

LINKING ENDOTHELIAL DYSFUNCTION WITH FAMILY AGGREGATION BY PATIENTS WITH METABOLIC SYNDROME

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SUMMARY: Background and aims: The metabolic syndrome (MS) is a recently defined constellation of risk factors that has been associated with an increased risk of cardiovascular disease and diabetes as well. Endothelial dysfunction is one of the key earliest manifestations of the many changes induced in the natural history of the chronic inflammation in arterial wall by the impact of metabolic abnormalities that contributes to the development and progression of atherosclerosis¹. The aim of the study was to assess the influence of the heredity (one of the parents with MS) on endothelial dysfunction by patients with MS. **Methods and results:** The study included 116 patients with metabolic syndrome. The metabolic syndrome was defined according to the IDF criteria. We measured the flow-mediated dilatation (FMD) of the brachial artery (endothelium dependent vasodilatation) on B-mode ultrasound images, with the use of a 10 MHz linear-array transducer in terms of fasting for 8 hours. Endothelial dysfunction was diagnosed if flow-mediated dilatation was less than 10%. The mean value of FMD% by patients with MS without heredity was $5, 90\% \pm 5, 61$ and of FMD% by patients with metabolic syndrome and known heredity (mother or father with MS) was $1, 61\% \pm 6, 68$. **Conclusion:** Endothelial dysfunction is more severe by metabolic patients with known metabolic syndrome in the family. Diagnosing early the population at high risk could improve the effort to optimize therapeutic strategies to reduce cardiovascular morbidity and mortality.

Key Words: metabolic syndrome, flow mediated vasodilatation, heredity.

DISFUNȚIA ENDOTELIALĂ CU AGREGARE FAMILIARĂ LA PACENȚI CU SINDROM METABOLIC

Rezumat: Premise și obiective: Sindromul metabolic (SM) este definit ca o constelație de factori de risc de origine metabolică asociat cu un risc crescut de afecțiuni cardio-vasculare și diabet. Disfuncția endotelială este una din manifestările timpurii din istoria inflamației cronice ce contribuie datorită anomaliilor metabolice la dezvoltarea și progresia aterosclerozei la nivelul peretului arterial. Boala cardio-vasculară reprezintă una din principalele cauze de morbiditate și mortalitate a țărilor dezvoltate având la bază procesul de ateroscleroză. Obiectivele noastre prin acest studiu au fost de a evalua influența eredității metabolice (unul dintre părinți cu SM) asupra disfuncției endoteliale la pacienți cu SM.

Metode și rezultate: Studiul a cuprins 116 de pacienți cu sindrom metabolic, 75 bărbați (64,65%) și 41 femei (35,34%) cu vârsta medie de $50,70 \pm 8,39$. Criteriile de includere au ținut cont de definiția sindromului metabolic elaborată de IDF în 2005. Am măsurat dilatarea mediata de flux (FMD) la nivelul arterei brahiale pe imagini obținute în B-mode, cu utilizarea unui transducer liniar de 10 MHz în condiții a jeun de 8 ore. Disfuncția endotelială a fost considerată la valori mai mici de 10% a FMD%. Valoarea medie a FMD% la pacienți cu SM fără ereditate a fost de $5, 90\% \pm 5, 61$ și a FMD% la pacienți cu sindrom metabolic ereditate metabolică cunoscută (mama sau tatal cu SM) a fost de $1, 61\% \pm 6, 68$ cu un $P(\text{one tail}) = 0,0087$ foarte semnificativ. Dintre criteriile de includere a SM s-a observat că valoarea circumferinței abdominale și cea a glicemiei plasmatice sunt în medie mai ridicate la pacienții cu SM și ereditate metabolică. **Concluzii:** Disfuncția endotelială determinată prin FMD% este prezentă la pacienții cu SM. Pacienții cu ereditate metabolică și SM au prezentat o disfuncție endotelială mai accentuată decât cei cu SM dar fără ereditate metabolică. Diagnosticarea precoce a populației cu risc ar putea îmbunătăți efortul de a optimiza strategiile terapeutice de reducere a morbidității și mortalității cardiovasculare, având ținta disfuncția endotelială.

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INTRODUCTION

The MS is a recently defined constellation of risk factors that has been associated with an increased risk of cardiovascular disease and diabetes as well. MS causes moderate increase in all-cause and CVD mortality [1, 2]. In the general population, metabolic syndrome is associated with a marked increase in the risk not only of new onset diabetes mellitus but also of new onset office and daily-life hypertension, and left ventricular hypertrophy[3].

Although MS is related to CHD, there is no epidemiological justification for using it, rather than other criteria, as a risk predictor for CHD4. The MS seems to have 3 potential etiological categories: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (e.g., molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well. The patterns of MS components and the longitudinal changes that lead to the MS are different in men and women. Interestingly, components with the highest prevalence prior to MS development, such as elevated blood pressure, are not necessarily the stronger risk factors [5] but several analyses from the ARIC study have shown that the metabolic syndrome, as well as individual metabolic syndrome components, is predictive of the prevalence and incidence of coronary heart disease, ischemic stroke, carotid artery disease and diabetes [6].

Endothelial dysfunction is characterized by reduced vasodilation and a proinflammatory state. It is associated with most forms of cardiovascular disease. Mechanisms that participate in the reduced vasodilatory responses in endothelial dysfunction include reduced nitric oxide generation, oxidative excess, and reduced production of hyperpolarizing factor [7]. Endothelial dysfunction is a systemic disorder. Endothelial dysfunction reflects a vascular phenotype prone to atherogenesis and may therefore serve as a marker of the inherent atherosclerotic risk in an individual. It is known that arterial stiffness is increased in patients with metabolic syndrome irrespective of the definition criteria [8]. Impaired endothelial function may be a common denominator of pathogenesis of microvascular complications and atherosclerosis in T2DM [9].

The aim of the study was to assess the influence of the heredity (one of the parents with MS) on endothelial dysfunction by patients with metabolic syndrome.

Identification of people without any MS risk components is clinically valuable, as these people seem to have a substantially reduced risk of developing CHD [10].

METHODS

The study enrolled 116 patients with MS, 75 men (64.65%) and 41 women (35,34%) with a mean age of 50.70 ± 8.39 . The MS was defined according to the IDF criteria 2005: Central obesity (defined as waist circumference >94 cm by male and >80 cm female) plus any two of the following four factors: raised TG level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality; raised blood pressure: systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension; raised fasting plasma glucose (FPG) > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes (If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome).

The exclusion criteria's were: smokers, chronicle arteriopathy of lower limbs, cerebrovascular disease (stroke), coronary disease, diabetes treated by insulin, kidney and liver failure, psychiatric disorders, malignancies, consumption of alcohol per day over 30gr.

We subdivided the study group in two groups: patients with MS without heredity and patients with MS with known heredity (mother or father known with metabolic syndrome).

The method of assessing the endothelial dysfunction was flow mediated vasodilation. We measured the flow-mediated dilatation (FMD) of the brachial artery (endothelium dependent vasodilatation) on B-mode ultrasound images, with the use of a 10 MHz linear-array transducer in terms of fasting for 8 hours.

The vascular diameter in systolic and diastolic longitudinal plane was measured guided by the principle of "leading-edge", followed by determination of basal medium velocity by pulse Doppler (average of at least 3 determinations). To obtain stimulate blood flow in the brachial artery is placed the sphygmomanometer antecubital at the forearm. After recording the basal velocity average, the sphygmomanometer cuff was swollen above the systolic blood pressure (usually over 50 mmHg) for 5 minutes, to achieve brachial artery ischemia.

Dilation of the resistance vessels downstream through the mechanism of self sudden deflation of the cuff increased the blood flow in brachial artery (active hyperemia) and the shearing stress at this level with consecutive dilation of the brachial artery. The maximum velocity was measured by pulse Doppler in first 15 seconds of cuff deflation and maximum diameter of the brachial artery was determined at 45-60 seconds post hyperemia. The brachial artery diameter was measured in the same cardiac cycle to avoid variations caused by arterial compliance [11, 12, 13]. Endothelial dysfunction

was diagnosed if flow-mediated dilatation was less than 10%.

RESULTS

MS with known heredity (mother or father with known MS) was present by 14 (12.06%) patients. 102 patients were with MS without heredity (none of their parents with MS).

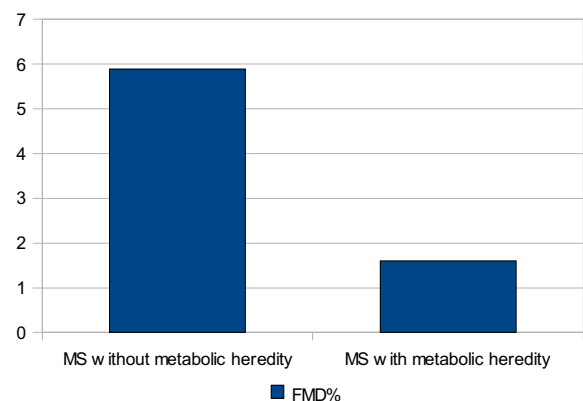
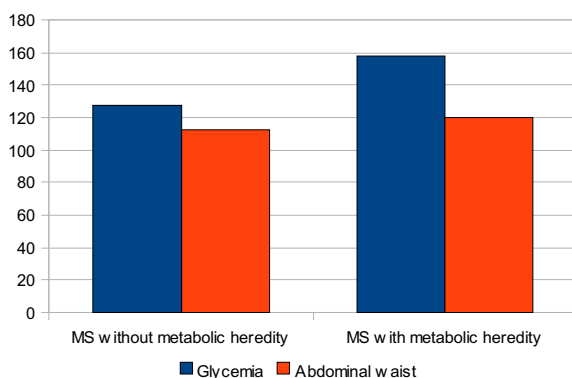
After adjustment for covariates the mean value of FMD% by patients with MS without heredity was 5, 90% ± 5, 61 and of FMD% by patients with MS and known

Table 1. Characteristics of the study group:

Parameters	MS with metabolic heredity		Ms without metabolic heredity	
	Men	Women	Men	Women
Number	8	6	67	35
Age	49.25 ± 10.55	49.05 ± 9.85	49.36 ± 8.87	52.46 ± 6.57
Height	177.25 ± 6.25	164.83 ± 5.71	174.13 ± 7.44	163.94 ± 7.68
Weight	112.5 ± 20.96	94 ± 17.17	95.75 ± 18.12	91.46 ± 18.39
BMI	35.65 ± 5.32	34.47 ± 5.28	31.48 ± 5.09	33.97 ± 6.05

Table 2. t-Test: Two-Sample Assuming Unequal Variances for MS with and without metabolic heredity

Parameters	MS without metabolic heredity	MS with metabolic heredity	P(T<=t) one-tail
FMD%	5.90 ± 5.61	1.61 ± 6.68	0.0087
HDL	40.15 ± 11.13	39.57 ± 9.67	0.4200
Glycemia	127.82 ± 44.20	158.21 ± 62.29	0.0489
Triglycerides	187.42 ± 117.07	233.14 ± 104.69	0.0742
Abdominal waist	112.57 ± 12.15	120.25 ± 14.49	0.0426



heredity was 1, 61% ± 6, 68 with P (T<=t) one-tail = 0.0087. (p<0.05 significant)

The mean values of plasma glucose were higher by patients with MS and known heredity 158,21 mg % ± 62, 29 than by patients with MS without metabolic heredity 127,82 mg% ± 44,20 with a P(T<=t) one-tail = 0,0489.

The abdominal waist as well seems to be influenced by the metabolic heredity: patients with MS and known metabolic heredity had a mean waist of 120, 25 cm ± 14, 49 and patients with MS without metabolic heredity of 112,57cm ± 12, 15 with a P(T<=t) one-tail = 0,0426.

CONCLUSIONS

Endothelial dysfunction is present in patients with MS. Known metabolic heredity influenced the endothelial dysfunction in patients with MS. Severe impaired endothelial function was noticed by patients with MS and metabolic heredity.

Diagnosing early the population at high risk could improve the effort to optimize therapeutic strategies to reduce cardiovascular morbidity and mortality.

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