not differ between the two groups. The pathogenesis of atherosclerosis in patients with DKD is multifactorial, with both conventional and emerging risk factors playing a role [7]. Recently, sterol-O-acyltransferase-1, an enzyme that esterifies free cholesterol, the NLRP3 inflammasome pathway and the interleukin-33/ST2 pathway have also been implicated in the atherogenic process in these patients [25–31]. Several previous reports observed greater atherosclerotic burden in the carotid arteries of patients with DKD than in diabetic patients with preserved renal function [32–35]. However, most of these studies were performed in non-Caucasians and none evaluated multiple indices of carotid atherosclerosis (i.e., cIMT, degree of stenosis and plaque thickness) [32–35]. Interestingly, prospective studies suggest that carotid atherosclerosis predicts, not only cardiovascular events, but also renal function decline in patients with DKD [36,37]. Therefore, evaluation of carotid atherosclerosis in this population might be a useful tool for optimizing the management of risk factors to prevent cardiorenal morbidity, which might potentially include novel agents [38]. However, in our study, stenosis in only the left carotid artery differed between patients with and without DKD, whereas other markers of carotid atherosclerosis were similar in the two groups. In addition, small degrees of stenosis might be due to error. Therefore, it is important to validate these findings in larger, independent cohorts.

In the present study, the ABI did not differ between patients with and without DKD. ABI is the recommended test for diagnosing PAD and is an independent predictor of cardiovascular events [10,14]. To the best of our knowledge, this is the first study that evaluated the association between DKD and ABI in Caucasian patients with T2DM. A study in Japanese patients showed no correlation between ABI and eGFR [39], whereas a report from Taiwan revealed an independent association between ABI and DKD [40]. Given these limited data, particularly in non-Asians, and that ABI is an inexpensive, non-invasive, easily performed and sensitive marker of cardiovascular risk [10,14], more studies are needed to characterize the usefulness of ABI as a risk stratification tool in patients with DKD.

Even though patients with DKD are considered to be already at very high cardiovascular risk and guidelines recommend aggressive medical treatment with high-dose, high-intensity statins and aspirin [41], the identification of subclinical vascular disease in this population might have implications for their management. Indeed, several approaches have shown benefit in very high-risk populations, including double antiplatelet treatment [42], combined of antiplatelet agents and low-dose direct-acting anticoagulants [43], anti-inflammatory agents [44] or more aggressive lipid-lowering treatment with the addition of ezetimibe and PCSK-9 inhibitors to achieve LDL < 40 mg/dL [45–47]. In addition, even though guidelines recommend aggressive medical treatment in all patients with diabetes mellitus, many patients do not adhere to treatment and many physicians do not adhere to guidelines [48]. It is possible that the identification of subclinical arterial disease might improve adherence of both patients and physicians.

In conclusion, patients with DKD appear to have more pronounced arterial stiffness and carotid atherosclerosis than patients with T2DM and preserved kidney function despite the similar prevalence of traditional cardiovascular risk factors in the two groups. Therefore, the presence of DKD might represent an independent risk factor for vascular disease and the evaluation of the presence of subclinical vascular disease in these patients could be a useful tool for the personalization of their treatment and the prevention of cardiovascular events. However, the present study included relatively few patients and larger studies are needed to confirm our findings.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon request.

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