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Plasma sICAM levels during standard exercise test are higher in postmenopausal women with mixed hyperlipemia. sICAM level in postmenopausal women

Stężenie osoczowe sICAM podczas standardowego testu wysiłkowego jest wyższe u kobiet po menopauzie z hiperlipidemią mieszaną. Poziomy sICAM u kobiet po menopauzie

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Dodatkowe słowa kluczowe:
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Aim: Plasma sICAM, sVCAM, endothelin-1 (ET-1), TNF-a, its soluble receptor levels and nitric oxide production evaluation during standard exercise test in postmenopausal women with mixed hyperlipidemia.

Material and methods: 35 white, normotensive, non-smoking, postmenopusal women. Group A consisted of 24 women normal plasma cholesterol and triglicerides. Group B- 11 women hypercholesterolemic and hypertriglyceridemic.

Basic fasting plasma FSH, 17b--estradiol, total cholesterol, LDL-cholesterol, triglicerides, HDL-cholesterol were measured. Standard exercise test was carried out according to Bruce protocol. During the test blood samples were taken trice (prior to, at peak exercise, at15th minute of recovery). The sICAM, sVCAM, ET-1, TNF-a, its soluble receptor and secretion of nitric oxide were measured. Statistical analysis: Fisher test and t-Welch test were used.

Results: There were no differences between groups A and B in mean plasma concentrations of FSH, estradiol and HDL-cholesterol. Mean plasma total cholesterol, triglicerides and LDL-cholesterol levels were higher in group B compared to group A. Plasma levels of sICAM prior to standard exercise test, at peak exercise and at the 15th minute of recovery were significantly lower in group A compared to group B. Mean plasma sVCAM levels did no differ between groups. NO3 plasma levels was significantly higher at peak exercise in group B compared to group A. There were no significant differences between groups in regard to mean plasma NO2, endothelin-1, TNF-a, and TNF-a receptor levels.

Conclusion: Plasma soluble intracellular adhesion molecules levels are higher at rest and during exercise in postmenopausal women with atherosclerosis risk factors.

Cel: Ocena Stężenia sICAM, sVCAM, endoteliny 1 (ET-1), TNF alfa, receptora TNF alfa oraz stężenia tlenku azotu u kobiet po menopauzie z hiperlipidemią mieszaną w standardowym teście wysiłkowym.

Materiały i metody: 35 kobiet rasy białej po menopauzie, z prawidłowymi wartościami ciśnienia tętniczego, nie palące. Grupa A- 24 kobiety z prawidłowymi wartościami cholesterolu oraz triglicerydów. Grupa B- 11 kobiet z hipercholesterolemią i hipertriglicerydemią we krwi.

U wszystkich kobiet oznaczono FSH, 17b-estradiol, cholesterol całkowity, LDL-cholesterol, HDL-cholesteroloraz-triglicerydy w osoczu na czczo. Standardowy test wysiłkowy przeprowadzono według protokołu Bruce'a. Podczas badania trzykrotnie pobrano krew (przed, na szczycie wysiłku oraz 15 minut po zakończeniu). Każdorazowo oznaczono sICAM, sVCAM, ET-1, TNF-a, stężenie rozpuszczalnego receptora TNF-alfa oraz wydzielanie tlenku azotu.

Wyniki: Nie stwierdzono różnic między grupami A i B w średnim stężeniu FSH, estradiolu i cholesterolu HDL. Średnie stężenie triglicerydów, cholesterolu całkowitego i cholesterolu LDL były wyższe w grupie B w porównaniu z grupą A. Poziomy sICAM przed rozpoczęciem testu,na szczycie wysiłku oraz 15 minut po zakończeniu były istotnie niższe w grupie A w porównaniu z grupą B. Średnie stężenia sVCAM w osoczu nie różniły się między grupami. Poziomy NO3 były znacznie wyższe na szczycie wysiłku w grupie B w porównaniu do grupy A. Nie było znaczących różnic pomiędzy grupami w odniesieniu do poziomu NO2, endoteliny-1, stężenia TNF-a i receptora TNF-a.

Wnioski: Osoczowe stężenia rozpuszczalnych wewnątrzkomórko-wych cząsteczek adhezyjnych są wyższe w spoczynku i podczas wysiłku fizycznego u kobiet po menopauzie z czynnikami ryzyka miażdżycy.

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Introduction

The cessation of ovarian function doubles the risk of the coronary heart disease in women [1]. Cardiorespiratory fitness and regular physical activity are associated with a reduction in cardiovascular disease risk factors and mortality [2-5]. One of the mechanisms through which physical fitness might promote cardiovascular health is supporting anti-inflammatory processes [6,7]. Vascular inflammation is related to the pathogenesis of atherosclerosis [8,9]. An important step in the inflammatory process of relevance to cardiovascular disease is the cell adhesion molecule-mediated adhesion of leukocytes to the vascular endothelium [10]. Earlier phases of vascular inflammation are enhanced by an increased production of chemokines, particularly adhesion molecules: intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1) by dysfunctional endothelium [11]. There are current data that soluble adhesion molecules (particularly VCAM-1 and ICAM-1) are over-expressed as a result of endothelial dysfunction and thereafter released as measurable forms into the circulation [11,12]. Several studies demonstrated that circulating levels of endothelial adhesion molecules (particularly ICAM), C-reactive protein and tumour necrosis factor-α receptors are reliable markers of endothelial dysfunction and inflammation and can be used to predict the risk of future cardiovascular events [13-22]. Schoppen et al showed that sICAM plasma levels are higher in postmenopausal women compared to premenopausal ones [23]. Soluble ICAM plasma levels are influenced by age, menopause and also by other factors like diet and physical exercise [23-25]. The strenuous acute exercise can induce the release of several inflammation-related cytokines and the expression of endothelial adhesion molecules [26,27]. However only limited information is available about the effects of moderate-intensity aerobic exercise on the expression of plasma biomarkers of endothelial dysfunction and inflammation [26,28-32].

Few studies showed the effects of physical activity on cardiovascular biomarkers, and these studies have been mostly limited to men [33-36] or small numbers of women [37-39]. Geffken et al. found in an elderly cohort an indirect association between physical activity and inflammatory markers [40]. Moderate-intensity exercise training can augment endothelial, nitric oxide (NO)-dependent vasodilation in both large and small vessels [28,41-44]. These exercise-induced effects on the vascular endothelial function seem to be mediated by an up-regulation of e-NOS protein expression and phosphorylation [41-42]. Our earlier study showed the higher plasma levels of adhesion molecules and inflammatory mediators in hypercholesterolemic postmenopausal women [45]. Therefore we wanted to evaluate the effect of simultaneous high level of total cholesterol and triglycerides on adhesion molecules plasma levels in postmenopausal women during physical exercise.

Aim: The evaluation of plasma sICAM, sVCAM, endothelin-1 (ET-1), TNF-a, its soluble receptor levels and nitric oxide production during standard exercise test in postmenopausal women with mixed hyperlipidemia.

Material and methods

Patients: 34 white, normotensive, non-smoking, postmenopusal women who neither received hormonal therapy nor cholesterol lowering treatment. Neither of women was diabetic nor suffered from ischemic heart disease. They had no contraindications to standard exercise test. Group A consisted of 24 women with normal plasma cholesterol and triglicerides. Group B comprises 11 women with increased total cholesterol and triglicerides.

Intervention: Basic fasting plasma FSH, 17 β-estradiol as well as total cholesterol, LDL-cholesterol, triglicerides were measured and HDL-cholesterol was calculated. Standard exercise test was carried out between 8-10 a.m. according to Bruce protocol. During the test blood samples were taken from antecubital vein, with minimal stasis, trice (prior to, at peak exercise, at15th minute of recovery). The sICAM, sVCAM, ET-1, TNF-a, its soluble receptor and secretion of nitric oxide were measured in each sample.

FSH plasma level measurement was carried out by electrochemiluminescence immunoassay Roche kits. Estradiol plasma levels were assessed by Abbot Meia ELISA kits. Total cholesterol, LDL-cholesterol, HDL-cholesterol plasma levels were measured by CHOD-PAP Boehringer Mannheim kits whereas triglicerides levels were measured by means of GPO-PAP Boehringer Mannheim kits. (Nitric oxide NO2/NO3) Assay R&D Systems Ins USA. Soluble ICAM, soluble VCAM plasma levels as well as TNF-a and TNF-a receptor plasma levels were measured by means of R&D Systems INC USA kits. Endothelin-1 (ET-1), plasma levels were assessed by ELISA ENDOTHELIN (1-21) kits manufactured by Biomedica GmbH Austria.

Data are expressed as mean plus or minus SD. Fisher test and t-Welch test were used to compare results in the groups and U Manna-Whitneya test was applied to compare the results between groups. P<0.05 was considered as significant.

Results:There were no differences between groups in mean plasma concentrations of FSH and estradiol and HDL-cholesterol between groups A and B (Tab. I). Mean plasma total cholesterol, triglicerides and LDL-cholesterol levels were higher in group B compared to group A (Tab. I).

Mean plasma sVCAM levels did no differ between groups. NO_3 plasma levels was significantly higher at peak exercise in group B compared to group A (Tab. III). There were no significant differences between groups in regard to mean plasma NO2, endothelin-1, TNF-a, and TNF-a receptor levels (Tab. III, IV).

Discussion

Our present results show the increased plasma level of soluble intracellular adhesive molecule both during rest and short physical exercise in postmenopausal women with simultaneous hypercholesterolemia and hypertriglyceridemia (mixed hyperlipidemia).

Table I

Selected laboratory parameters according to group.

Wybrane parametry laboratoryjne w zależności od grupy.

Parameter	Group A (normal lipids) n=24	Group B (mixed hyperlipids) n=11	P
Age (yrs)	56.1±4.4	55.8±5.1	NS
BMI (kg/m2)	27.1±6.2	27.6±5.8	NS
FSH 9U/L)	72.0±21.0	70.0±28.0	NS
Estradiol (ug/l)	14.0±9.0	18.0±11.0	NS
TSH	1.8±1.1	1.9±0.8	NS
Total cholesterol (mmol/l)	4.7±0.6	7.0±0.8	<0.001
HDL (mmol/l)	1.7±0.4	1.7±0.4	NS
LDL (mmol/l)	2.8±0.8	4.5±0.9	<0.01
Triglicerides (mmol/l)	1.1±0.2	2.5±0.8	<0.01

***Plasma levels of sICAM prior to standard exercise test, at peak exercise and at the 15th minute of recovery were significantly lower in group A compared to group B (Tab. II).**

Table II

Plasma levels of sICAM and sVCAM prior to standard exercise test, at peak exercise and at the 15th minute of recovery according to group.

Stężenie cząsteczek adhezyjnych sICAM, sVCAM przed rozpoczęciem testu, na szczycie wysiłku oraz 15 minut po zakończeniu testu wysiłkowego w zależności od grupy.

Parameter	Group A (normal lipids) n=24	Group B (mixed hyperlipids) n=11	P
sICAM base (mg/l)	257.0±47.0	325.0±34.0	<0.05
sICAM max (mg/l)	260.0±48	331.0±29.0	<0.05
sICAM recovery (mg/l)	257.0±52	323.0±33	<0.05
sVCAM base (mg/l)	598.0±155.0	563.0±163.0	NS
sVCAM max (mg/l)	622.0±168.0	689.0±220	NS
sVCAM recovery (mg/l)	595.0±147.0	594.0±215.0	NS

Table III

Plasma levels of NO_3, NO_2, NO_2/NO_3, endothelin-1 , prior to standard exercise test, at peak exercise and at the 15th minute of recovery according to group.

Stężenie NO_3, NO_2, NO_2/NO_3,endoteliny 1 przed rozpoczęciem testu, na szczycie wysiłku oraz 15 minut po zakończeniu testu wysiłkowego w zależności od grupy.

Parameter	Group A (normal lipids) n=24	Group B (mixed hyperlipids) n=11	P
NO_3 base (mmol/l)	43.0±13.0	57.0±15.0	NS
NO_3 max (mmol/l)	46.0±11.0	67.0±27.0	<0.02
NO_3 recovery (mmol/l)	52.0±29.0	53.0±14.0	NS
NO_2 base (mmol/l)	7.0±6.0	6.0±3.0	NS
NO_2 max (mmol/l)	5.5±2.3	6.9±2.3	NS
NO_2 recovery (mmol/l)	6.3±2.4	4.7±1.8	NS
NO_2/ NO_3 base (mmol/l)	38.0±13	41.0±14.0	NS
NO_2/ NO_3 max (mmol/l)	40.0±11.0	51.0±28.0	NS
NO_2/ NO_3 recovery (mmol/l)	45.0±29.0	48.0±14.0	NS
Et-1 base (nmol/l)	1.7±3.8	2.2±2.1	NS
Et-1 max (nmol/l)	1.8±3.9	2.3±2.3	NS
Et-1 recovery (nmol/l)	1.9±4.3	2.0±2.0	NS

Table IV

Plasma levels of TNF-a and TNF-a receptor levels prior to standard exercise test, at peak exercise and at the 15th minute of recovery according to group.

Stężenie TNF-a oraz receptora TNF-aprzed rozpoczęciem testu, na szczycie wysiłku oraz 15 minut po zakończeniu testu wysiłkowego w zależności od grupy.

Parameter	Group A (normal lipids) n=24	Group B (mixed hyperlipids) n=11	p
hs TNFa base (ng/l)	1.8±1.1	2.1±1.1	NS
hs TNFa max (ng/l)	1.7±1.1	2.1±1.7	NS
hs TNFa recovery (ng/l)	1.6±1.1	2.3±1.6	NS
TNFa recept base (ng/l)	933.0±250.0	946.0±249.0	NS
TNFa recept max (ng/l)	962.0±250	952.0±228.0	NS
TNFa recept recovery (ng/l)	946.0±218.0	960.0±205.0	NS

Our previous study showed that postmenopausal women with hypercholesterolemia had increased sVCAM and TNF-a plasma levels only during short physical exercise [45]. There was no difference in mean triglicerides levels between groups of postmenopausal women with high total cholesterol level and normal cholesterol level [45]. Taking into consideration the present and previous data it may be suggested that triglicerides may enhance the release of sICAM in postmenopausal women both at rest and during short physical exercise. Abe et al. [46] and Lupatelli et al. [47] showed the higher sICAM at rest in patients with hypertriglyceridaemia. Schumacher et al. showed the indirect relation between physical performance and proinflamatory markers plasma levels, but no effect on sICAM was obtained with a 6-month lifestyle intervention program in coronary heart disease patients when compared with patients who received usual care follow-up [48]. Hammett et al. showed no effect of 12 weeks' long physical exercise on sICAM plasma levels [49,50]. However both study groups comprises smokers. Beckie et al. showed the decrease in plasma levels of ICAM women with coronary artery disease after 12 weeks of in cardiac rehabilitation [48].

We also showed higher plasma concentration of NOx at peak exercise. Maeda et al. showed the plasma concentration of NOx increase after 3 months of moderate (on a cycle ergometer for 30 min/day, 5 days/week at 80% of their individual ventilatory threshold) exercise in elderly (59-69 yrs of age) women. However they measured the NOx concentration prior and after 3 months' exercise program, not during the particular episode of exercise [43].

There are several limitations of our study. The first is the small number of women mainly in group B. It resulted from tough criteria of inclusion to the study (normotensive, non-smokers). There would be interesting to evaluate the influence of smoking on the carried out comparison, and the present set of postmenopausal women consisted of non--smokers. We took into the analysis set of women with combined hyperlipidemia and in the previous study we took into the analysis the set of women only with hypercholesterolemia. It would be of interest to study the group of postmenopausal women only with hypertriglyceridemia to evaluate the direct effect of high triglycerides on the secretion of adhesive molecules in postmenopausal women during short physical exercise. In the present study the subgroup of women with high triglycerides only was too small to submit it to statistical analysis.

Conclusion

Plasma soluble intracellular adhesion molecules levels are higher at rest and during exercise in postmenopausal women with atherosclerosis risk factors.

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