ARTERIAL STIFFNESS AND IMPAIRED RENAL FUNCTION IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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Abstract

Background and aims: Cardio-Ankle Vascular Index (CAVI) was developed as an index of arterial stiffness independently of blood pressure and other markers of early atherosclerosis. The aim of the study was to assess the correlations between CAVI and renal disease in type 2 diabetic patients compared with those without diabetes.

Material and methods: We evaluated anthropometric, biochemical and vascular parameters (through CAVI) in 133 patients with and 80 without type 2 diabetes mellitus (T2DM) mean aged 59.34 ± 11.94 years. Results: We found that 52.04 % of subjects with T2DM and 22.22 % of patients without T2DM had pathological arterial stiffness. Mean CAVI value was significantly higher in T2DM (p = 0.04), positively correlated with age and negatively with glomerular filtration rate. The prevalence of chronic kidney disease in patients with pathological vascular stiffness was 5.28 times higher in T2DM compared with the control group. Conclusion: The prevalence of pathological vascular stiffness, mean CAVI and prevalence of chronic kidney disease (CKD) were also higher in patients with T2DM than in the control group. Arterial stiffness plays an important role in renal impairment both in normoglycemic subjects and patients with T2DM, so preventive measures to optimize lifestyle and treatment must target the decrease of CAVI.

key words: diabetes mellitus, vascular stiffness, atherosclerosis.

Background and Aims

Cardiovascular diseases are responsible for 35-48% of worldwide deaths [1]. In the last 30 years an important decrease in cardiovascular mortality was obtained, mainly due to the implementation of primary and secondary prevention programs [1].

Arteriosclerosis is a major contributor to cardiovascular and cerebrovascular diseases. The substrate of cardiovascular disease is atherosclerosis [2]. Therefore, early diagnosis is very valuable, especially in asymptomatic patients with diabetes mellitus [3].

In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular diseases. Increased arterial stiffness is an early marker for cardiovascular disease risk as rigid vessels predict heart attack and stroke in adults,
especially in those with type 2 diabetes mellitus [4]. Following several studies for the identification of a reproducible parameter, easy to use in clinical practice, CAVI (Cardio-Ankle Vascular Index) has been proposed as a non-invasive measurement of arterial stiffness [5]. CAVI is calculated from the electrocardiogram, phonocardiogram, brachial artery waveform and ankle artery waveform, using a mathematical algorithm. CAVI is a marker of early atherosclerosis, independent of blood pressure and compliance of descending aorta [5].

There have been various studies which have shown that patients with diabetes have a higher vascular stiffness compared with healthy subjects, starting from the age of 20 years [6]. It is known that CAVI value increases with age both in females and males. Also, the frequency of chronic complications increases with the duration of diabetes mellitus [7].

Starting from these premises, the aim of our study was to evaluate the correlation between CAVI (as a marker of vascular stiffness) and renal function (expressed by MDRD = Modified Diet in Renal Disease) in patients with diabetes mellitus compared with people without diabetes.

**Material and methods**

**Subject inclusion**

The study was approved by the Local Ethics Committee of “Elias” Emergency Hospital, Bucharest. From 500 patients evaluated in the Endocrinology, Diabetes and Metabolic Diseases Department between December 2012-December 2013, 213 patients gave their written informed consent, according to Helsinki Declaration, and were included in the study.

The exclusion criteria were: age over 85, chronic atrial fibrillation, left ventricular dysfunction (ejection fraction below 50%), severe valvular diseases, aortic dissection and aortic aneurysm. Based on these criteria 154 patients were excluded from the study. For 133 patients we could not obtain the informed consent and these were not included in our study.

**Clinical evaluation**

We recorded data regarding anthropometric parameters including height, weight, waist and hip circumference. Weight was measured in light clothing without shoes and height was measured using a stadiometer. Waist and hip circumference were measured with the patient standing, at the level of umbilicus and greater trochanter respectively.

**Paraclinical evaluation**

The vascular screening was performed using a Fukuda Denshi Vasera TM VS 1000 Co.Ltd. device. Patient preparation for investigation was done to mitigate any possible vascular stress. The patient remained at rest 15 minutes before the investigation, in a comfortable environment. During the investigation the patient did not sleep and neither spoke. He was advised not to smoke, eat or drink coffee 4 hours before testing. He was allowed to take his regular medications.

Normal CAVI values were considered below 8 m/s. An estimated vascular age is obtained by applying the calculated right/left CAVI to age graph, with the actual age entered in patient information and the standard deviations of CAVI taken into consideration.

**Laboratory evaluation**

Blood samples were drawn for biochemical tests after 12 hours overnight fast. We evaluated the metabolic control (glycemia, HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceridemia).

Chronic kidney disease (CKD) was defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and the stage of CKD was assigned based on the
level of kidney function, according to the KDOQI Classification [8].

Data about patient's lifestyle: smoking habits and alcohol consumption were also recorded. The patients were divided into 3 groups depending on alcohol consumption levels in: abstainer, mild-moderate drinker (with 30-60 g alcohol per day) and heavy drinker (with more than 60 g alcohol per day).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Software (SPSS) version 17. Data are presented as mean ± standard deviation (SD). Clinical characteristics were compared using the t Student Test. The Pearson coefficients were calculated to evaluate correlations between variables. Significance was defined at p value under 0.05.

Results

From the 213 subjects included in the study, 133 patients were diagnosed with type 2 diabetes mellitus (T2DM) and 80 were control subjects. Age ranged between 25-85 years (mean age 59.34 ± 11.94 years). The main patients characteristics are presented in Table 1.

Table 1. Characteristics of subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Diabetes mellitus</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M/F)</td>
<td>80 (31/49)</td>
<td>133 (65/68)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>47.16±12.08</td>
<td>62.08±11.56</td>
<td>NS</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>108.5±23.54</td>
<td>111.8±28.45</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glycemia (mg/dl)</td>
<td>97.38±6.07</td>
<td>203.36±7.14</td>
<td>N/A</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-</td>
<td>9.17±6.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>216.5±24.56</td>
<td>243.9±30.16</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>224.2±34.98</td>
<td>201±35.67</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>38.3±15.97</td>
<td>41.5±18.34</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>123.8±23.78</td>
<td>162.1±34.89</td>
<td>0.03</td>
</tr>
<tr>
<td>CAVI (m/s)</td>
<td>6.65±2.05</td>
<td>8.75±3.15</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All values have been expressed as mean ± SD   NS=no statistically significant   N/A= no available

The two groups were similar in terms of age and waist circumference, also the mean value of total cholesterol and triglyceride were similar. The patients with T2DM had higher mean LDL-cholesterol and HDL-cholesterol compared with normoglycemic subjects. Diabetic patients had a mean duration disease of 8.6 ± 2.3 years and mean HbA1c was 9.17 ± 1.93%, suggesting a poor metabolic control. In our study, no differences in gender distribution were observed.

The prevalence of vascular stiffness in the whole study group was 52.04%. Overall, 78 (58.64%) patients with type 2 diabetes and 18 (22.5%) controls had CAVI values > 8 m/s.

As expected, the mean CAVI was higher in subjects with diabetes mellitus, compared to the
control group (8.75 ± 2.32 m/s vs. 6.65 ± 1.70 m/s, p = 0.04). However, we did not found a statistically significant correlation between CAVI and HbA1c in patients with type 2 diabetes. Arterial stiffness was higher in smokers and former smokers compared to non-smokers (8.7 m/s vs. 7.9 m/s, p = 0.03). The mean CAVI value was significant higher in heavy drinkers compared with mild-moderate drinkers (8.73 vs. 6.04 m/s, p = 0.005), without significant differences compared to abstainers.

Regarding the increasing of arterial stiffness with age we found a positive correlation both in diabetics (r = 0.34) and in controls (r = 0.2), without statistically significant differences between the two groups.

The prevalence of CKD was 58.64% in patients with diabetes and 37.5% in control subjects. In the whole study group there were no patients within stage 5 of CKD, these cases being referred to specialized nephrology departments.

In diabetic patients, the highest CAVI value of 9.14 m/s was recorded in stage 3 CKD. In this group we didn’t find significant differences between the mean CAVI value in subjects within stage 1 of CKD and those in stage 4 of CKD (7.78 m/s vs. 8.95 m/s, p = 0.18).

In the control group, the mean difference between CAVI value in subjects within stage 1 of CKD and those in stage 4 of CKD was statistically significant (5.76 m/s vs. 9.20 m/s, p = 0.004), as shown in Figure 1.

There was a negative correlation between CAVI and MDRD both in diabetics (r = -0.42) and in normoglycemic subjects (r = -0.19).

![Figure 1. Mean CAVI and stage of CKD in the control group.](image)

In patients with increased arterial stiffness (CAVI >8 m/s) the prevalence of CKD was 58.97% (46) in diabetic and 11.11% (2) in control patients.

Out of 78 patients diagnosed with CKD and diabetes, 53 (68%) had increased CAVI values. Out of 30 patients with CKD without diabetes, 8 patients (26.66%) were recorded with increased CAVI values.

Splitting the whole group of patients into 4 subgroups according to the presence of diabetes mellitus and CKD, we obtained the following mean CAVI values: without diabetes without CKD = 1.04 m/s, without diabetes with CKD = 7.24 m/s, with diabetes without CKD = 6.8 m/s and with diabetes with CKD = 10.04 m/s. The difference between the first and the last group was statistically significant (p = 0.003), as shown in Figure 2.

**Discussions**

At inclusion, patients with type 2 diabetes had (after 8.6 years duration of disease) a poor metabolic control, evidenced by an HbA1c of...
9.17%. It should be noted that these patients were selected from those who were referred to our department and were admitted in order to improve the metabolic imbalance.

Figure 2. Mean CAVI according to presence of DM and CKD.

The pathological vascular stiffness had an increased prevalence in the entire group and was observed 2.6 times more frequently in patients with diabetes compared with controls, although the difference between the mean age of the two groups was not statistically significant. The age difference is clinically relevant and it could be significant maybe, on a larger group of patients. In accordance with data reported by most publications, diabetic patients have higher arterial stiffness compared with healthy controls, although vascular damage may begin early before progression to type 2 diabetes in the presence of deteriorating glucose tolerance status [9].

Interestingly, in our study the vascular stiffness was increased in heavy drinkers compared with mild-moderate drinkers. In a Japanese study aimed to elucidate the relationship between alcohol consumption and arterial stiffness measured by CAVI in healthy middle-age men, multiple linear regression analysis revealed that low alcohol consumption was associated with lower arterial stiffness after adjusted confounding factors such as age, smoking, blood pressure, body mass index and lipid profile [10]. However, studies assessing the relationship between alcohol consumption and pulse wave velocity (PWV) as a marker of arterial stiffness have provided inconsistent results. In addition, data regarding the effect of alcohol on arterial stiffness in women has been limited. A recent study aimed to clarify the relationship between alcohol consumption and PWV among female and male workers in Japan. In middle-aged Japanese women and men, light-to-moderate alcohol consumption is associated with lower PWV [11].

Vascular stiffness correlated with age increase in both groups. Several studies have shown that arterial stiffness (estimated by PWV) gradually increases with age, from about 4 m/s in the third decade to 10 m/s in the ninth decade [3]. Despite the fact that in our study no difference in gender distribution was observed, several papers have shown that arterial stiffness is higher in males (with about 0.2 m/s) and the vessels age is 4-5 years higher than in females [6].

In contrast to previous studies [12], we found no association of CAVI with glycemic control in patients with type 2 diabetes mellitus. As estimated arterial stiffness reflected in real time the vascular wall injury, while HbA1c is a
parameter that can change in a few weeks with proper treatment, sometimes discordant results could be explicable between metabolic control and CAVI [13].

Arterial wall properties in subjects with CKD may be influenced by many factors such as age, gender, smoking, blood pressure and diabetes [14]. In diabetic patients, the highest CAVI value was recorded in stage 3 CKD. Arterial stiffness increased with renal impairment in patients with type 2 diabetes, irrespective of age and metabolic control.

In patients with pathological vascular stiffness, the prevalence of CKD was 5.3 times higher in diabetics as compared to normoglycemic subjects in our study. We also found significant differences between CAVI in patients with stage 4 CKD compared to stage 1 CKD in the control group but not in diabetic patients. A small Korean study showed that CAVI value was higher in non-diabetic continuous ambulatory peritoneal dialysis (CADP) patients than in the general population and CAVI were independently associated with hypoalbuminemia [14].

Three small studies have found an association between vascular stiffness and CKD. Taal et al. use radial-dorsalis pedis PWV as a measure of arterial stiffness in 35 patients with advanced (stages 4 and 5) CKD and found that PWV predicts progression to end-stage renal disease (ESRD) [15]. In a Japanese study of 41 subjects with non-diabetic CKD the augmentation index (Aix) predicted a greater decline in renal function [16]. Interestingly, a subsequent study by this group in 42 patients failed to replicate this finding and did not demonstrate any relationship between PWV or Aix and progression of renal dysfunction [17]. A third study of 133 patients with stage 3-4 of CKD showed PWV to be a predictor of decline in renal function [18].

Anyway, recent prospective studies have demonstrated that arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in end-stage renal disease patients and also in the general population [19,20].

**Conclusion**

In our study, the prevalence of pathological vascular stiffness, mean CAVI and prevalence of chronic kidney disease (CKD) were higher in patients with T2DM than in the control group.

The vascular stiffness plays an important role in renal impairment both in normoglycemic and especially in patients with diabetes mellitus, so preventive measures to optimize lifestyle and improve treatment must also target the decrease of CAVI value.

CAVI is a noninvasive tool useful for atherosclerosis evaluation in the general population. This measurement is most likely to be useful for the identification of at risk patients, during early stages of atherosclerotic disease, when functional wall properties are still reversible. However, further studies are necessary to evaluate whether this tool provides any additional prognostic value, when used in combination with clinical risk scores, before it can be implemented on large scale in clinical practice.

**REFERENCES**


