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PAI-1 and hyperuricaemia: another face of endothelium dysfunction in essential hypertension. Endothelium, hypertension, metabolism

PAI-1 a hiperurykemia: kolejne oblicze dysfunkcji śródbłonka w nadciśnieniu tętniczym. Śródbłonek, nadciśnienie, metabolizm

Streszczenie

Wstęp Uważa się, że dysfunkcja śródbłonka odgrywa kluczową rolę w rozwoju miażdżycy i powstawaniu powikłań układu sercowo-naczyniowego w nadciśnieniu tętniczym.
Materiał i metody Celem oceny dysfunkcji śródbłonka u nieleczonych chorych z pierwotnym nadciśnieniem tętniczym, bez cukrzycy, z prawidłowym klirensem kreatyniny zbadaliśmy 29 ambulatoryjnych pacjentów (13K/16M; wiek: 41,17 ± 11,95) w porównaniu z grupą 14 zdrowych ochotników (7K/7M), zgodnych wiekowo. W obu grupach we krwi żylnej na czczo oznaczono: HbA1c, całkowitą homocysteinę, kwas moczowy, insulinę, glukozę, vWF:Ag, TM, PAI-1, E-selektyny. Obliczono HOMA-IR. W 24-godzinnej zbiórce moczu oznaczono mikroalbuminurię (MA) i N-acetylo-β-D-glukozaminidazę (NAG).
Wyniki Chorzy z nadciśnieniem prezentowali wyższe wartości BMI, WHR, MAP, PP, cechowali się insulinoopornością i wyższym stężeniem kwasu moczowego. Grupy nie różniły się pod względem MA i vWF:Ag. Chorzy mieli wyższe wartości PAI-1 i NAG niż kontrola. Jedynie u chorych stwierdzono dodatnie korelacje liniowe: PP *vs.* MA_{log10}, PAI-1 *vs.* MA_{log10}, PAI-1 *vs.* kwas moczowy, PAI-1 *vs.* BMI, PAI-1 *vs.* WHR, WHR *vs.* kwas moczowy, BMI *vs.* HOMA-IR.
Wnioski Nasze dane mogą wskazywać, że we wczesnych etapach nadciśnienia tętniczego, chorzy z insulinoopornością cechują się zwiększonym ryzykiem sercowo-naczyniowym związanym z uogólnioną miażdżycą, stanem prozakrzepowym i zwiększoną sztywnością tętnic. Kwas moczowy prawdopodobnie wpływa na śródbłonek poprzez mediowany przez PAI-1 mechanizm, który nie jest jasny. Odbiciem tego faktu jest podwyższona wartość PP wynikająca ze zmniejszenia podatności tętnic. Zwiększone wydalanie NAG z moczem u chorych w obliczu normoalbuminurii może wskazywać na uszkodzenie śródmiąższu nerek, które wyprzedza uszkodzenie kłębuszka i jest istotne dla dalszego rokowania.
słowa kluczowe: śródbłonek, nadciśnienie, kwas moczowy, nerka, metabolizm
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Introduction

There is a potential relationship between endothelial dysfunction (ED) and non-diabetic renal disease in essential arterial hypertension. ED is now re-

cognised as a key factor in the onset and progression of atherosclerosis, which results in fatal cardiovascular events such as stroke and myocardial infarction. The balance of substances derived from the endothelium determines vascular tone and permeability and affects coagulation, inflammation, proliferation, adhesion and platelet and leucocyte function. Numerous traditional and non-traditional risk factors are involved in this process, although arterial hypertension with elements of insulin resistance syndrome is crucial [1]. Growing attention is also being paid to microcirculation and capillary rarefaction, which may become a new target for treatment.

Micro-albuminuria (MA) is not only recognised as a risk factor of renal damage but is also treated as a marker of generalised endothelial malfunction [2, 3]. MA is an independent predictor of cardiovascular disease and death, according to JNC VII, and often coexists with composed metabolic disturbances such as insulin resistance [4], although MA is not a determinant of insulin resistance [5].

MA is also common in the non-diabetic, non-hypertensive healthy population and is an independent indicator of cardiovascular risk and cardiovascular morbidity in this group [6, 7]. It seems that there is a continuous relationship between urine albumin excretion and all-cause and cardiovascular mortality in the general population (EPIC-Norfolk Study). Homocysteine lowering therapy with folic acid decreases MA. ED may precede and predict MA [8].

The role of uric acid in vascular damage is still a matter of discussion [9]. However, a pharmacological decrease in uric acid level does not result in increased life expectancy [10].

On the other hand, the elevated pulsative component of blood pressure, pulse pressure (PP) value, defined as the difference between systolic and diastolic blood pressure, is closely related to a high risk of cardiovascular death or it is caused by a decrease of compliance in the large arteries and an elevation of blood wave reflection from the peripheral arteries, increasing arterial stiffness [11, 12].

Materials and methods

The aim of our study was to evaluate generalised endothelial dysfunction in non-diabetic untreated essential hypertensives with a normal creatinine clearance range. We therefore examined 29 ambulatory patients (13F/16M; age: 41.17 ± 11.95) and compared them with 14 healthy controls (7F/7M), matched for age.

We measured BMI and WHR using routine procedures. We obtained SBP, DBP, PP and MAP using a standardised mercury sphygmomanometer and the Korotkoff method with the patient in sitting position after 5 minutes' rest. Fasting venous blood was withdrawn for: HbA1c, total homocysteine, uric acid, insulin and glucose, vWF:Ag, TM, PAI-1 and E-selectins in both groups. The insulin resistance index (HOMA-IR) was calculated using Matthews' formula. The 24-h urine was collected for albumin and N-acetyl-β-D-glucosaminidase (NAG) urine excretion in both groups.

The results are expressed as a mean ± standard deviation when normal distribution is found. Data without normal distribution are presented as median and range. The Statistica 5 program was used to perform the statistical analysis. We considered $p < 0.05$ statistically significant and the SN abbreviation was used to represent no significance. The significance of differences between means of measurements for the two groups was determined by Student's test or the Cochran-Cox test after an analysis of variances by the Fisher test. The Mann-Whitney U non-parametric test was also used for unpaired data without normal distribution. Pearson's correlation co-efficients were performed to assess linear relationship.

The study protocol was approved by the Ethics Committee at The Ludwik Rydygier Medical University in Bydgoszcz, Poland. Written informed consent was obtained from all study participants.

Results

The results are presented in table I.

Discussion

Our study has some limitations and may be underpowered as a result of the low number of patients. Our patients had higher BMI and WHR values than the controls and they revealed some metabolic disturbances such as insulin resistance (elevated HOMA-IR) and hyperuricaemia in comparison with the healthy volunteers. There was a linear correlation between BMI and HOMA-IR ($r = 0.64$; $p < 0.01$) in hypertensives only. The groups did not differ as regards vWF:Ag level and the albuminuria was the same in both hypertensives and controls.

This suggests no endothelial dysfunction in the hypertensives. In view of the similarity in the amount of albumin excretion in the hypertensives and the normotensive controls, the mechanisms underlying this process must be different. This assumption is based on the following correlations, which were found in the hypertensives only:

Table I. Baseline characteristics of hypertensives and healthy controls
Tabela I. Wstępna charakterystyka pacjentów

Parameter	Hypertensives	Controls	p
BMI	28.83 ± 4.45	23.07± 2.43	< 0.01
WHR	0.91 ± 0.09	0.83 ± 0.10	< 0.01
SBP [mm Hg]	164 ± 16	105 ± 7	< 0.01
DBP [mm Hg]	115 ± 14	69 ± 9	< 0.01
PP [mm Hg]	59 ± 12	46 ± 7	< 0.001
MAP [mm Hg]	125 ± 9	84 ± 10	< 0.001
HbA1c (%)	5.94 ± 0.55	5.61 ± 0.76	NS
Uric acid [mmol/L]	370,7 ± 105	263,6 ± 70.8	< 0.01
Total homocysteine [mmol/L]	9.71 ± 2.68	8.39 ± 2.55	NS
HOMA-IR	3.27 ± 1.71	1.59 ± 0.53	< 0.001
PAI-1 [ng/mL]	39.02 ± 22.12	25.26 ± 16.84	< 0.05
vWF:Ag (%)	227.98 ± 133.97	244.10 ± 121.32	NS
TM [U/mL]	3.60 ± 1.05	3.59 ± 0.93	NS
E-selectin [ng/mL]	62.68 ± 39.71	39.66 ± 11.48	< 0.01
Creatinine clearance [mL/min/1,73m^2]	99.04 ± 30.29	110.36 ± 39.84	NS
NAG [U/L/g creat]	1.95 (0.94–10.60) 2.83 ± 2.11	1.28 (0,25–5.89) 1.82 ± 1.46	< 0.05
Albuminuria [mg/24 h]	13.20 (4.50–75.20) 16.69 ± 13.06	10.53 (6.00–57.63) 16.18 ± 15.13	NS

PP *vs.* MA_{log10} ($r = 0.48$; $p < 0.05$), PAI-1 *vs.* MA_{log10} ($r = 0.39$; $p < 0.05$), PAI-1 *vs.* uric acid ($r = 0.56$; $p < 0.01$), PAI-1 *vs.* BMI ($r = 0.57$; $p < 0.01$), PAI-1 *vs.* WHR ($r = 0.41$; $p < 0.01$), WHR *vs.* uric acid ($r = 0.46$; $p < 0.05$).

These correlations suggest that it is the quantity rather than quality of metabolic disturbances in hypertensives which drive unfavourable events in the endothelium. This study suggests that a role is played by PAI-1 in the association between metabolic processes and the function of the cardiovascular system in hypertensives. Nowadays PAI-1 is known as a direct and indirect profibrotic intravascular factor interacting through the inhibition of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). The activation of the renin-angiotensin-aldosteron system (both angiotensin II and aldosterone) directly induces undesirable expression of PAI-1 [13, 14]. Consequently PAI-1 may indirectly enhance arterial stiffness causing higher pulse pressure.

Nevertheless, hypertensives had higher PAI-1 levels than the controls, suggesting the undesirable effect of the prothrombotic state of the fibrinolytic system, which may reduce the efficiency of vascular and tissue remodelling.

The association between hyperuricaemia and vascular damage is a well-known fact but the question of what is meant by its primary and secondary effects remains unresolved.

It is proposed that uric acid is elevated in hypertensives owing to increased renal proximal tubular reabsorption (as a result of hyperinsulinaemia), decreased renal blood flow and local renal ischemia arising from increased sympathetic activity. However, it is possible that uric acid is also a pathogenic factor with broad biological actions (pro-inflammatory and with pro-oxidative and anti-oxidative properties depending on conditions) with regard to endothelial damage in hypertension and cardiovascular disease [9]. There is a reciprocal pattern of uric acid and nitric oxide levels during the day, which may be a reflection of ED [15].

Hyperuricaemia may lead to intrarenal vascular injury and may be a mediator of renal disease in rats [16]. Experimental hyperuricaemia in rats causes hypertension and stimulates vascular smooth muscle cell proliferation [17]. These observations provide new in sights into hyperuricaemia in humans. Our study was not planned to determine the effect of a lowering of uric acid on PAI-1 levels.

Both positive correlations between PAI-1 and uric acid, PAI-1 and MA_{log10} may suggest that in the early stage of untreated essential hypertension uric acid is able to affect the endothelium through a PAI-1 mediated mechanism. A reflection of this is the increased PP which results from higher arterial stiffness. No significant statistical correlation was found between PP and the other factors measured either in the hypertensives or in the controls.

Our data may suggest that in the very early stages of essential arterial hypertension the hypertensives with probable insulin resistance are at high risk of serious cardiovascular complications related to diffuse atherosclerosis, a prothrombotic state and elevated arterial stiffness. Hypertensives had higher NAG urine excretion than the controls while showing no endothelial dysfunction (estimated with MA) and normal creatinine clearance. This may indicate the early renal tubulo-interstitium tissue damage resulting from probable intrarenal vessel damage due to hyperuricaemia in the face of elevated PAI-1 which precedes glomerular injury and is important for the future clinical prognosis. No linear correlation was found between NAG urine excretion and homocysteine, MA, PP, HOMA, PAI-1, BMI, WHR, insulin. Nor was there any correlation between NAG excretion and MAP, which we found in a similar group of untreated hypertensives [18]. Our results, although obtained from a relatively small group of patients, are consistent with the data of Tsioufis and Viazzi [11], who proposed that PP may be a marker of preclinical vascular injury in young hypertensive patients.

Summary

Background Attention is increasingly being paid to endothelial dysfunction (ED) as a key aspect of atherosclerosis and target organ damage in arterial hypertension.

Material and methods In order to evaluate generalised ED in non-diabetic untreated essential hypertensives with normal creatinine clearance we examined 29 ambulatory patients (13F/16M; age: 41.17 ± 11.95) and compared them with 14 healthy controls (7F/7M) matched for age. Fasting blood was withdrawn for the following: HbA_{1c}, total homocysteine, uric acid, insulin, glucose, vWF:Ag, TM, PAI-1 and E-selectins in both groups. HOMA-IR was calculated. 24-h urine was collected for microalbuminuria (MA) and N-acetyl-ß-D-glucosaminidase (NAG) urine excretion.

Results The hypertensives had higher BMI, WHR, MAP and PP and were insulin resistant. They revealed hyperuricaemia. No difference was found in MA and vWF:Ag. The hypertensives also had higher PAI-1 levels and NAG excretion than the controls. The only positive linear correlations found in the hypertensives were the following: PP *vs.* MA_{log10}, PAI-1 *vs.* MA_{log10}, PAI-1 *vs.* uric acid, PAI-1 *vs.* BMI, PAI-1 *vs.* WHR, WHR *vs.* uric acid, BMI *vs.* HOMA-IR.

Conclusion Our data may suggest that in the early stages of essential hypertension patients with insulin resistance are at high risk of serious cardiovascular complications related to diffuse atherosclerosis, a prothrombotic state and elevated arterial stiffness. Uric acid is able to affect endothelium through a PAI-1 mediated mechanism, which remains unclear. This fact is reflected in the increased PP which results from increased arterial stiffness. Higher NAG urine excretion where there is no endothelial dysfunction may indicate the early renal tubulo-interstitium tissue damage which precedes glomerular injury and is important for future clinical prognosis.

key words: endothelium, hypertension, uric acid, kidney, metabolism

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