Markers of increased vascular risk in women with hypertension and type 2 diabetes mellitus

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Abstract: Background. Diabetes mellitus and arterial hypertension have important effects on vascular system and their major complications are caused by alterations of vasculature. These diseases are frequently associated. Beyond classical risk factors implicated in both diseases, in recent years some novel markers of vascular involvement have been studied, such as intima–media thickness (IMT) and parameters of arterial stiffness. Women seem to have an increased vascular risk associated with diabetes than do men. The aim of our study was to determine the consequences of hypertension associated with diabetes on intima media thickness and arterial stiffness in women.

Patients and methods. We studied 54 women, 33 with diabetes mellitus and hypertension and 21 healthy controls (HC), matched for age. We evaluated classical risk factors for atherosclerosis, such as age, body mass index, smoking, lipid and glucose profile. We determined IMT of the carotid artery using an ultrasound device (ALOKA ProSound α 10) and parameters of aortic stiffness – pulse wave velocity (PWV) and augmentation index (Aix) in all subjects using Arteriograph device (Tensio Med Ltd., Budapest, Hungary).

Results. PWV was increased in patients compared HC (p=0.001). Alx, SBPao (aortic systolic blood pressure) and PPao (aortic pulse pressure) were also higher in patients but they did not have statistical power. IMT was significantly increased in patients compared with HC (p=0.01). In the group of patients IMT was significantly correlated with age, arterial pressure and SBPao. Patients had higher body mass index (BMI) and arterial pressure. There were no smokers in the study population. Of biochemical parameters only fasting plasma glucose was significantly higher in diabetic patients.

Conclusion. In our study women with hypertension and diabetes had increased arterial stiffness and IMT compared to HC. Coexistence of diabetes and hypertension in women is associated with increased markers of vascular disease that may be a link to the important cardiovascular risk seen in these patients.

Key-Words: vascular risk, diabetes, hypertension, arterial stiffness, intima-media thickness

1. Introduction

Association of hypertension in diabetes is very frequent. The prevalence of hypertension in diabetic patients is nearly twice that of the non diabetic persons [1]. The presence of both diseases seems to accelerate vascular complications and increases cardiovascular and cerebrovascular risk. Cardiovascular events are two times more frequent in patients with diabetes and hypertension than in patients with either disease alone [2]. Women seem to have greater cardiovascular morbidity associated with diabetes than do men [3].

In recent years non invasive assessment of preclinical atherosclerosis was the subject of many research studies that aimed to diagnose this disease in a precocious stage. Arterial stiffness and IMT are important markers of preclinical atherosclerosis. There is increasing evidence that arterial stiffness is an independent predictor of future cardiovascular risk in a variety of populations [4]. Carotid-femoral PWV is considered as the “gold standard” measurement of arterial stiffness [5].
Augmentation index (Aix) is a parameter of wave reflection and an indirect marker of arterial stiffness [6].

Carotid IMT is associated with cardiovascular risk factors and with the degree of atherosclerosis in different arterial sites though, it can be used as a surrogate marker of atherosclerosis [7,8].

2. Problem Formulation

2.1. Aim of the study

The deleterious effect of hypertension and diabetes on arterial wall is well-known. There are still some unresolved problems such as differential stiffening of central vs peripheral arterial segments, the impact of sex and the correlation of arterial parameters with different classical cardiovascular risk factors [5].

The aim of our study was to determine the influence of arterial hypertension and diabetes mellitus on parameters of arterial stiffness and carotid IMT in women and to compare them with healthy controls.

2.2 Patients and methods.

A total of 54 women were included in the study, 33 with diabetes and hypertension and 21 healthy controls. They gave informed consent to participate in the study and the protocol was approved by the ethical committee of our institution. All patients were non-smokers. Exclusion criteria were: cardiac insufficiency, arrhythmia, diabetes mellitus type 1 or diabetes associated with specific syndromes, and renal insufficiency.

Diagnosis of diabetes was made according to the American Diabetes Association Criteria [9]. Hypertension was defined as repeated measurements of \( \geq 140 \) mmHg for systolic blood pressure (SBP) or \( \geq 90 \) mmHg for diastolic blood pressure (DBP), or permanent antihypertensive drug treatment. We measured body weight and height and we calculated body mass index (BMI).

**Carotid measurements of IMT**

We used an ultrasound device (ALOKA ProSound \( \alpha \) 10) equipped with a linear transducer operating at a fundamental frequency of 10 Mhz to measure carotid IMT.

Carotid IMT was measured at the far wall of the common carotid artery, 1 cm before bifurcation. We calculated the mean values obtained from the measurements of the two common carotid arteries. We followed the protocol approved by the Society for Vascular Medicine [10]. Scanning from proximal common carotid artery through internal carotid artery was done for identification of plaques.

**Measurement of arterial stiffness parameters.**

For the measurement of arterial stiffness we used a recently developed device, the Arteriograph (TensioMed Ltd., Budapest, Hungary). It uses an oscillometric method to determine parameters of arterial stiffness. Pulsatile pressure changes in the brachial artery registered in the upper arm are detected by plethysmography. Variation in pulsatile pressure in the artery beneath an inflated cuff induces periodic pressure change in the cuff [11]. The Arteriograph measures simultaneously brachial blood pressure (BP), PWV, Alx, SBP ao and PPao. It initially measures the BP in the upper arm oscilometrically and than produces a cuff pressure superior with 35 mmHg to the SBP measured. The fluctuations of pressure in the brachial artery are detected by the cuff. They are transmitted to the computer that analyzes the pulse waves. The distance traveled by the waves is assimilated as the distance between the the jugulum and the symphysis. The difference in time between the first wave and the beginning of the second second wave is related to the distance between the sternal notch and the symphysis resulting in the PWV (m/s) [11,12].

The Alx corresponds to the pressure difference between the first and the second wave in relation to pulse pressure (PP). The Arteriograph calculates Alx on the basis of the formula Alx%=\((P2-P1)/PP\)\times100 [10,11].

The measurements were done in the supine position after 10 min of rest in a quiet room at a temperature of 22°C.
Subjects have to refrain, for at least 3 hours before measurements, from drinking beverages containing caffeine and from smoking [10].

**Blood measurements**

Blood was drawn in the morning after an overnight fast for 12 hours. We determined fasting plasma glucose (FGP), total cholesterol (TC), triglycerides (TG), creatinine (Cr). In diabetic patients we also measured hemoglobin A1c (HbA1c).

**Statistical analysis**

All data were analyzed using Statistical Package of Social Sciences (SPSS, version 10.0). Measurements are reported as mean and standard error (SE). Continuous data were analysed using independent t test or Mann-Whitney U test. Two frequencies were compared using Chi-Square test. A p value < 0.05 was considered significant. For comparison between quantitative variables in each group we used Person’s correlations.

## 3. Problem Solution

### 3.1. Results

We included in this study only women.

Clinical data and laboratory parameters of the study groups are summarized in table 1.

The groups were comparable in age, laboratory values for TC, TG, and creatinine values. Also heart rate that can influence parameters of arterial stiffness was comparable between the groups.

BMI was significantly higher in patients than in controls and also fasting plasma glucose was significantly augmented in diabetic patients. Mean value for Hgb A1c (%) in patients with diabetes was 6.55 +/- 0.15.

The mean period of evolution for diabetes was 7.5 +/- 3.2 years and for hypertension 8.6 +/- 2.9 years, in patient group.

### Table 1. Clinical characteristics of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=21)</th>
<th>Hypertensive and diabetic patients (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8 +/- 2.0</td>
<td>62.7 +/- 1.39</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 +/- 0.89</td>
<td>30.8 +/- 0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>93.8 +/- 1.91</td>
<td>153.8 +/- 7.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>194.9 +/- 8.56</td>
<td>223.4 +/- 9.6</td>
<td>0.08</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>108.3 +/- 9.1</td>
<td>143 +/- 13</td>
<td>0.18</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.85 +/- 0.04</td>
<td>0.9 +/- 0.05</td>
<td>0.97</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>70.3 +/- 1.5</td>
<td>70.9 +/- 1.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data are mean +/-SE. BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; Cr, creatinine; HR, heart rate.

Values of vascular parameters found in patients and controls are shown in table 2.

### Table 2. Vascular parameters in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=21)</th>
<th>Hypertensive and diabetic patients (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic PWV(m/s)</td>
<td>8.85 +/- 0.28</td>
<td>10.48 +/- 0.41</td>
<td>0.001</td>
</tr>
<tr>
<td>AIX (%)</td>
<td>-3.40 +/- 3.60</td>
<td>1.69 +/- 3.74</td>
<td>0.68</td>
</tr>
<tr>
<td>PPao (mmHg)</td>
<td>57.50 +/- 1.54</td>
<td>60.7 +/- 2.87</td>
<td>0.27</td>
</tr>
<tr>
<td>SBP ao (mmHg)</td>
<td>129.75 +/- 2.67</td>
<td>141.31 +/- 2.97</td>
<td>0.06</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126.86 +/- 2.79</td>
<td>138.45 +/- 2.52</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75.86 +/- 1.85</td>
<td>82.48 +/- 1.70</td>
<td>0.03</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>92.76 +/- 1.91</td>
<td>100.42 +/- 1.84</td>
<td>0.01</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.76 +/- 0.03</td>
<td>0.91 +/- 0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>4 (19%)</td>
<td>18 (54.5%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are mean +/-SE; PWV, pulse wave velocity; AIX, augmentation index; PPao, pulse pressure aortic; SBPao, aortic systolic blood pressure; SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; MBP, brachial mean blood pressure; IMT, intima-media thickness
Aortic PWV was significantly higher in patients than controls (P=0.001). Also values of SBP, DBP and MBP were elevated in patients. AIx, SBPao and PPao were also higher in patients compared to healthy women but they did not have statistical power.

IMT was significantly higher in patients than controls. Carotid plaques were found more frequently in patients than in controls (p<0.01).

In the group of patients we found significant correlations between intima-media thickness and age (p=0.04), SBP (p=0.04), DBP (p<0.001), MBP (p=0.01), and SBPao (p=0.01).

### 3.2. Discussion

Coexistence of high arterial pressure and diabetes is associated with increased cardiovascular morbidity and mortality. We already know that elevated arterial pressure is one of the most important risk factors for cardiovascular disease. Diabetics have a substantial cardiovascular risk, and a subject with noninsulin-dependent diabetes is probably at a similar risk with a nondiabetic that has sustained a myocardial infarction [13].

It is discussed a possible “additive” effect of various risk factors, such as diabetes, hypertension, hyperlipidemia, smoking, etc., that imposed a global approach correlated with the overall risk profile of the patient [14]. This increased cardiovascular risk could be mediated by functional and structural alterations of the vascular wall, such as increased arterial stiffness and carotid intima-media thickness.

In our study we found increased arterial stiffness as measured by aortic PWV in women with diabetes and hypertension. Aortic pulse wave velocity is now considered as the “gold standard” measurement of arterial stiffness. We also found increased SBPao, PPao and augmentation index in patients in comparison with controls but these values lack statistical power.

This is not surprisingly as these parameters, in contrast to PWV, are only indirect, surrogate measures of arterial stiffness. They are influenced by the speed of wave travel, the amplitude of reflective wave, and the duration and pattern of ventricular ejection [15], whereas aortic PWV represents intrinsically arterial stiffness[5].

Increased arterial stiffness in women with diabetes has been reported previously and there are studies that suggest a stronger correlation in women than in men, even if this is not clear from the current literature [16,17].

Our patients had also increased IMT compared with controls. More over, carotid plaques were significantly more frequent in patients group indicated an established atherosclerotic process at this arterial site. In the group of patients we found significant correlation of IMT with age, brachial arterial pressure and also with systolic aortic blood pressure an indirect marker of arterial stiffness. In recent studies SBPao seems to have a superior impact on prognosis and cardiovascular risk than does peripheral blood pressure [18].

Pathophysiologically, the association of increased arterial stiffness and intima-media thickness could be explained by the effects of hypertension and diabetes on vascular structure and function. Hypertension induces alterations in the extracellular matrix [19], diabetes is responsible for nonenzymatic glycation with collagen cross linkage [20] and both diseases are associated with endothelial dysfunction and angiogenesis [21].

### 4. Conclusion

In conclusion, our study showed that women with diabetes and hypertension have increased arterial stiffness and intima-media thickness that could be linked to their great cardiovascular morbidity.

If this association is stronger in women than in men is still a subject of debate. Analysis of these data in men and women separately seems to be more appropriate in elucidating this problem.
References


