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Cardio-ankle vascular index is associated with diabetic retinopathy in younger than 70 years patients with type 2 diabetes mellitus

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ABSTRACT

Aims: This study aimed to investigate the relationship between cardio-ankle vascular index (CAVI) and diabetic retinopathy (DR) in Caucasian patients with type 2 Diabetes Mellitus (T2DM).

Methods: This was a cross-sectional study of 299 T2DM patients admitted to Endocrine Unit of Foggia. DR was diagnosed using the International Clinical Disease Severity Scale of American Academy of Ophthalmology. The VaSera VS-1500N was used to measure CAVI. Because age is the most powerful determinant of arterial stiffness and affects the progression of DR, we divided the whole sample into two subgroups: above (older) and below (younger) 70 years.

Results: The mean age of patients was 60.4 ± 12.6 years and the mean CAVI value was 8.6 ± 1.7. In the whole population DR was diagnosed in 74 (24.7%) patients. CAVI value was clearly higher in patients with DR (9.5 ± 1.6) than in those without (8.7 ± 1.7) ($P = 0.001$) although this difference was not any more significant when adjusted by age and gender ($P = 0.067$). In the multivariate model taking into account several possible confounders, the correlation between DR and CAVI remained significant only in younger subjects. In the same subgroup we found a significant association between the stages of DR and CAVI ($p = 0.019$ adjusted by age and gender).

Conclusions: This study shows that CAVI is significantly higher in younger patients with DR than in those without, with a relationship between the stages of DR and CAVI in the same subgroup. Physicians should pay attention to sub-clinical macroangiopathy in younger T2DM patients who have DR.

1. Introduction

Diabetic retinopathy (DR), one of the most common microvascular complications of diabetes, is associated with increased risk of cardiovascular (CV) morbidity and mortality either in type 1 and type 2 diabetes mellitus [1]. The exact mechanisms underlying this association are poorly understood, however the shared risk factors between DR and CV disease such as

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glycated haemoglobin (HbA1c), hypertension, and dyslipidemia might, at least partially, explain it. Therefore, it is plausible that changes in the eyes could reflect changes in the CV system [1].

Increased arterial stiffness, a predictor of cardiovascular risk, has also been recently associated with DR in patients with type 2 diabetes (T2DM) [2,3]. Arterial stiffness, which is principally affected by age and blood pressure, is the most frequently used measure of vascular aging [4,5]. A number of methods are utilized to assess arterial stiffness, among them the most recognized and established index is the pulse wave velocity (PWV) [6]. To overcome the blood pressure (at the time of measurement) dependency of PWV, the Cardio Ankle Vascular Index (CAVI), a new arterial wall stiffness parameter, has been recently developed [7]. Several reports showed that high values of CAVI are associated with arteriosclerotic diseases, such as coronary artery diseases, cerebral infarction, chronic kidney disease, and with many coronary risk factors [8,9,10]. Furthermore, CAVI showed to be a sensitive marker of the arterial aging process [11]. To our knowledge, only one study has compared, in Asian T2DM patients, CAVI with DR reporting negative results. To deeply study this issue, we have investigated the relationship between increased CAVI values and DR in Caucasian patients with T2DM.

2. Subjects, material and methods

This study was conducted in Caucasian patients with T2DM (according to American Diabetes Association 2003 criteria) who were resident in Apulia, Southeast Italy. A total of 299 patients were consecutively recruited at Endocrine Unit of University of Foggia. All patients were interviewed at the entry into the study regarding duration of diabetes and ongoing antidiabetic, hypolipidemic, and antihypertensive treatments.

2.1. Clinical and biochemical data collection

All subjects underwent physical examination, including measurements of height, weight, waist circumference, and blood pressure (i.e., two measurements rounded to the nearest 2 mmHg in the sitting position after at least 5 min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V). Fasting venous blood was sampled from an antecubital vein from all patients for the measurement of standardized serum creatinine by using the modified kinetic Jaffe´ reaction (Hitachi 737 Autoanalyzer), total serum cholesterol, (enzymatic method, Cobas; Roche Diagnostics, Welwin Garden City, U. K.), HDL cholesterol, serum triglycerides (enzymatic method, Cobas), and HbA1c (HPLC Diamat Analyzer; Bio-Rad, Richmond, CA). Urinary albumin and creatinine concentrations were determined on the morning of the clinical examination using an early morning first void sterile urine sample with the immunoturbidimetric and the Jaffé reaction-rate method, respectively (Behring Nephelometer Analyzer; Behring, Marburg, Germany). Urine albumin excretion was assessed by a single-void urine sample and expressed as the ratio of concentrations of albumin-to-creatinine ratio (ACR), as advised by National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [12]. Microalbuminuria was diagnosed if the ACR was $\geq$30 mg/g but <300 mg/g. Macroalbuminuria was defined as an ACR $\geq$ 300 mg/g. Glomerular filtration rate (e-GFR) was estimated by Epidemiology Chronic Kidney disease equation [13]. Patients were considered to have arterial hypertension if systolic blood pressure was $\geq$140 mmHg and diastolic blood pressure was $\geq$90 mmHg or they were currently receiving antihypertensive treatment [14]. Patients were considered to have dyslipidemia if they were currently receiving lipid-lowering treatment or had total cholesterol $\geq$200 mg/dl, HDL cholesterol $\leq$40 mg/dl in men and 50 mg/dl in women, and triglycerides $\geq$150 mg/dl [15].

2.2. Classification of diabetic retinopathy

The presence of retinopathy was defined on funduscopy examination or as a history of therapy. High-quality three 45° fundus photographs of both eyes were taken by digital retinal camera (TRC-NW6S, Topcon, Japan) in all participants and the grading was performed by a trained examinator who was blinded to the patients' characteristics, using the International Clinical Diabetic Retinopathy Disease Severity Scale of American Academy of Ophthalmology [16]. Participants were divided into the following three groups using the previous classification and accounting the worst eye: no diabetic retinopathy (NDR); non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In particularly NPDR was subclassified in mild if there were only microaneurysms, moderate if more than just microaneurysms but less than severe NPDR, severe if there was any of the following: more than 20 intraretinal hemorrhages in each of four quadrants, or definitive venous beading in two or more quadrants, or prominent IRMA (intraretinal microvascular abnormalities) in one or more quadrants and no signs of proliferative retinopathy. Patients were defined affected by PDR if neovascularization and/or vitreous/preretinal hemorrhage were present. Those patients with other findings such as other retina pathologies or retinal photographs of insufficient quality for grading were excluded.

2.3. Measurement of CAVI

The CAVI was measured using the VaSera VS-1500N (Fukuda Denshi Co. Ltd., Tokyo, Japan). This method is based on the estimate of the arterial stiffness index β, of the aorta and the iliac, femoral, and tibial arteries. It is a surrogate measure of the increase in arterial stiffness occurring from end-diastole to end-systole (diastolic-to-systolic "stiffening"), and incorporates information on arterial properties during the entirety of systole. Four blood pressure cuffs were wrapped on the four extremities to measure the CAVI. Electrocardiography electrodes were attached to both arms, and a microphone was placed on the sternum in the second intercostal space. After the patient had been stabilized in the supine position for 10 min, electrocardiography and phonocardiography were monitored. CAVI was calculated using Bramwell-Hill's equation [17,18]: $CAVI = a\,[(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2] + b$, where 'Ps' is the systolic blood pressure; 'Pd' is the diastolic blood pressure; 'ΔP' is Ps–Pd; 'PWV' is the cardio-ankle pulse wave

velocity; 'ρ' is the blood viscosity; and 'a' and 'b' are the constants for converting the CAVI value to a value obtained using the Hasegawa method. The higher of the measured right- and left-side CAVI values were used for the analysis. Because age is the most powerful determinant of arterial stiffness and also affects the progression of retinopathy, it could potentially confound the relationship between CAVI and retinopathy. To address this, we divided the sample into two groups, above (older) and below (younger) 70 years.

2.4. Ethics statement

The study was performed according to the Helsinki Declaration, and the protocol was approved by the local ethics committee. All subjects provided written informed consent.

2.5. Statistical analysis

Data are reported as means ± SD or median (range) and categorical variables are described as frequencies and percentages. Mean differences of normally distributed variables were compared by an unpaired Student's *t* test. In a univariate analysis we tested the relationship between CAVI and biochemical and anthropometric parameters. In a General Linear Model we explored the association between CAVI and DR adjusting for confounders (i.e., age, gender, duration of disease, eGFR, LDL Cholesterol and SBP). For these analyses, skewed distributed variables (i.e., ACR and triglycerides) were logarithmically transformed. Statistical package SPSS version 11.5 (SPSS, Chicago, IL) was used. A *P* value < 0.05 was considered to be significant.

3. Results

The main clinical features of the whole sample (n = 299), "older" (n = 65) and "younger" (n = 234) subjects are summarized in Table 1. Overall, there were 166 men and 133 women with a mean age of 60.4 ± 12.6 years, and a mean duration of diabetes of 11.9 ± 9.7 years. The glycemic control was unfair, in fact the mean value of HbA1c was 8.8 ± 2.4%. The mean value of CAVI was 8.6 ± 1.7. As expected, older patients had a longer duration of diabetes, lower values of weight, eGFR,

Table 1 – Baseline clinical features of the whole sample of 299 T2DM patients and of those below (Younger) and above (Older) 70 years old.

	Whole sample n = 299	Younger n = 234	Older n = 65	P value
Male sex n (%)	166 (55.5)	136 (58.1)	30 (46.2)	0.058
Age (years)	60.5 ± 12.7	56.3 ± 11.0	75.6 ± 3.5	<0.0001
Duration of diabetes (years)	11.9 ± 9.7	10.5 ± 8.5	16.9 ± 11.7	<0.0001
Weight (kg)	82.4 ± 17.7	84.8 ± 18.5	73.9 ± 10.9	<0.0001
BMI (Kg/m^2)	30.1 ± 5.8	30.4 ± 6.2	29.0 ± 3.6	0.020
Waist circumference (cm)	105.1 ± 13.8	105.6 ± 14.7	103.4 ± 10.5	0.204
HbA1c (%; mmol/mol)	8.8 ± 2.4 (73 ± 26)	8.9 ± 2.5 (74 ± 27)	8.4 ± 2.0 (68 ± 22)	0.096
SBP (mmHg)	127.8 ± 17.8	125.8 ± 17.1	135.1 ± 18.5	<0.0001
DBP (mmHg)	76.7 ± 9.7	77.3 ± 9.6	74.5 ± 9.8	0.043
Total cholesterol (mg/dl)	177.1 ± 44.2	180.6 ± 44.0	164.4 ± 42.6	0.008
HDL cholesterol (mg/dl)	45.1 ± 12.1	44.5 ± 11.5	47.1 ± 13.9	0.183
LDL cholesterol (mg/dl)	106.8 ± 34.9	110.2 ± 35.4	94.3 ± 30.5	<0.0001
Triglycerides (mg/dl)	138.0 (36–825)	146.0 (36–825)	124.5 (49–518)	0.229
e-GFR ($mL/min \times 1.73\ m^2$)	85.9 ± 24.7	91.8 ± 22.4	65.5 ± 21.3	<0.0001
ACR (mg/g)	15.4 (0–2813)	14.1 (0–2813)	20.7 (1–811)	0.214
Micro or macroalbuminuria n (%)	94 (31.4)	73 (31.2)	21 (32.3)	0.488
Diabetic retinopathy n (%)	74 (24.7)	54 (23.1)	20 (30.8)	0.13
Stage of diabetic retinopathy				
Non proliferative diabetic retinopathy mild n (%)	41 (13.7)	27 (11.5)	14 (21.5)	0.797
Non proliferative diabetic retinopathy moderate n (%)	8 (2.7)	7 (3.0)	1 (1.5)	
Non proliferative diabetic retinopathy severe n (%)	1 (0.3)	1 (0.4)	0 (0)	
Proliferative diabetic retinopathy n (%)	24 (8.0)	19 (8.1)	5 (7.7)	
Antidiabetic treatment				
Diet alone n (%)	24 (8.0)	21 (9.0)	3 (4.6)	0.431
OHA n (%)	143 (47.8)	111 (47.4)	32 (49.2)	
Insulin and/or OHA n (%)	132 (44.1)	102 (43.6)	30 (46.2)	
Dyslipidemia n (%)	254 (84.9)	193 (82.5)	61 (93.8)	0.014
Lipid-lowering treatment n (%)	165 (55.2)	122 (52.1)	43 (66.2)	0.030
Arterial Hypertension n (%)	218 (72.9)	162 (69.2)	56 (86.2)	0.004
Treatment with ACE-Is/ARBs n (%)	170 (56.9)	125 (53.4)	45 (69.2)	0.043
CAVI	8.9 ± 1.7	8.6 ± 1.7	9.9 ± 1.4	<0.0001

Data are n (%), means ± SD, or median (range). P values for comparison between patients with ≤ or >70 years old. BMI indicates body mass index; HbA1c glycated haemoglobin; SBP systolic blood pressure; DBP diastolic blood pressure; HDL high-density lipoprotein cholesterol; LDL low-density lipoprotein cholesterol; e-GFR estimated glomerular filtration rate; ACR albumin-creatinine ratio; OHA, oral hypoglycemic agent; ACE-Is angiotensin converting enzyme-inhibitors; ARB angiotensin II receptor blocker; CAVI cardio-ankle vascular index.

LDL cholesterol and a higher prevalence of lipid-lowering treatment as compared to younger patients. Furthermore, they had higher values of SBP despite a greater prevalence of antihypertensive treatment. Regarding the microvascular complications, in the whole population the presence of DR was confirmed in 74 (24.7%) patients. Forty-one patients (13.7%) had a mild NPDR, 8 patients (2.7%) had a moderate NPDR, 1 patient (0.3%) had a severe NPDR, 24 patients (8%) had a PDR. In the whole sample, 68.6% of patients (N = 205) were normoalbuminuric, 22.4% (n = 67) had microalbuminuria and 9% (N = 27) had macroalbuminuria. As expected, older patients tended to have more presence of albuminuria and retinopathy (Table 1). Variables significantly correlated with CAVI were age (r = 0.519, p < 0.0001), duration of diabetes (r = 0.210, p < 0.0001), BMI (r = −0.208, p < 0.0001), SBP (r = 0.181, p = 0.002), total cholesterol (r = −0.136, p = 0.018), LDL cholesterol (r = −0.176, p = 0.002) and eGFR (r = −0.283, p = <0.0001). When we analyzed the population stratified by presence/absence of retinopathy, patients with DR were older with longer duration of disease as compared to patients without DR. Patients with DR had higher values of SBP despite a greater prevalence of antihypertensive treatment, higher frequency of micro-macroalbuminuria and lower levels of eGFR. CAVI value was clearly higher in patients with DR (9.5 ± 1.6) than those in patients without DR (8.7 ± 1.7) (P = 0.001) (Table 2), although this difference was not any more significant when adjusted by age and gender (P = 0.067). Because age, DR and CAVI are statistically and biologically highly interrelated and correlated, to investigate whether age may have confounded the relationship between CAVI and DR, we divided the whole sample into two age groups above (older) and below (younger) 70 years. Of note, in the multivariate model taking into account several possible confounders, the correlation between DR and CAVI remained significant only in younger subjects (Table 3). In addition, in the same subgroup we found a significant association between the stages of DR and CAVI. In fact, CAVI value was 8.4 ± 1.6 in NDR (*n* = 180), 9.6 ± 1.9 in NPDR (*n* = 35), 9.3 ± 1.5 in PDR (*n* = 19) (p = 0.019 adjusted by age and gender) while in the older subjects the values of CAVI were 10.0 ± 1.4 in NDR (*n* = 45), 9.5 ± 0.9 in NPDR (n = 14) and 9.5 ± 1.5 in PDR (n = 5) (p = 0.052 adjusted by age and gender).

4. Discussion

Several studies have shown that DR is associated with cardiovascular complications [19,20]. In the present report, arterial stiffness, a strong predictor of CV events in patients with T2DM, assessed by CAVI was significantly increased in younger patients with DR than in those without. In addition, we showed a significant relationship between CAVI and stages of DR in the same subgroup. This relationship was weaker and not significant in older patients. Our finding supports the results of previous studies [21,22] investigating the association between DR and arterial stiffness assessed by the carotid-femoral PWV (cfPWV) [23]. However, due to the

Table 2 – Comparison of baseline clinical features of 299 T2DM patients with or without Diabetic Retinopathy.

	NDR (n. 225)	DR (n. 74)	P value
Male sex n (%)	126 (56.0)	40 (54.1)	0.437
Age (years)	59.0 ± 13.4	64.9 ± 8.7	<0.0001
Duration of diabetes (years)	9.6 ± 8.6	19.0 ± 9.2	<0.0001
Weight (kg)	83.2 ± 18.9	80.0 ± 12.8	0.100
BMI (Kg/m^2)	30.2 ± 6.1	29.8 ± 4.5	0.550
Waist circumference (cm)	104.9 ± 13.9	105.7 ± 13.8	0.682
HbA1c (%; mmol/mol)	8.7 ± 2.4 (72 ± 26)	9.2 ± 2.2 (77 ± 24)	0.081
SBP (mmHg)	126.2 ± 17.8	132.4 ± 17.1	0.009
DBP (mmHg)	77.1 ± 9.9	75.5 ± 9.2	0.209
Total cholesterol (mg/dl)	177.5 ± 43.2	175.8 ± 47.2	0.790
HDL cholesterol (mg/dl)	45.2 ± 11.4	44.6 ± 13.9	0.723
LDL cholesterol (mg/dl)	106.8 ± 34.8	106.7 ± 35.8	0.983
Triglycerides (mg/dl)	135.0 (36–825)	159.0 (43–547)	0.42
e-GFR (mL/min × 1.73 m^2)	88.7 ± 23.2	79.5 ± 26.9	0.022
ACR (mg/g)	12.1 (0–1714)	26.8 (1–2813)	<0.0001
Micro or macroalbuminuria n (%)	60 (26.7)	34 (45.9%)	0.002
Antidiabetic treatment			
Diet alone n (%)	24 (10.7)	0 (0)	<0.0001
OHA n (%)	123 (54.7)	20 (27.0)	
Insulin and/or OHA n (%)	78 (34.7)	54 (73.0)	
Dyslipidemia n (%)	188 (83.6)	66 (89.2)	0.162
Lipid-lowering treatment n (%)	116 (51.6)	49 (66.2)	0.019
Arterial Hypertension n (%)	159 (70.7)	59 (79.7)	0.08
Treatment with ACE Is/ARBs n (%)	123 (54.7)	47 (63.5)	0.026
CAVI	8.7 ± 1.7	9.5 ± 1.6	0.001

Data are n(%), means ± SD, or median (range). P values for comparison between patients with or without DR. BMI indicates body mass index; HbA1c glycated haemoglobin; SBP systolic blood pressure; DBP diastolic blood pressure; HDL high-density lipoprotein cholesterol; LDL low-density lipoprotein cholesterol; e-GFR estimated glomerular filtration rate; ACR albumin-creatinine ratio; OHA, oral hypoglycemic agent; ACE-Is angiotensin converting enzyme-inhibitors; ARB angiotensin II receptor blocker; CAVI cardio-ankle vascular index.

Table 3 – Unadjiusted and Adjiusted models evaluating the association between CAVI and diabetic retinopathy in both younger and older T2DM patients.

	Younger		*Older*	
	R squared	*P value*	*R squared*	*P value*
Unadjusted model	0.073	<0.0001	0.033	0.146
Model 1 adjiusted for age and gender	0.251	0.006	0.111	0.274
Model 2 adjiusted for age, gender and duration of diabetes	0.255	0.047	0.115	0.346
Model 3 adjiusted for age, gender, duration of diabetes and LDL cholesterol	0.272	0.018	0.121	0.361
Model 4 adjiusted for age, gender, duration of diabetes, LDL cholesterol and e-GFR	0.323	0.042	0.208	0.957
Model 5 adjiusted for age, gender, duration of diabetes, LDL cholesterol, e-GFR and SBP	0.323	0.044	0.227	0.912

LDL low-density lipoprotein cholesterol; e-GFR estimated glomerular filtration rate; SBP systolic blood pressure.

time-consuming of this method which is partly operator dependent, cfPWV measurement has not become part of the daily routine in clinical work up of T2DM patients. Moreover, all techniques utilized to measure PWV are intrinsically dependent on BP values at the time of measurement. The measurement of CAVI is the approach suggested to overcome blood pressure dependency of PWV [18]. CAVI has been widely applied in clinical studies mostly performed in Asian population affected by cardiovascular disease as well as by hypertension, diabetes, and obesity [18,24]. At our knowledge, only one study has explored the relationship between CAVI and microvascular complications in T2DM patients [25], showing a significant association between CAVI with microalbuminuria and neuropathy but not with RD. This discrepancy respect to our result can be explained by different population studied (Asians vs Caucasians), different duration of diabetes and clinical characteristics (i.e. BMI, age of our population vs KIM's population, respectively). The relationship we found between CAVI and DR in younger patients does not appear to be spurious. In fact it does not change when adjusted by age and duration of disease which are the most powerful determinant of arterial rigidity. In the light of our and other authors finding, we can speculate that arterial stiffness might mediate, at least partially, the well documented relationship between DR and CV disease. The association between CAVI and DR remains significant also when adjusted by traditional CV risk factors such as, e-GFR, LDL Cholesterol and SBP thus suggesting that a possible unmeasured variable may be the link between these two conditions. We can also speculate that in older patients with long-duration of disease, CAVI may not add any predictive value as aging per se strongly influences the determinants of arterial stiffness. This group of patients may also have other factors affecting DR such as hypertension. Several limitations should be taken into account when considering the results of this study. First, the cross-sectional study design. Thus, the association between arterial stiffness and DR cannot be taken as a causal relationship. Nonetheless, this result may help shed light on the pathophysiological connections between the development and progression of macro- and microangiopathy in diabetes. Second, the small sample size for each stage of DR in our study make it difficult to infer the association between CAVI and retinopathy. Furthermore, some caveats need to be considered when assessing the clinical meaning of CAVI. First, the tenet that β and CAVI are unaffected by BP has been recently questioned [26]. In order to avoid wrong conclusions, when the prognostic implications of CAVI are investigated, it may be important to take into account the effect of this BP dependency, even if it is less than that of PWV [27]. It is worth noting that CAVI measures the properties of the aorta, femoral artery and tibial artery as a whole [17]. The aorta is an elastic vessel, while the femoral artery and tibial artery are muscular vessels under the control of nerves. Accordingly, an elevated CAVI may represent not only vascular stiffness caused by pathological changes in the arterial wall, but can also be attributed to an increased vascular tone brought about by smooth muscle contraction. On the other hand, the well-characterized and homogeneous population and the single recruiting center are major strengths of the study, which gives missing information about this issue in Italy. In conclusion, this study shows that CAVI is significantly higher in younger patients with DR than in those without, and that there is a relationship between the stages of DR and CAVI in T2DM patients. Physicians should pay attention to sub-clinical macroangiopathy in younger T2DM patients who have DR.

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Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107793.

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