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Please cite this article SIGNIFICANCE OF THE PULSATILITY INDEX IN THE EVALUATION OF HEMODYNAMIC CHANGES IN PERIPHERAL ARTERIAL CIRCULATION IN THE OBESE TREATED WITH ORLISTAT

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UDC:

DOI: [https://doi.org/10.2298/VSP180912190H](https://doi.org/10.2298/VSP180912190H)

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
SIGNIFICANCE OF THE PULSATILITY INDEX IN THE EVALUATION OF HEMODYNAMIC CHANGES IN PERIPHERAL ARTERIAL CIRCULATION IN THE OBESE TREATED WITH ORLISTAT

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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 are flow-mediated endothelium-dependent vasodilation, impulse wave analysis, intima-media thickness assessment, venous plethysmography and so on, however, each having certain limitations in results interpretation. The aim of this study was to indicate the correlation of pulsatility index that shows peripheral arterial contractility with the changes in metabolic parameters under the conditions of insulin resistance. Methods. The study included a total of 30 healthy obese subjects with the values of body mass index more than 30 kg/m² randomized with double blind design into two groups: placebo and orlistat. The extent of insulin sensitivity was calculated on the basis of the values of glycemia and insulinemia using the formula. Results. The obtained results suggest a statistically significant improvement in the pulsatility index in the group orlistat (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 as a significantly favorable factor for peripheral arterial circulation additionally supported by the reduction in the level of lipid fractions, especially triglycerides. Early hemodynamic changes under the conditions of the reduced insulin resistance are characterized by the increase in arterial wall contractility evaluated with pulsatility index determination.

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 danas postoje različite metode merenja kao što su protokom posredovana endotel zavisna vazodilatacija-FMD (flow mediated vasodilatation), analiza pulsnog talasa, procena debljine intime i medije (FMD), venska pletizmografija...svaka sa određenim ograničenjima u tumačenju rezultata. Cilj našeg rada je bio da ukazemo na povezanost pulzatielnog indeksa (PI)-koji pokazuje kontraktilnost perifernih arerija, sa izmenjenim metaboličkim parametrima u uslovima insulininske rezistencije. Metode. Ispitivanjem je bilo obuhvaćeno 30 zdravih gojaznih osoba, sa vrednostima BMI iznad 3o kg/m², koji su po metodi duplo slepog dizajna bili randomizovani u dve grupe-placebo i orlistat. Na osnovu vrednosti glikemija i insulinemija, primenom formule bio je izračunat nivo insulininske senzitivnosti (ISI). Rezultati. Naši rezultati pokazuju da je, u orlistat (p<0,002) grupi, došlo do statistički značajnog poboljšanja PI, dok u placebo grupi nije bilo signifikantnog uvećanja PI. Zaključak. Dobijeni rezultati ukazuju, da je poboljšanje insulininske senzitivnosti, u fazi rane ateroskleroze, značajan faktor povoljnih uticaja na perifernu arterijsku cirkulaciju, čemu dodatno doprinosi redukcija nivoa lipidnih frakcija, posebno triglicerida. Prve hemodinamske promene, u uslovima smanjene insulininske rezistencije, karakteriše porast kontraktilnosti arterijskog zida, procenjeno određivanjem PI.
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 right 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 vasodilative and vasculoprotective agents on one side, and vasoconstrictive and proliferative 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 are myocardial infarction and stroke (18-24).

Methods for evaluation of peripheral artery disease pathophysiology

Contrast angiography could not be used for reliable measuring preclinical atherosclerotic lesions. For the last two decades various methods have been in use such are flow-mediated endothelium-dependent vasodilation (FMD), and intima-media thickness assessment (IMT), 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 a correlation of some other hemodynamic parameters such is pulsatility index (PI) with some metabolic syndrome components and changes in morphofunctional characteristics of peripheral arteries (34, 35). PI is mainly used for the evaluation of arterial subocclusive and occlusive 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 insulin resistance. 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 values of PI 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 more than 30 kg/m² randomized with double blind design into two groups: placebo and orlistat. The subjects of the placebo group were given placebo capsule 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/m²; LDL cholesterol of 4 mmol/l, triglyceride less than 4.5 mmol/l, normotensive nonsmokers, no surgery nor myocardial infarction six months prior to this study, no other diseases.

Using standard techniques body height, body mass, body mass index of the subjects were measured, as well as 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 level (ISL) was calculated on the basis of the values of glycemia and insulinemia using the formula as follows:

\[
ISL = \frac{10000}{\sqrt{(G_0 \times I_0)} (G_x \times I_x)}
\]

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 airconditioned room at 20°C. Prior to that the subjects were at the state of rest to adapt to microclimatic conditions. Intima-media thickness (IMT) measurement was done on the surface femoral artery (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). PI was determined at the same site by activating impulse doppler and applicable commands on the ultrasound apparatus. Each echoangiographic measurenet 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 a number of subjects (n = 10) also after six months.

Results

There were 30 patients involved in the study, which were devided up in two groups (orlistat and placebo). The orlistat patients were 48.25 ± 7.32 years old on the average, over-weight with BMI 32.4 ± 2.71 kg/m (m2); with changes in lipid fractions (cholesterol 6.78 ± 1.56 mmol/l; LDL 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 the blood pressure was Tas 135 ± 10 mmHg and Tad 80.0 ± 8mmHg. 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).

The morphofunctional parametres on the right femural artery were determined intially, as well: IMT 1.9 ± 0.25 mm; MN 18.2 ± 4.8 cm/sec, and PI was 5.43 ± 1.96.

After three month period in both groups the body mass (BMI) was significantly reduced. In the orlistat group the levels of the blood pressure and lipid fractions were stastically significantly reduced, especially the values of triglycerides with p < 0.1 (Tas -5
mmHg; Tad -2 mmHg; Cholesterol -0.68 mmol/l; LDL 0.71 mol/l; Triglycerides -1.55 mmol/l). The values of the observed parameters in orlistat group after three months of treatment were in most cases statistically significantly different compared to the values of the same parameters in the placebo group (Table 2). As the result of insulin resistance reduction, especially the rise of the ISI values stands out in orlistat group +16.20 ± 22.8, which was not the case in placebo group (-5.9 ± 8.5) (Table 3). As the reflection of peripheral artery vasodilation, in orlistat group MN is reduced in relation to the beginning of the study (-2.7 ± 5.6 cm/sec) (Figure 1). Finally, all together it contributes to the improvement of AFS contractility in orlistat group (PI +1.3 ± 1.6) (Table 4).

All registered statistical significances in orlistat group after three month observing are maintained or improved even after 6 months, but not in placebo group (Table 4, 5).

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

**Discussion**

It is known for sure today that insulin resistance condition precedes type 2 diabetes. As early as in that period appears vascular disorder with the damage of endothelial function, often followed with hypertension, dyslipidemia, disordered fibrinolysis, 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 are soluble vascular adhesion molecules (sVCAM), intercellular adhesion molecules (ICAMs), E-selectin, P-selectin, endothelin, thrombomodulin, and von Willebrand factor (VWF). As a response to inflammation and adhesion of circulating leukocytes, cellular adhesion molecules (CAMs) 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 endothel in arterial stiffness regulation, and the majority of them refer to the correlation of nitric oxide and endothelin (48-59).

**Pulsatility index in insulin resistance syndrome**

The pulsatility index was firstly defined by Gosling and Woodcock. It is calculated out of the values of waves amplitudes and the mean blood velocity (Figure 2). Each arterial level has its normal values of this parameter. The normal value of PI for the surface femoral artery (AFS) ranges from 5 to 10. This study contributed to the previous knowledge by showing the association of changes in the PI with the changes of individual components of the IR syndrome estimated on the AFS (60).

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 concluded the presence of a significant correlation of changes in the level of insulin sensitivity ($p < 0.025$) and triglyceride ($p < 0.05$) to changes in PI. Multivariate regression analysis showed the changes in insulin sensitivity ($p < 0.02$) and triglyceride ($p < 0.04$) also as independent predictors of PI changes. All the subjects with a reduction in insulin resistance had increased values of PI. In a number of subjects of the placebo group, there was no improvement of insulin sensibility, but there was a reduction in the level of triglyceride, while not showing improvement in PI. That could indicate the fact that changes in insulin resistance mainly affect the contractility of arterial wall regardless the level of lipid fractions.

Gerald Raven reported the results of a study on the influence of orlistat and a reduced body mass on decreasing the risk of a coronary disease in those with syndrome x. In the group with syndrome x there was a significant reduction of insulin concentration in plasma, decrease of triglyceride and increase of HDL as compared with the group with no characteristics of metabolic syndrome. Our results are in compliance with these results since it turned out that there was a significant positive correlation between improvement of insulin sensitivity, reduction of the level of triglyceride, 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 the effects of orlistat and hypocaloric diet on the reduction of hyperinsulinemia, as well as on the 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 affects the increase in insulin sensitivity (42%) together with the correction of the majority of the changed metabolic parameters. The reduction of IR significantly correlates ($p < 0.001$) with decreasing of the level of glycemia on an empty stomach, triglycerides, impulse pressure, and the improvement of the pulsatility of arterial wall.

**Conclusion**

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


Table 1. Data on the subjects at the beginning of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Orlistat (n=20) (X ± SD)</th>
<th>Placebo (n=10) (X ± SD)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>48.25±7.32</td>
<td>52.73±8.87</td>
<td>0.094</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.40±2.71</td>
<td>32.31±2.40</td>
<td>0.930</td>
</tr>
<tr>
<td>WHR</td>
<td>0.97±0.1</td>
<td>0.98±0.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Tas (mmHg)</td>
<td>135±10</td>
<td>130±10</td>
<td>0.207</td>
</tr>
<tr>
<td>Tad (mmHg)</td>
<td>80±8</td>
<td>80±5</td>
<td>1.000</td>
</tr>
<tr>
<td>TA/impulse (mmHg)</td>
<td>55±6</td>
<td>50±9</td>
<td>0.080</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>3.65±1.9</td>
<td>3.75±1.92</td>
<td>0.893</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.78±1.56</td>
<td>6.90±1.70</td>
<td>0.848</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>4.11±0.98</td>
<td>4.10±0.96</td>
<td>0.979</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.60±1.40</td>
<td>6.02±1.12</td>
<td>0.265</td>
</tr>
<tr>
<td>Insulin on an empty stomach (mU/L)</td>
<td>23±2.20</td>
<td>21.40±1.7</td>
<td>0.054</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>1.9±0.25</td>
<td>1.7±0.23</td>
<td>0.758</td>
</tr>
<tr>
<td>MN (cm/s)</td>
<td>18.2±4.8</td>
<td>18.1±3.0</td>
<td>0.205</td>
</tr>
<tr>
<td>ISI</td>
<td>42.2±21.6</td>
<td>66.9±26.2</td>
<td>0.221</td>
</tr>
<tr>
<td>PI</td>
<td>5.43±1.96</td>
<td>4.74±0.5</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*p<0.05; 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.
Table 2. Effects of three and six month treatment with orlistat on the studied risk factors

<table>
<thead>
<tr>
<th>Parameters</th>
<th>After three months</th>
<th>Orlistat</th>
<th>Placebo</th>
<th>p*</th>
<th>After six months</th>
<th>Orlistat</th>
<th>Placebo</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>-3.24</td>
<td>-1.51</td>
<td>0.0001</td>
<td>-5.06</td>
<td>-3.41</td>
<td>0.021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>-1.90</td>
<td>-1.60</td>
<td>0.281</td>
<td>-5.50</td>
<td>-3.20</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tas (mmHg)</td>
<td>-5</td>
<td>-1.5</td>
<td>0.0001</td>
<td>-15</td>
<td>-5</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tad (mmHg)</td>
<td>-2</td>
<td>-0.5</td>
<td>0.0001</td>
<td>-5</td>
<td>-2</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA/impulse (mmHg)</td>
<td>-3</td>
<td>-1</td>
<td>0.0001</td>
<td>-10</td>
<td>-3</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>-1.55</td>
<td>-1.14</td>
<td>0.301</td>
<td>-2.43</td>
<td>-1.60</td>
<td>0.121</td>
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<td></td>
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<tr>
<td>Cholesterol (mmol/L)</td>
<td>-0.68</td>
<td>-0.20</td>
<td>0.0001</td>
<td>-1.58</td>
<td>-0.80</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/L)</td>
<td>-0.71</td>
<td>-0.20</td>
<td>0.0001</td>
<td>-1.21</td>
<td>-0.70</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>-0.90</td>
<td>-0.07</td>
<td>0.0001</td>
<td>-1.00</td>
<td>-0.22</td>
<td>0.738</td>
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<td></td>
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<tr>
<td>Insulin on an empty stomach (mU/L)</td>
<td>-6.50</td>
<td>-0.50</td>
<td>0.0001</td>
<td>-11.90</td>
<td>-3.30</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI</td>
<td>16.2</td>
<td>-5.9</td>
<td>0.005</td>
<td>26.9</td>
<td>-7.14</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05; BMI – body mass index; WHR- waist-hip ratio; Tas–systolic arterial blood pressure; Tad–diastolic arterial blood pressure; LDL – low density lipoprotein; ISI- Insulin sensitivity Index.

Tbl. 3. ISI- Insulin sensitivity Index (X ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>ISI-1 ± SD</th>
<th>ISI-3 ± SD</th>
<th>X ± SD</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>42.2±21.6</td>
<td>58.4±27.7</td>
<td>16.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Placebo</td>
<td>66.9±26.2</td>
<td>60.9±22.1</td>
<td>-5.9</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*p<0.05;
Table 4. Orlistat group (n=20)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At the beginning</th>
<th>After 3 months</th>
<th>p*</th>
<th>After 6 months</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>1.9±0.25</td>
<td>1.8±0.91</td>
<td>0.132</td>
<td>1.8±0.24</td>
<td>0.001</td>
</tr>
<tr>
<td>MN (cm/s)</td>
<td>18.2±4.8</td>
<td>15.4±5.1</td>
<td>0.039</td>
<td>14.2±3.8</td>
<td>0.021</td>
</tr>
<tr>
<td>PI</td>
<td>5.40±1.9</td>
<td>6.30±1.5</td>
<td>0.002</td>
<td>6.80±1.6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*p<0.05;

Table 5. Placebo group (n=10)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At the beginning</th>
<th>After 3 months</th>
<th>p*</th>
<th>After 6 months</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>1.7±0.23</td>
<td>1.7±0.11</td>
<td>0.071</td>
<td>1.6±0.93</td>
<td>0.068</td>
</tr>
<tr>
<td>MN (cm/s)</td>
<td>18.1±3.0</td>
<td>17.7±3.9</td>
<td>0.435</td>
<td>17.0±2.34</td>
<td>0.361</td>
</tr>
<tr>
<td>PI</td>
<td>4.70±0.5</td>
<td>5.00±1.0</td>
<td>0.213</td>
<td>5.10±1.0</td>
<td>0.292</td>
</tr>
</tbody>
</table>

*p<0.05;

Fig.1- MN- mean velocity of blood flow - before, after 3 and 6 months of orlistat treatment versus placebo.
Received on September 12, 2018.
Revised on November 11, 2018.
Accepted on November 23, 2018.
Online First December, 2018.