CORRELATIONS OF VISFATIN WITH THE LIPIDIC METABOLISM IN DIABETIC AND OBESE PATIENTS

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Received December 12, 2011

Obesity and type 2 diabetes mellitus are the most frequent nutritional disorders found in the developed countries and are associated with a high cardiovascular mortality and morbidity. They are multifactorial associations and nutritional disorders, resulting from a genetic component and a multitude of environmental factors. The clinical observation determined the association of the obesity and diabetes mellitus with high blood pressure, dislipidemia and atherosclerosis. These conditions represent a public health problem, due to the high prevalence and its association with high risk cardiovascular diseases; both conditions have a high incidence in developed countries. Visfatin is an adipocytokine identified in 2005, its name suggesting the idea that it is predominantly produced in the visceral fat. It has a molecular weight of 52 kDa and it has in its structure, 491 aminoacid residues. It is identical to PBEF, that was described in 1994 as a lymphocytes produced cytokine.

Key words: visfatin, diabetes mellitus, cholesterol, obesity, LDL, HDL.

INTRODUCTION

Diabetes mellitus, hypertension, dyslipidemia and atherosclerosis, were defined as conditions specific for a certain lifestyle. A common feature for these diseases is overfeeding and its consequence, obesity. The researches in the biology of the adipose tissue have shown that the adipose tissue is not only an energy storing organ but also an endocrine secretion organ.

Visfatin is an adipocytokine identified in 2005, its name suggesting the idea that it is produced predominantly by the visceral fat. It has a molecular weight of 52 kDa and it has in its structure 491 aminoacid residues. It is identical to PBEF, described in 1994 as a lymphocyte produced cytokine. Visfatin has an expression in hepatocytes and muscles as well as in the adipocytes, kidneys and heart, in animals. Numerous publications reported various effects and correlations of visfatin with different medical conditions. In this way, increasing of the visfatin level can be observed in atherosclerosis, endothelial dysfunctions, metabolic syndrome, renal insufficiency, obesity and visceral fat. The relationship with diabetes mellitus and visceral fat is controversial.

In some studies it was reported that visfatin is strongly expressed in foam cells in atherosclerotic lesions with the increase of expressivity, especially in atheroma plaques in symptomatic plaques. Chang et al. have not find in their study, on a 53 group of Taiwanese adults, differences in the visfatin expression between the visceral and subcutaneous adipose tissue. Revollo et al., have shown that visfatin is an essential enzyme in the NAD production.

This protein is also a cytokine that promote the B cell maturation and inhibits the neutrophiles apoptosis. The enzyme belongs to the family of glycosyltransferases, being a pentosyltransferase. This enzyme plays an important role in the metabolism of the nicotinic derivatives and nicotinamides.

Dogrü et al. studied the visfatin values in 40 patients with recently discovered diabetes or with altered tolerance to glucose and discovered high levels of visfatin in diabetic partients as compared to the control group.

Takebayashi et al. didn’t find any correlation between visfatin and diabetes, and other study proved that there is a positive correlation between the decrease of visfatin and type 1 diabetes and negative correlation between HbA1c and visfatin levels.

It was proven that oxidized LDL increases the visfatin expression in the monocytes cell cultures. More than that, visfatin determines the expression increase of some extracellular degrading molecules, causing the instability of the atheroma plaque.

The high interest for the adipose tissue, as a secretory active organ and the observation of similarities between adipocytes and inflammatory immune cells, generated a high amount of information that revolutionized the understanding of the adipose tissue role in the physiologic and pathologic processes. The researches performed are too recent to allow therapeutic indications due to the fact that we must understand all the details regarding the adipokines and cytokines produced by the adipose tissue, as well as the differences between the visceral and subcutaneous adipose tissue and its exact role.

MATERIAL AND METHODS

Study group characteristic

We studied a total number of 60 subjects. These were divided into three groups according to the original condition, as it follows: group I – 25 patients with type 2 diabetes, group 2 – 15 obese patients and control group – 20 normal weight, apparently healthy volunteers (Table I).

Group I included type 2 diabetic patients with duration of diabetes higher then 5 years, registered in Arad Antidiabetes Center database. The inclusion criteria for type II diabetes were according to the IDF recommendations.

Group II was formed from 15 obese patients, without diabetes and cardiovascular diseases. The inclusion criteria was the BMI>30kg/m², according to the WHO recommendations.

The control group was formed from subjects that were clinically healthy having a normal weight (BMI<25 kg/m²).

Laboratory methods

Biochemical determinations were performed in the biochemistry lab department of the Faculty of Medicine, Pharmacy and Dentistry at the “Vasile Goldis” Western University and in a private medical laboratory, SC Laborator Analyze SRL, accredited by the Romanian Accreditation Association, RENAR.

Plasma lipids determinations were performed from a blood sample collected in the morning, after an overnight fasting of minimum 10 hours. The total cholesterol and HDL-cholesterol and triglycerides were determined through an enzymatic, photometrical method. LDL-cholesterol was calculated by the Friedewald formula:

\[
LDL\text{c} = \text{Total cholesterol} – \text{HDL\text{c}} – (\text{triglycerides}/2.2).
\]

There were determined the ratios between total cholesterol/ HDLc and LDLc/HDLc, the values over 5 being considered having a high atherogenic risk.

The plasma levels of lipids was appreciated according to the recommendations of the National Cholesterol Education Program, National Heart, Lung, and Blood Institute. Dyslipidemia was considered at total cholesterol values > 4.5 mmol/l, LDLc > 2.5 mmol/l, triglycerides > 1.7 mmol/l and HDLc < 1.00 mmol/l in males and < 1.3 mmol/l in females.

The changes that appeared in the carbohydrates metabolism were interpreted according to the criteria from the glycometabolic classification of WHO.

The basal plasma glucose was determined through enzymatic method with glucose-6 phosphate. The normal values of plasma glucose were considered at a plasma glucose value below 6.1 mmol/l.

The glycated hemoglobin (HbA1c) was appreciated according to the IDF criteria. It was analyzed through the latex turbidimetry. The glycated hemoglobin level, according to the European guides, for non-diabetics, is < 6.1 % and for diabetics, < 6.5 %.

The determination of visfatin was done from blood collected in the morning, in a fasting state, through ELISA (R&D System), according to the reagents working protocol attached to the analyzing kit.

To determine the correlation, we used the Pearson coefficient.

Statistically significant were considered the differences in the cases where the bilateral value, p < 0.05

In all the groups, including the control, we determined the visfatin levels.

### Table 1

Clinical characteristics and risk factors in the population studied.

<table>
<thead>
<tr>
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<th>Group I Diabetic</th>
<th>Group II Obese</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>25</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.7±11.55</td>
<td>42±3.64</td>
<td>41±11.17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.79±4.55</td>
<td>36.85±5.28</td>
<td>23.02±1.65</td>
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</table>
RESULTS AND DISCUSSION

Analyzing the lipid spectra to determine the dyslipidemia frequency, we obtained total cholesterol values >4.5 mmol/l in 21 cases in group I and 15 in group II.

Values of LDLc >2.5 mmol/l were found in 23 patients in group I and 15 patients in group II. (Table 2).

In Table 3 it can be observed the visfatin values in the volunteers taken into our study according to their mean BMI.

We obtained a statistically significant value higher in diabetic group as compared to the control one p < 0.0001. Also in the case of the obese group there was a statistical significance p = 0.0002. Comparing visfatin of the diabetic group divided according to their BMI, with the control group, we obtained statistical significance with each one of the groups studied (with the obese diabetics p = 0.001, with overweight diabetics p = 0.0002, with normal weight diabetics p < 0.0001).

Regarding the visfatin distribution, compared to the lipid metabolism parameters in the case of diabetic patients, we obtained positive correlations with LDLc (r = 0.64, p = 0.0006) (Figure 1) and with the ratio LDL/HDL (r = 0.50, p = 0.01) (Figure 2) and negative correlations with the ratio TC/HDL (r = 0.43, p = 0.03) (Figure 3) and HDL-cholesterol (r = -0.30, p = 0.15) (Figure 4). With the other lipid metabolism parameters total cholesterol (r = 0.10, p = 0.63), triglyceride (r = -0.24, p = 0.17), we didn’t obtain linear correlations.

Table 2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=25)</th>
<th>Group II (n=15)</th>
<th>Control group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.44±0.95</td>
<td>5.54±0.46</td>
<td>4.13±0.35</td>
</tr>
<tr>
<td>LDLcholesterol (mmol/l)</td>
<td>3.27±0.65</td>
<td>3.56±0.56</td>
<td>2.18±0.42</td>
</tr>
<tr>
<td>HDLcholesterol (mmol/l)</td>
<td>1.26±0.56</td>
<td>1.09±0.30</td>
<td>1.51±0.22</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.93±1.09</td>
<td>1.82±0.56</td>
<td>0.96 ± 0.24</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>4.98±2.02</td>
<td>5.45±1.17</td>
<td>2.72±0.49</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>3.15±1.70</td>
<td>3.59±1.35</td>
<td>1.48±0.43</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Visfatin values compared to IMC.</th>
<th>BMI (Kg/m²)</th>
<th>Visfatin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>&lt; 25</td>
<td>77 ± 6.93</td>
</tr>
<tr>
<td></td>
<td>25 – 29.9</td>
<td>58.85 ± 31.0</td>
</tr>
<tr>
<td></td>
<td>≥ 30</td>
<td>59.56± 39.13</td>
</tr>
<tr>
<td>Group II</td>
<td>&lt; 25</td>
<td>41.13±2.843</td>
</tr>
<tr>
<td></td>
<td>≥ 30</td>
<td>26.10±12.13</td>
</tr>
<tr>
<td>Control group</td>
<td>&lt; 25</td>
<td>26.10±12.13</td>
</tr>
</tbody>
</table>

In the case of visfatin distribution compared to the lipid metabolism parameters in group II, obese patients, there was a negative linear correlation in case of visfatin vs. HDLc (r = -0.45, p = 0.09) (Figure 5) and a positive linear correlation in the case of visfatin vs. TC/HDL (r = 0.30, p = 0.27) (Figure 6) and in the case of visfatin vs LDL/HDL (r = 0.33, p = 0.22) (Figure 7); in all other cases there wasn’t any linear correlation: visfatin vs triglycerides (r = 0.05, p = 0.85); visfatin vs LDLc (r = 0.16, p = 0.56); visfatin vs total cholesterol (r = 0.06, p = 0.83).

Regarding the visfatin values in the control group, there is a linear correlation with: HDLc (r = 0.45, p = 0.04) (Figure 8), LDLc (r = -0.45, p = 0.04) (Figure 9) and with the ratio CT/HDL (r = -0.43, p = 0.05) (Figure 10), LDL/HDL (r = -0.44, p = 0.05) (Figure 11); correlation is missing in the case of triglycerides (r = -0.11, p = 0.64) and total cholesterol (r = -0.28, p = 0.23).

The changes in the lipid metabolism in most patients with type 2 diabetes mellitus and obese, determined a boom in this research area and to enlighten in other areas of the lipid metabolism. In this way it was introduced the term “lipid triad”, characterized by the decrease of HDL, increase of triglycerides and the appearance of some small and dense LDL particles.

High plasmatic values of visfatin are found in obesity associated with high LDL and low HDL-cholesterol. However, the effects of visfatin remain controversial and the relationship with carbohydrates metabolism are uncertain.

When discovered visfatin, Fukuhara et al. have shown that this molecule was characterized by effects similar to insulin. In this study, the authors have shown that this adipocytokine is a strong adipogenic agent through the in vitro glucose transport stimulation and lipogenesis. In reality it seems to induce an increase of the in vitro glucose transport in 3T3 pre-adipocytes or L6 myocytes. The administration of visfatin in diabetic mice
seemed to ameliorate the insulin sensitivity. This hypothesis is confirmed through the presence of an original hyperglycemia in heterozygous animals to invalidate visfatin. This thing is explained by the fact that visfatin can bind to the insulin receptors with an affinity similar to insulin, but at a different site. 

![Fig. 1. Visfatin distribution as compared to the LDLc in the diabetic patients group.](image1)

![Fig. 2. Visfatin distribution as compared to the LDL/HDL in the diabetic patients group.](image2)

![Fig. 3. Visfatin distribution as compared to the TC/HDL in the diabetic patients group.](image3)

![Fig. 4. Visfatin distribution as compared to the HDLc in the diabetic patients group.](image4)

![Fig. 5. Visfatin distribution as compared to the HDLc in the obese patients group.](image5)

![Fig. 6. Visfatin distribution as compared to the TC/HDL in the obese patients group.](image6)
In humans, the preliminary studies have shown that the plasma levels of visfatin increased during obesity, without any correlation with insulin resistance. There are some studies showing that the plasma levels of visfatin are not correlated with the amount of visceral adipose tissue and there was not observed any differences in expression of visfatin in subcutaneous vs visceral adipose tissue. Even though more studies have shown a relationship between visfatin and obesity, its real metabolic role must be clarified.

In our study there were not observed any significant changes of visfatin in diabetic patients as compared to the control group. Neither, did we obtain values that were statistically significant with the obese group; the values in group II, obese, were higher than in the control group but statistically non-significant.

Positive correlations we obtained in the case of visfatin with LDLc, TC/HDLc ratio and LDL/HDL ratio. Knowing the fact that LDL is an atherogenic
molecule, we can state that visfatin could be involved or used as marker in the atherosclerosis pathology.

CONCLUSIONS

The mean values of visfatin were higher in diabetic group as compared to the obese and control group.

We obtained negative correlations of visfatin with triglycerides, in diabetic patients.

In the case of visfatin against HDLc, there were obtained negative correlations in diabetic and obese patients and positive correlations in the control group. Could visfatin also have anti-inflammatory properties?

Even though the role of visfatin in the diabetes mellitus pathology is far from being revealed, there are studies that indicate the fact that the visfatin values are independent and significantly associated with type 2 diabetes, plasma visfatin being increased in type 2 diabetes patients, while adiponectin is decreased and resistin doesn’t show differences in comparison to the control group.

REFERENCES


