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Significance of the pulsatility index in the evaluation of hemodynamic changes in peripheral arterial circulation in obese persons treated with orlistat

Značaj pulsatilnog indeksa za procenu hemodinamskih promena u perifernoj arterijskoj cirkulaciji gojaznih osoba lečenih orlistatom

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Abstract

Background/Aim. Prolonged hyperinsulinemia accelerates the process of endothelial dysfunction and arteriosclerotic changes affecting the development of cardiovascular and cerebrovascular diseases. There are various measuring techniques for the evaluation of early functional changes in the arterial wall such as: flow-mediated endothelium-dependent vasodilation, impulse wave analysis, intima-media thickness assessment, venous plethysmography and so on; however, each has certain limitations in results interpretation. The aim of this study was to indicate the association of the pulsatility index (PI) that shows peripheral arterial contractility, with the changes in metabolic parameters under insulin resistance conditions. **Methods.** The study included a total of 30 healthy obese subjects with the values of body mass index more than 30 kg/m^2, randomized with double blind design into two groups: placebo and orlistat. The extent of insulin sensitivity was calculated on the basis of glycemia and insulinemia values using an appropriate formula. **Results.** The obtained results suggest a statistically significant improvement in the PI index in the orlistat group ($p < 0.002$), while there was no such improvement in the placebo group. **Conclusion.** The results obtained in this study indicate the improvement in insulin sensitivity within early arteriosclerosis is a significantly favorable effect of orlistat on peripheral arterial circulation additionally supported by the reduction in levels of lipid fractions, especially triglycerides. Early hemodynamic changes under conditions of the reduced insulin resistance are characterized by the increase in arterial wall contractility evaluated by the PI determination.

Key words:
arteries; atherosclerosis; blood flow velocity; insulin resistance; obesity; orlistat; prognosis; triglycerides.

Apstrakt

Uvod/Cilj. Dugotrajna hiperinsulinemija ubrzava proces endotelne disfunkcije i nastajanja arteriosklerotskih promena, što utiče na nastanak kardiovaskularnih i cerebrovaskularnih oboljenja. Za procenu ranih funkcionalnih promena u arterijskom zidu koriste se različite metode merenja kao što su: protokom posredovana endotel-zavisna vazodilatacija, analiza pulsnog talasa, procena debljine intime i medije, venska pletizmografija i drugo; međutim, svaka od njih ima određena ograničenja u tumačenju rezultata. Cilj ove studije bio je da se ukaže na povezanost pulsatilnog indeksa (PI), koji pokazuje kontraktilnost perifernih arerija, sa izmenjenim metaboličkim parametrima u uslovima insulinske rezistencije. **Metode**. Ispitivanjem je bilo obuhvaćeno 30 zdravih gojaznih osoba, sa vrednostima indeksa telesne mase iznad 30 kg/m^2, koje su po metodi duplo slepog dizajna bile randomizovane u dve grupe – placebo i orlistat. Na osnovu vrednosti glikemije i insulinemije, primenom odgovarajuće formule bio je izračunat nivo insulinske senzitivnosti. **Rezultati**. U orlistat grupi, došlo je do statistički značajnog poboljšanja PI ($p < 0,002$), dok u placebo grupi nije bilo značajnog uvećanja PI. **Zaključak**. Dobijeni rezultati ukazuju na to da je poboljšanje insulinske senzitivnosti u fazi rane ateroskleroze značajan faktor povoljnih uticaja orlistata na perifernu arterijsku cirkulaciju, čemu dodatno doprinosi redukcija nivoa lipidnih frakcija, posebno triglicerida. Prve hemodinamske promene u uslovima smanjene insulinske rezistencije karakteriše porast kontraktilnosti arterijskog zida, procenjeno određivanjem PI.

Ključne reči:
arterije; ateroskleroza; krv, brzina protoka; insulin, rezistencija; gojaznost; orlistat; prognoza; trigliceridi.

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Introduction

The majority of obese people are commonly characterized by the increase in endogenous insulin secretion, reduced response of peripheral tissue to its effects and the occurrence of insulin resistance (IR) – metabolic syndrome. Recent studies point out a relationship between IR and morphofunctional endothelial changes mostly responsible for the occurrence of early and accelerated atherosclerosis [1–5].

It has been proven that endothelium is not only semipermeable barrier between blood and the layer of smooth muscle of blood vessels. It is a multifunctional highly active endocrine organ, one of its major functions being keeping balance between vasodilatory and vasculoprotective agents on one side, and vasoconstrictive and proliferative ones, on the other side [6–17].

Especially interesting is the fact that early hemodynamic and morphologic disorders in arteries occur much earlier than the picture of metabolic syndrome manifests itself. In some individuals, particularly in the so-called healthy obese ones, prolonged unrecognized hyperinsulinemia and endothelial dysfunction could cause sudden vascular disorders, such as myocardial infarction (MI) and stroke [18–24].

Methods for evaluation of peripheral artery disease pathophysiology

Contrast angiography could not be used for reliable measuring of preclinical atherosclerotic lesions. For the last two decades, various methods have been in use such as: flow-mediated endothelium-dependent vasodilation, and intima-media thickness (IMT) assessment, while venous plethysmography, and impulse wave analysis are less dependable. Magnetic resonance is mainly used for arterial compliance and large blood vessels analysis [25–33].

The aim of this study was to indicate the presence of an association of some other hemodynamic parameters such as the pulsatility index (PI) with some metabolic syndrome components and changes in morphofunctional characteristics of peripheral arteries [34, 35]. The PI is mainly used for the evaluation of arterial subocclusal and occlusal diseases [36]. Modern ultrasound diagnostics has not enough data on the association of this parameter with functional changes in peripheral arteries under the conditions of IR. The determination of PI implies also the study of arterial wall properties. Considering the known facts on comorbidity of endothelial changes and arterial compliance damage, it could be supposed that the changed PI values reflect not only advanced morphologic changes, but also early functional changes in the wall of peripheral arteries [37–39].

Methods

The study included a total of 30 healthy obese subjects with the values of body mass index (BMI) more than 30 kg/m^2, randomized with double blind design into two groups: placebo and orlistat. The subjects of the placebo group were given placebo capsules three times daily, per one with main meals, while those from the orlistat group were given per one orlistat capsule of 120 mg also with main meals. Each subject was on individually evaluated hypocaloric diet. Inclusion criteria were age of 35 to 60 years, BMI of 30 to 35 kg/m^2, low density lipoprotein (LDL) cholesterol of 4 mmol/L, triglyceride less than 4.5 mmol/L, normotensive nonsmokers, no surgery nor myocardial infarction six months prior to the study, and no other diseases.

Using standard techniques, body height, body mass, BMI of the subjects were measured, as well as the Oral Glucose Tolerance Test (OGTT) with 75 g of glucose and determination of the value of insulin and C-peptide. The level of HbA1c was also determined. Insulin sensitivity index (ISI) was calculated on the basis of the values of glycemia and insulinemia using the formula as follows:

$$ISI = \frac{10{,}000}{\sqrt{(G_0 \times I_0)\,(G_x \times I_x)}}$$

where: G_0 is glycemia on an empty stomach, I_0 is insulinemia on an empty stomach, G_x is average glycemia within the test, I_x is average insulinemia within the test [40].

Each subject was submitted to the determination of triglyceride concentration, total and LDL cholesterol.

Echoangiographic measurements were performed with the ultrasound apparatus type Hewlett Packard equipped with a linear probe of 7.5 MHz in an air conditioned room at 20°C. Prior to that, the subjects were at the state of rest to adapt to microclimatic conditions. IMT measurement was done on the femoral artery surface (AFS) of the right leg, in the middle of the line that connects the inguinal ligament to the inner extension of the proximal edge of tibia (Hunter's canal). The PI was determined at the same site by activating impulse Doppler and applicable commands on the ultrasound apparatus. Each echoangiographic measurement was repeated three times, and the average value was used as a final result at the beginning and at the end of three months, while in 10 subjects also after six months.

Results

There were 30 patients involved in the study, which were divided into two groups (orlistat and placebo). The orlistat patients were 48.25 ± 7.32 years old on the average, overweight with BMI 32.4 ± 2.71 kg/m^2, with changes in lipid fractions (cholesterol 6.78 ± 1.56 mmol/L; LDL cholesterol 4.11 ± 0.98 mmol/L; triglycerides 3.65 ± 1.9). The examined subjects were not treated for diabetes or arterial hypertension. The average level of systolic arterial blood pressure (Tas) was 135 ± 10 mmHg and that od diastolic arterial blood pressure (Tad) 80.0 ± 8 mmHg. In the orlistat group the average glycemia was 6.6 ± 1.4 mmol/L. The fasting insulin level was 23 ± 2.2 mU/L, and the index of the insulin sensitivity was 42.2 ± 21.6. The mentioned parametres did not have any statistical differrence in relation to the placebo group (Table 1).

Table 1

Data on the subjects at the beginning of the study

Parameters	Groups, mean ± SD		*p*
	Orlistat (n = 20)	Placebo (n = 10)	
Age (year)	48.25 ± 7.32	52.73 ± 8,87	0.094
BMI (kg/m^2)	32.40 ± 2.71	32.31 ± 2.40	0.930
WHR	0.97 ± 0.1	0.98 ± 0.1	0.078
Tas (mmHg)	135 ± 10	130 ± 10	0.207
Tad (mmHg)	80 ± 8	80 ± 5	1.000
TA/impulse (mmHg)	55 ± 6	50 ± 9	0.080
Triglycerides (mmol/L)	3.65 ± 1.9	3.75 ± 1.92	0.893
Cholesterol (mmol/L)	6.78 ± 1.56	6.90 ± 1.70	0.848
LDL-cholesterol (mmol/L)	4.11 ± 0.98	4.10 ± 0.96	0.979
Glucose (mmol/L)	6.60 ± 1.40	6.02 ± 1.12	0.265
Insilin on an empty stomach (mU/L)	23 ± 2.20	21.40 ± 1.7	0.054
IMT (mm)	1.9 ± 0.25	1.7 ± 0.23	0.758
MN (cm/s)	18.2 ± 4.8	18.1 ± 3.0	0.205
ISI	42.2 ± 21.6	66.9 ± 26.2	0.221
PI	5.43 ± 1.96	4.74 ± 0.5	0.36

BMI – body mass index; WHR – waist-hip ratio; TAs – systolic arterial blood pressure; TAd – diastolic arterial blood pressure; IMT – intima-media thickness; MN – mean velocity of blood flow; ISI – insulin sensitivity index; PI – pulsatility index; SD – standard deviation.

Table 2

Effects of three and six-month treatment with orlistat *versus* placebo on the studied risk factors

Parameters	After three months		*p*	After six months		*p*
	Orlistat	Placebo		Orlistat	Placebo	
BMI (kg/m^2)	-3.24	-1.51	0.0001	-5.06	-3.41	0.021
WHR	-1.90	-1.60	0.281	-5.50	-3.20	0.0001
Tas (mmHg)	-5	-1,5	0.0001	-15	-5	0.0001
Tad (mmHg)	-2	-0.5	0.0001	-5	-2	0.0001
TA/impulse (mmHg)	-3	-1	0.0001	-10	-3	0.0001
Triglycerides (mmol/L)	-1.55	-1.14	0.301	-2.43	-1.60	0.121
Cholesterol (mmol/L)	-0.68	-0.20	0.0001	-1.58	-0.80	0.006
LDL cholesterol (mmol/L)	-0.71	-0.20	0.0001	-1.21	-0.70	0.002
Glucose (mmol/L)	-0.90	-0.07	0.0001	-1.00	-0.22	0.738
Insulin on an empty stomach (μU/L)	-6.50	-0.50	0.0001	-11.90	-3.30	0.0001
ISI	16.2	-5.9	0.005	26.9	-7.14	0.0001

***Note*: Results are presented as differences of values after three and six months in relation to the values at the beginning of the study.**

BMI – body mass index; WHR – waist-hip ratio; TA – arterial blood poressure; Tas – systolic arterial blood pressure; Tad – diastolic arterial blood pressure; LDL – low density lipoprotein; ISI – insulin sensitivity index.

The morphofunctional parametres on the right femoral artery were determined intially, as well: IMT 1.9 ± 0.25 mm; mean velocity of blood flow (MN) 18.2 ± 4.8 cm/sec, and the PI 5.43 ± 1.96.

After three month period, BMI in both groups was significantly reduced. In the orlistat group, levels of blood pressure and lipid fractions were stastically significantly reduced, especially values of triglycerides (Tas -5 mmHg; Tad -2 mmHg; cholesterol -0.68 mmol/L; LDL cholesterol 0.71 mol/L; triglycerides -1.55 mmol/L). The values of the observed parametres in the orlistat group after three months of the treatment were in most cases statistically significantly different compared to the values of the same parametres in the placebo group (Table 2). As the result of IR reduction, the rise of ISI values especially stood out in the orlistat group (+16.20 ± 22.8), which was not the case in the placebo group (-5.9 ± 8.5) (Table 3).

Table 3

Insulin sensitivity index (ISI), mean ± SD

Group	ISI-1	ISI-3	Δ	*p*
Orlistat	42.2 ± 21.6	58.4 ± 27.7	16.2	0.005
Placebo	66.9 ± 26.2	60.9 ± 22.1	-6.0	0.018

ISI-1– values at the beginning of the study; ISI-3 – values after three months of the treatment; Δ **– mean difference between ISI-3 and ISI-1 values; SD – standard deviation.**

Table 4
Morphofunctional parametres determined on the right femoral artery in the orlistat and the placebo group (mean ± SD)

Parameters	At the beginning	After 3 months	*p*	After 6 months	*p*
Orlistat group (n = 20)					
IMT (mm)	1.9 ± 0.25	1.8 ± 0.91	0.132	1.8 ± 0.24	0.001
MN (cm/s)	18.2 ± 4.8	15.4 ± 5.1	0.039	14.2 ± 3.8	0.021
PI	5.40 ± 1.9	6.30 ± 1.5	0.002	6.80 ± 1.6	0.002
Placebo group (n = 10)					
IMT (mm)	1.7 ± 0.23	1.7 ± 0.11	0.071	1.6 ± 0.93	0.068
MN (cm/s)	18.1 ± 3.0	17.7 ± 3.9	0.435	17.0 ± 2.34	0.361
PI	4.70 ± 0.5	5.00 ± 1.0	0.213	5.10 ± 1.0	0.292

IMT – intima-media thickness; MN – mean velocity of blood flow; PI – pulsatility index; SD – standard deviation.

As the reflection of peripheral artery vasodilation, in the orlistat group, MN is reduced in relation to the beginning of the study (-2.7 ± 5.6 cm/sec) (Table 4). Finally, all together it contributed to the improvement AFS contractility in the orlistat group (PI +1.3 ± 1.6) (Table 4).

All registrated statistical significances in the orlistat group after three month observing were maintained or improved even after 6 months, but not in the placebo group (Table 4).

Statistical analysis showed that the rise of IR and the reduction of triglyceride levels had the biggest significance (importance) for the PI improvement as the reflection of contractility of peripheral arteries.

Discussion

It is known today that IR condition precedes type 2 diabetes. As early as in that period vascular disorders with the damage of endothelial function appear, often followed with hypertension, dyslipidemia, disordered fibrinolysis, and most often associated with obesity. In prediabetes stage we could find more or less changes in the relation between vasoconstrictive and vasodilatory, proatherogenic and antiatherogenic, procoagulant and anticoagulant agents, as well as stimulators and inhibitors of growth factor of endothelial cells [40–45].

Endothelial damage causes the production of numerous vasoactive substances such as: soluble vascular adhesion molecules, intercellular adhesion molecules, E-selectin, P-selectin, endothelin, thrombomodulin, and von Willebrand factor. As a response to inflammation and adhesion of circulating leukocytes, cellular adhesion molecules appear on the surface of endothelial cells. These endothelial factors, at the phase of prediabetes, could be the markers of endothelial activation [46, 47].

Arterial stiffness is partially regulated with basal release of nitric oxide as a regulator of vascular tonus in arteriolar resistance. Numerous studies emphasize the role of endothelium in arterial stiffness regulation, and the majority of them refer to the correlation of nitric oxide and endothelin [48–59].

The PI is calculated out of e values of waves amplitudes and the mean blood velocity. Each arterial level has its normal values of this parameter. The normal value of PI for the AFS ranges from 5 to 10. There is the association of changes in the PI with the changes of individual components of the IR syndrome estimated on the AFS [47].

The obtained results indicate a statistically significant improvement of the PI ($p = 0.002$) in the orlistat group within three months, while there was no significant PI increase in the placebo group. One of the main facts that affect the improvement of pulsatility is a reduced blood flow velocity, especially pronounced in the orlistat group ($p = 0.03$), while it was not so pronounced in the placebo group ($p = 0.435$). Univariate regression analysis in the orlistat group showed the presence of a significant correlation of changes in the level of insulin sensitivity ($p = 0.025$) and triglyceride ($p < 0.05$) with changes in the PI. Multivariate regression analysis showed the changes in insulin sensitivity ($p= 0.02$) and triglyceride levels ($p = 0.04$) also as independent predictors of PI changes. All the subjects with a reduction in IR had increased PI values. In a number of subjects of the placebo group, there was no improvement of insulin sensitivity, but there was a reduction in triglyceride levels, with no improvement in the PI. These finding that changes in IR mainly affect the contractility of arterial wall regardless of levels of lipid fractions.

Reaven et al. [60, 61] reported the results on the influence of orlistat and a reduced body mass on decreasing the risk of coronary artery disease in those with syndrome x. In the group with syndrome x there was a significant reduction of plasma insulin concentrations, decrease of triglyceride levels and an increase of HDL cholesterol levels as compared with the group with no characteristics of metabolic syndrome. Our results are in compliance with these results since there was a significant positive correlation between improvement of insulin sensitivity, reduction of triglyceride levels, lowering of blood pressure, and improvement of hemodynamic parameters, particularly in the group of those treated with orlistat ($p < 0.001$).

There were no studies published till now on effects of orlistat and hypocaloric diet on the reduction of hyperinsulinemia, as well as effects on hemodynamic parameters and atherosclerotic changes in peripheral arteries evaluated with ultrasound measurements. The results of our study confirmed that already in three months orlistat leads to the increase in insulin sensitivity (42%) together with the correction of majority of metabolic parameters changed. The reduction of IR significantly correlates ($p < 0.001$) with decreasing of the level of glycemia on an empty

stomach, triglyceride levels, impulse pressure, and with an improvement of the pulsatility of arterial wall.

Conclusion

The obtained results indicate that an improvement of insulin sensitivity in the stage of early arteriosclerosis is a significant factor of favorable effects of orlistat on peripheral arterial circulation, additionally supported by the reduction of lipid fractions, especially triglycerides. The first hemodynamic changes in the conditions of reduced IR are characterized with the increase of contractility of arterial wall, evaluated by the PI determination.

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