Vascular risk factors in women with hypertension and diabetes mellitus type 2

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Abstract
Background. Diabetes mellitus and arterial hypertension are two very frequent diseases. Both of them have important effects on vascular system and their major complications are caused by alterations of vasculature. Arterial hypertension and type 2 diabetes 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 but this is not clean from the current literature. The aim of our study was to determine the consequences of hypertension and of hypertension associated with diabetes on intima media thickness and arterial stiffness in women.
Patients and methods. We studied 30 women with hypertension (group 1), 33 with diabetes mellitus and hypertension (group 2) and 21 healthy controls (HC), matched for age. We evaluated some classical risk factors for atherosclerosis, such as age, body mass index, smoking, lipid and glucose profile in all patients and controls. We determined IMT of the common carotid artery using an ultrasound device (ALOKA prosound □10) and parameters of aortic stiffness – pulse wave velocity (PWV) and augmentation index (Aix) in all patients and controls using an oscillometric device, Arteriograph (Tensio Med Ltd., Budapest, Hungary). We also determined with the same device central aortic systolic blood pressure (SBPao) and aortic pulse pressure (PPao). We compared data obtained between the three different groups examined.
Results. We found that PWV was increased in group 1 patients compared HC ($p<0.05$) but those from group 2 had even higher values of PWV compared to HC ($p=0.001$). IMT was increased in patients from group 1 compared with HC and diabetic patients had a supplementary increase of this parameter compared with hypertensive patients but the values were significantly higher only when compared to controls. From the classical risk factors, BMI and also fasting plasma glucose were significantly higher in diabetic patients. Parameters of arterial stiffness were correlated with age. IMT was correlated with age, fasting plasma glucose, values of brachial systolic, diastolic and mean pressure and with aortic systolic blood pressure. IMT was also correlated with parameters of arterial stiffness, PWV and AIx.
Conclusion. Women with hypertension had increased arterial stiffness compared to controls. Those with hypertension and diabetes had more increased arterial stiffness and also increased IMT compared to hypertensive women and to HC. In our patients age was an important determinant of parameters of arterial stiffness. IMT was correlated with age, values of peripheral and central arterial pressure and with parameters of arterial stiffness. Coexistent 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, arterial stiffness, intima-media thickness, hypertension, diabetes mellitus

1 Introduction

Arterial hypertension and type 2 diabetes mellitus are two important diseases, frequently associated. 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].

The deleterious effect of hypertension and diabetes on arterial wall in 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 [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. Augmentation index (Aix) is a parameter of wave reflection and an indirect marker of arterial stiffness [5].

Recent research showed that central blood pressure and especially its pulsatile component, central pulse pressure, is one of the most important factors determining event-free survival. Results of several prospective studies indicated an independent predictive value of central pulse pressure and also its advantage over brachial pressure [6]. Recent results suggest that some drugs used in antihypertensive treatment, such as those acting on the rennin-angiotensin system, can influence central blood pressure more consistently than peripheral blood pressure [6,7].

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 [8,9].

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

2 Problem formulation

2.1 Patients and methods

We studied 33 women with diabetes and hypertension, 31 with hypertension and 21 healthy women which represented 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. Diabetic patients with microangiopatic complications and renal insufficiency were also excluded.

Diagnosis of diabetes was made according to the American Diabetes Association Criteria [10]. Hypertension was defined as repeated measurements of $\geq$ 140 mmHg for systolic blood pressure (SBP) or $\geq$ 90 mmHg diastolic blood pressure (DBP) or permanent antihypertensive drug treatment. We measured body weight and height and we calculated body mass index (BMI).

Measurement of haemodynamic parameters. For the measurement of arterial stiffness we used a recently developed device, Arteriograph (TensioMed Ltd., Budapest, Hungary). It uses an oscillometric method to determine PWV and AIx. Pulsatile pressure changes in the brachial artery registered in the upper arm are detected by pletismography. Variation in pulsatile pressure in the artery beneath an inflated cuff induces periodic pressure change in the cuff [12]. The Arteriograph measures simultaneously brachial blood pressure (BP), PWV and AIx. 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) [12,13].

The AIx corresponds to the pressure difference between the first and the second wave in relation to pulse pressure (PP). The Arteriograph calculates AIx on the basis of the formula AIx%=[(P2-P1)/PP]x100 (10,11). SBP, DBP, MBP and heart rate were also recorded by the same device.

The measurements were done in the supine position after 10 min of rest in a quit 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].

Carotid measurements of IMT. For the measurement of IMT we used an ultrasound device (ALOKA prosound □10) with a linear transducer operating at a fundamental frequency of 10 Mhz. Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans, with the first line representing the lumen-intimal interface and the second line representing upper layer of the adventitia. Carotid IMT was measured at the far wall of the common carotid artery 1 cm before bifurcation000. 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 [11]. The carotid IMT was measured in a region free of plaque (defined as carotid IMT > 1,5 mm). a complete scan of the carotid arteries was done to identify plaques.

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).

2.2 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

The clinical characteristics of the study groups are summarized in table 1.

Table 1. Clinical characteristics

	HC (n=21)	Group 1 (n=30)	Group 2 (n=33)
Age (years)	62.8 +/-2.0	62.9+/-1.3	62.7+/-1.39
BMI	27.1+/-0.9	29.4+/-0.8	30.8+/-0.88*
FGP (mg/dl)	93.8+/-1.9	96.7+/-1.75	153.8+/-7.36*
TC (mg/dl)	194.9+/-8.5	204.2+/-7.9	223.4+/-9.6
TG (mg/dl)	108.3+/-9.1	120+/-6.7	143+/-13
Cr (mg/dl)	0.85+/-0.04	0.86+/-0.03	0.9+/-0.05

HC, healty controls. Group 1, hypertensive patients. Grop 2, patients with hypertension and diabetes.
Data are mean +/-SEM. BMI, body mass index;
FGP, fasting plasma glucose; TC, total cholesterol;
TG, triglyceride; Cr, creatinine
*P<0.05, versus healthy controls;
P<0.05, versus hypertensive patients

The groups were comparable in age. Laboratory values for lipid metabolism, TC and TG were higher in diabetic patients with statistical significance only when compared with controls. Values of fasting plasma glucose were significantly higher in diabetic patients as compared with non diabetic persons. BMI was significantly higher in patients with diabetes than in controls
The mean period of evolution of diabetes was 7,5 years and of hypertension 8,6 years.

There were no significant differences in vasoactive medications between the groups of patients (Table 2).

Table 2. Vasoactive medications in the groups of patients

Medications	Group 1 (n=30)	Group 2 (n=33)
ACIE	21(70%)	20(60%)
ARB	6 (20%)	8 (24,2%)
CCB	7 (23%)	5 (15%)
βblokers	5 (16,65)	5 (15%)
diuretics	4(13,3%)	6 (18,1%)
statins	9 (30%)	12 (36,3%)

Values of vascular parameters found in patients and controls are shown in tables 3, 4 and 5.

Table 3. Vascular parameters in patients with hypertension and controls.

	HC (n=21)	Group 1 (n=30)
Aortic PWV(m/s)	8.85+/- 0.28	9.88+/- 0.39*
AIx (%)	-3.40+/-3.60	0.25+/-4.14
PPao (mmHg)	57.50+/-1.54	58.3+/-2.32
SBPao (mmHg)	129.75+/2.67	135.7+/-3.68
SBP (mmHg)	126.86+/-2.79	133.17+/-2,79
DBP (mmHg)	75.86+/-1.85	78+/-1.7
MBP (mmHg)	92.76+/-1.91	96.5+/-2.13
HR (b/min)	70.3+/- 1.54	68.2+/-2.3
IMT (mm)	0.76+/-0.03	0.87+/-0.03*
Carotid plaques, n (%)	4 (19%)	9 (30%)

HC, healthy controls. Group 1, patients with hypertension. Group 2, patients with hypertension and diabetes. Continuous numerical 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; HR, heart rate; IMT, intima-media thickness
*p<0.05

Table 4. Vascular parameters in patients with hypertension and diabetes and controls.

	HC (n=21)	Group 2 (n=33)
Aortic PWV(m/s)	8.85+/- 0.28	10.48+/- 0.41*
AIx (%)	-3.40+/-3.60	1.69+/-3.74
PPao (mmHg)	57.50+/-1.54	60.7+/-2.87
SBPao (mmHg)	129.75+/2.67	141.31+/- 2.97
SBP (mmHg)	126.86+/-2.79	138.45+/- 2.52*
DBP (mmHg)	75.86+/-1.85	82.48+/- 1,70*
MBP (mmHg)	92.76+/-1.91	100.42+/- 1.84*
HR (b/min)	70.3+/- 1.54	70.9+/-1.9
IMT (mm)	0.76+/-0.03	0.91+/-0.03*
Carotid plaques, n (%)	4 (19%)	18 (54,5%)*

HC, healthy controls. Group 1, patients with hypertension. Group 2, patients with hypertension and diabetes. Continuous numerical 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; HR, heart rate; IMT, intima-media thickness
*p<0.

Table 5. Vascular parameters in patients with hypertension compared to those with both diseases.

	Group 1 (n=30)	Group 2 (n=33)
Aortic PWV(m/s)	9.88+/- 0.39	10.48+/-0.41*
AIx (%)	0.25+/-4.14	1.69+/-3.74
PPao (mmHg)	58.3+/-2.32	60.7+/-2.87
SBPao (mmHg)	135.7+/-3.68	141.31+/-2.97
SBP (mmHg)	133.17+/-2,79	138.45+/-2.52
DBP (mmHg)	78+/-1.7	82.48+/-1,70
MBP (mmHg)	96.5+/-2.13	100.42+/-1.84
HR (b/min)	68.2+/-2.3	70.9+/-1.9
IMT (mm)	0.87+/-0.03	0.91+/-0.03
Carotid plaques, n (%)	9 (30%)	18 (54,5%)*

HC, healthy controls. Group 1, patients with hypertension. Group 2, patients with hypertension and diabetes. Continuous numerical 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; HR, heart rate; IMT, intima-media thickness
*p<0.05

As shown in table 3, patients with hypertension had increased aortic PWV, PP, SBPao, brachial systolic, mean and diastolic blood pressure than controls. Patients with hypertension and diabetes (Table 4 and 5) have a supplementary increase in these parameters but the values were statistically significant only when compared to controls. Heart rate that can influence parameters of arterial stiffness was comaparable between the groups.Pulse pressure aortic was significantly higher in patients with diabetes and hypertension. This group had also significantly more patients with carotid plaques. We did not have patients with hemodynamically significant carotid stenosis in our study.

In linear regression analyze in the group of patients with hypertension and diabetes we found correlations for SBPao with age (r=0.47, p=0.010), carotid IMT was correlated with age (r=0.35, p=0.04), SBPao (r=0.46, p=0.01).

When taking into consideration the whole study population, IMT was correlated with age (r=0.40, p=0.01), fasting plasma glucose (r=0.28, p=0.01), brachial systolic pressure (r=0.27, p=0.01), brachial diastolic blood pressure (r=0.34, p <0.001), brachial mean arterial pressure (r=0.32, r <0.001), aortic systolic blood pressure (r=0.34, p 0.001). IMT was also correlated with aortic PWV (r=0.27, p=0.01) and AIx (r=0.31, p=0.005)

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 [14]. 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 [15]. 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. Atherosclerosis is a complex process with multiple clinical implications. Classical risk factors such as dylipidemia, smoking, age, male gender, hypertension, and others have been intensively studied. Recent data support the hypothesis of an inflammatory pathogenesis in atherosclerosis. This new theory determined important clinical and therapeutic implications. For example, many drugs used to diminish atherosclerotic process, like statins, angiotensin receptor blockers and others have gene-activating and anti-inflammatory effects [16].

It has been also recognized that around 50% of the patient risk for atherosclerotic coronary artery disease is not explained by the classical risk factors [17]. Recent researches focused on new cardiovascular risk markers, such as carotid IMT [8,18], endothelial dysfunction [18,19,20] or arterial stiffness [5]. Hemodynamic parameters that characterize endothelial dysfunction and arterial stiffness are closely correlated with intima-media thickness. They can be determined non invasively using magnetic resonance imaging methods [20] or ultrasonography [5]. Recent techniques for the evaluation of arterial elastic properties use tonometric and oscillometric principles [5,13].

In our study we found increased arterial stiffness as measured by aortic PWV in women with hypertension compared with controls. Patients with diabetes and hypertension had more increased PWV but the values had not statistical power when compared with hypertensive patients without diabetes. We also found increased SBPao and PPao in patients with hypertension. These two parameters, in contrast to PWV, are 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 [21], whereas aortic

PWV represents intrinsically arterial stiffness [5]. Augmentation index, which is also an indirect marker of arterial stiffness, was increased in patients but the differences do not reach statistical power maybe because this parameter is influenced by many external factors and also by the vasoactive medication indicated for the treatment of hypertension.

Aortic PWV is now considered as the "gold standard "measurement of arterial stiffness [5]. Aortic stiffness has also an independent predictive for all-cause and cardiovascular mortality, coronary events, and fatal strokes in patients with uncomplicated essential hypertension [4,5,22], type 2 diabetes [23], end stage renal disease [24], elderly subjects [25], and the general population [26]. Now aortic stiffness is considered an intermediate endpoint for cardiovascular events [5].

The alteration of central haemodynamic parameters (PWV, AIx, SBPao, PPao) was observed in our study in women with treated hypertension. Similar results were found in untreated hypertensives and also in treated patients with peripheral blood pressure control [27]. The importance of these parameters in assessing cardiovascular risk is the intensely discussed.

The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected at the bifurcations of arteries and mainly of the arterioles. The aortic blood pressure curve is the summation of a forward wave and going from the heart to the peripheral arteries and a reflected wave returning from the arterial tree bifurcations. In large and compliant arteries the reflected waves reaches the proximal aorta mostly during diastole augmenting aortic diastolic blood pressure and supporting coronary perfusion. When arteries are stiff, wave travels faster and the reflected wave returns earlier to the incident wave augmenting aortic systolic pressure. In this situation left ventricular afterload is increased and coronary flow diminished. Taking into consideration these aspects we can consider that central blood pressure is superior to brachial pressure in predicting cardiovascular risk and its action seems to be independent of atherosclerosis and other classical risk factors [6,28]. From a clinical point of view this may have some implications for the treatment of hypertensive patients. Vasodilators such as nitrates, angiotensin inhibitors and calcium entry blockers reduce amplitude of wave reflection and thus systolic blood pressure. In chronic hypertension arterial remodeling modifies elastic wall properties and the characteristics of reflection sites. Drugs that reduce vascular remodeling such as angiotensin blockers and calcium entry blockers diminish central systolic blood pressure but under a treatment with drugs that can not influence arterial structure, such as β-blocking agents, central blood pressure remains elevated [29].

In our study there were no differences between groups in vasoactive medications. Also we found no significant differences for classical risk factors between hypertensive patients and controls. Carotid IMT was increased in the group of patients with hypertension compared to controls.

In patients with diabetes and hypertension we found a supplementary increase in all parameters of arterial stiffness parameters compared to hypertensive patients but the values do not have statistical power. IMT was also increased but the differences were statistically significant only when compared to controls. Carotid plaques were significantly more frequent in patients with diabetes and hypertension indicating an established atherosclerotic process at this arterial site. At the same time all classical risk factors evaluated predominated in the group with diabetes and hypertension.

Many data support the increase of arterial stiffness in type 2 diabetes mellitus. This is an early phenomenon that begins in the impaired glucose metabolism state [30,31]. The pathophysiology of arterial stiffness in diabetes is largely unknown. An important role seems to play an important role because central arterial stiffness and insulin resistence are positively correlated [32]. Chronic hyperglycemia and

hyperinsulinemia increase the local activity of the rennin angiotensin-aldosterone system and expression of angiotensin type I receptor in vascular tissue, promoting development of wall hypertrophy and fibrosis [33]. Another mechanism particularly involved in diabetes is the formation of advanced glycation end-products on the arterial wall, causing cross-linking of collagen molecules, which may lead to loss of collagen elasticity and a subsequent increase in arterial stiffness [34]. Alterations of the extracellular matrix of the media and adventitia are implicated in the pathogenesis of age and blood pressure-related increase in arterial stiffness [35].

Our patients with hypertension and diabetes had increased BMI and important alterations of parameters of arterial stiffness. The differences were statistically significant if compared with healthy controls. When compared to hypertensive patients there was only a trend of increase without statistical power. A previous study by Tedesco et al, showed significant alterations in markers of arterial stiffness in patients with diabetes and hypertension compared to those with diabetes and high blood pressure alone, suggesting a synergistic effect of these diseases on vascular wall [36].

Increased arterial stiffness in women with diabetes has been reported previously and there are studies that suggest a stronger correlation in women than in man, even if this is not clear from the current literature [3,37]. Our study showed that women with diabetes and hypertension had increased markers of arterial stiffness compared to healthy women. There was also a trend of increase when compared to hypertensive patients.

Our patients had also increased IMT compared with controls. 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 [35], diabetes is responsible for nonenzymatic glycation with collagen cross linkage [34], and both diseases are associated with endothelial dysfunction and angiogenesis (38). The increased arterial stiffness and IMT in hypertensive-diabetics reflect both structural and functional abnormalities of the arterial wall [15].

In the whole study population we found that markers of arterial stiffness were correlated with age. IMT was correlated with age, fasting plasma glucose and values of brachial arterial pressure and central systolic arterial pressure. It was also correlated with parameters of arterial stiffness aortic PWV, AIx and SBPao.

Our results are concordant with other studies. It has been shown that age is an important determinant of IMT and arterial compliance. With advancing age the artery wall becomes thickened and less distensible [39].

The correlation of parameters of arterial stiffness with IMT was also described in general population. It was explained by the fact that it might be expected that changes in arterial wall compliance occur early in response to cardiovascular risk factors and over the long term this contribute to changes in arterial wall thickness [40].

4. Conclusion

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

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