

RELATIONSHIP BETWEEN ADIPONECTIN AND SOME METABOLIC PARAMETERS IN OBESE AND DIABETIC PATIENTS

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Abstract

It was recently discovered that the adipose tissue possesses a secreting role, biosynthesizing a series of bioactive substances that are transported through the blood and modulate the physiology of different organs. In this study, we analyzed the correlation of serum adiponectin with obesity, diabetes and dyslipidemia. We studied a total number of 110 subjects. These were divided into three groups, depending on their metabolic conditions. Group I – 60 patients diagnosed with type 2 diabetes, group II – 30 patients diagnosed with obesity and the control group – 20 subjects, healthy, normal weight. Comparing the mean values of adiponectin in diabetic patients with the mean values of adiponectin in the control group, we found that they were statistically significant lower for the diabetic patients ($t = 9.56$, $p < 0.0001$). Also, in patients from the second group, the adiponectin values were significantly lower when compared to the control group, $t = 9.13$; $p < 0.001$.

Rezumat

Recent, s-a descoperit că țesutul adipos are rol secretor, biosintetizând o serie de substanțe bioactive, care sunt transportate pe cale sangvină și modulează activitatea diferitelor organe. În acest studiu am analizat corelația dintre adiponectină serică, obezitate, diabet și dislipidemie. Am studiat un număr de 110 subiecți, împărțiți în trei loturi, în funcție de patologie. Lotul I – 60 de pacienți cu diabet zaharat tip 2, lotul II – 30 de pacienți cu obezitate și lotul martor – 20 de pacienți, sănătoși, cu greutate normală. Comparând valorile medii ale adiponectinei la pacienții diabetici cu valorile medii ale adiponectinei la lotul martor, acestea au fost semnificativ statistic mai mici la diabetici ($t = 9,56$; $p < 0,0001$). De asemenea, pacienții din al doilea lot, au prezentat valori semnificativ mai mici în comparație cu lotul martor $t = 9,13$; $p < 0,0001$.

Keywords: adiponectin, diabetes mellitus, dyslipidemia, obesity

Introduction

The adipose tissue is a special type of conjunctive tissue, where the adipocytes are predominant. The adipose tissue is distributed all over the

organism, representing 15-20% of the body weight in men and 20-25% in women [16].

In this study, we analyzed the correlation of adiponectin with obesity, diabetes and dyslipidemia [14,16]. The white adipose tissue is considered as an endocrine organ that biosynthesizes: fatty acids, cytokines (tumor necrosis factor- α , interleukin-6), adipocytokines (adiponectin, leptin, resistin and more recently, visfatin) [3,12,14,20]. These biomolecules could explain the relationship between obesity, insulin-resistance and the dysfunction of pancreatic β -cells.

Adiponectin is a plasma protein derived from the adipocyte. It was discovered in 1995 and it is made of 244 amino acids residues, having a structure homologous to that of collagen VII and X (N-terminal domain) and of the Cq1 complement (globular domain) [21,24]. Adiponectin is expressed especially in the white adipose tissue, its secretion being modulated by insulin, and it is highly possible that its expression may be regulated by the nutritional status [25]. Also, recent studies have shown that adiponectin is also produced by other organs such as the bone marrow [29], myocytes, cardiomyocytes [22] and the epithelial cells of the salivary glands [18]. Adiponectin lowers the triglycerides content in tissues and regulates the insulin signaling. In the skeletal muscle, the high expression of adiponectin is implicated in fatty acids transport. It was also shown that adiponectin activates the PPAR- α (peroxisome proliferator-activated receptor- α) and AMPK (adenosin monophosphate activated protein kinase) [17].

The normal plasma concentration of adiponectin range between 3-30 $\mu\text{g/mL}$, being the most abundant plasma protein synthesized in adipocytes [9,11]. Obese patients, type 2 diabetic, insulin resistant, dislipidemic and high blood pressure patients develop low levels of plasma adiponectin [11]. Even though the adiponectin is produced by adipocytes, the plasma concentration is low in obese patients, probably due to the high TNF- α (tumor necrosis factor- α) production in obese patients which determines a low expression and secretion of adiponectin [26].

Recent studies showed that adiponectin modulates certain metabolic processes, like the glucose and fatty acids catabolism [19]. So, it was proved that injecting adiponectin in mice, leads to reducing of plasma glucose and the fatty acid level [4,28], through the decrease of gluconeogenesis enzymes expression, lowering the glucose production and increasing the insulin effect in liver[4,11]. Adiponectin increases the sensitivity to insulin, reducing the free fatty acids in plasma and increasing the β -oxidation process of free fatty acids in muscles [29].

The aim of our study was to determine the level of adiponectin and the interpretation of the variation depending on some metabolic parameters.

Materials and Methods

Patients characteristics

We studied a total number of 110 subjects. These were divided in three groups, depending on the metabolic condition. Group I – 60 patients with type 2 diabetes, group II – 30 patients with obesity and a control group – 20 normal weight, healthy voluntaries. (Table I)

Table I
Clinical characteristics and risk factors in the studied population
(BMI = body mass index)

	Group I	Group II	Control group
Sex (M/F)	22/38	12/18	10/10
Age (years)	60.7±11.55	42±3.64	41±11.17
BMI (kg/m ²)	29.03±4.3	37.84±3.95	23.91±3.44

Group I included type 2 diabetic patients with a duration of diabetes higher than 5 years, registered in Arad Antidiabetes Center database (Romania). The inclusion criteria for type II diabetes were according to the International Diabetes Federation (IDF) recommendations [6].

Group II included 30 obese patients, without diabetes and cardiovascular diseases. The inclusion criteria was the BMI>30kg/m², according to the World Health Organization recommendations [27].

The control group included subjects that were clinically healthy and had normal weight values (BMI<25 kg/m²). [2]

We developed a clinical trial protocol, according to the ethical principles regarding research involving humans and was approved by the Ethics Board of the “Vasile Goldiș” Western University, Romania. The protocol was applied identically to all patients, in all the groups studied and the participation was voluntary and confidential. All the subjects signed an informed consent agreement.

Laboratory methods

Biochemical determinations were performed within the Biochemistry Laboratory of the Faculty of Medicine, Pharmacy and Dentistry, “Vasile Goldiș” Western University, Arad, Romania and in a private clinical laboratory (SC Laborator Analize SRL) accredited by the Romanian Accreditation Association, RENAR.

Plasma lipids determinations were performed from blood samples collected in the morning, after an overnight fasting of minimum 10 hours. The total cholesterol, HDL-cholesterol and triglycerides levels were determined through enzymatic and spectrophotometrical methods using the analysis kits from Diagnosticum Hungary, being processed on a Biochemistry Analyzer D-CHEM300. LDL-cholesterol was calculated through the Friederwald formula [13]:

$$\text{LDLc} = \text{Total cholesterol} - \text{HDLc} - (\text{triglycerides}/2.2).$$

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

The plasma levels of lipids were evaluated according to the recommendations of the National Cholesterol Education Program [23]. 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 carbohydrates metabolism was analyzed according to the criteria from the glycometabolic classification of WHO (World Health Organization) [28] and ADA (American Diabetes Association) [1].

The basal plasma glucose was determined through an enzymatic method using the analysis kit from Spin React Spain processed on the Biochemistry Analyzer D-CHEM300. The normal values of plasma glucose were considered the ones below 6.1 mmol/L.

The glycosilated hemoglobin (HbA1c) was assessed according to the IDF criteria for non-diabetics, is < 6.1 % and for diabetics > 6.5 %. It was analyzed by turbidimetry using the analysis kit from Diagon ltd. Hungary being processed on the Biochemistry Analyzer D-CHEM300.

Serum level of adiponectin was measured by using the ELISA sandwich test using Quantikine® reagent (R&D System USA): Human Total Adiponectin, according to the producer instructions, being processed on Microplate Reader MR-96 A from Mindray.

Statistical analysis

The statistical correlations were established using the Pearson coefficient.

The values in the tables and text are presented as mean values \pm standard deviation. Statistically significant were considered the differences in the cases where the bilateral value, $p < 0.05$.

Results and Discussion

Table II shows the characteristics of the lipid profile of the patients included in our study.

Table II

The characteristics of lipid metabolic profile in the studied groups

Plasma parameters	Group I (n=60)	Group II (n=30)	Control group (n=20)
Cholesterol (mmol/L)	5.53±0.97	5.48±0.44	4.13±0.35
LDLcholesterol (mmol/L)	3.62±0.81	3.63±0.48	2.17±0.42
HDLcholesterol (mmol/L)	1.02±0.44	0.99±0.26	1.51±0.22
Triglycerides (mmol/L)	1.94±0.96	1.87±0.47	0.92±0.31
Cholesterol/HDLc	6.1±2.11	5.78±1.52	2.78±0.49
LDLc/HDLc	4.05±1.65	3.92±1.19	1.48±0.43

Comparing the serum concentrations of adiponectin with the BMI, for the whole cohort studied, we obtained a negative correlation, statistically significant ($r = -0.47$, $p < 0.001$).

Table III details the BMI values and also the HbA1c and adiponectin plasmatic values, for all the studied groups.

In order to look at the behavior of the mean values of adiponectin according to the BMI, the diabetic group of patients was divided in 3 subgroups: normal weight ($BMI < 25 \text{ kg/m}^2$), overweight ($BMI = 25-29.9 \text{ kg/m}^2$) and obese ($BMI \geq 30 \text{ kg/m}^2$).

The plasma adiponectin concentrations in diabetic patients was statistically lower ($t = 9.56$, $p < 0.0001$) compared to the control group, they were statistically significant, lower in diabetic patients. Also, in patients from the second group, the adiponectin values were significantly lower when compared to the control group, $t=6.99$; $p < 0.0001$, $t=9.13$; $p < 0.0001$, respectively.

Table III

Serum adiponectin values for the studied groups

	BMI (Kg/m^2)	Adiponectin ($\mu\text{g/mL}$)	HbA1c %
Group I	< 25	22.03 ± 9.79	9.45 ± 1.71
	25 – 29.9	11.67 ± 5.71	8.76 ± 2.30
	≥ 30	8.76 ± 6.51	9.72 ± 2.23
Group II	≥ 30	10.79 ± 6.54	5.79 ± 0.54
Control group	< 25	33.99 ± 11.62	4.86 ± 0.41

Regarding the serum adiponectin distribution against BMI in diabetic subjects, it proved negatively correlated and statistically significant ($r = -0.47$; $p < 0.001$) (figure 1).

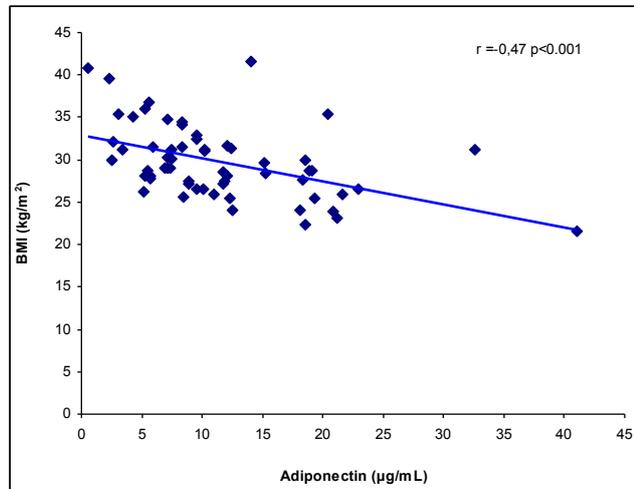


Figure 1

The distribution of serum adiponectin against the BMI in diabetic patients

The same negative correlation has been found between adiponectin and BMI in group 2 (obese subjects), but this relationship was not statistically significant (Figure 2). As expected, the adiponectin distribution within the control group (normal weight subjects) wasn't correlated with BMI ($r = -0.008$; $p > 0.05$).

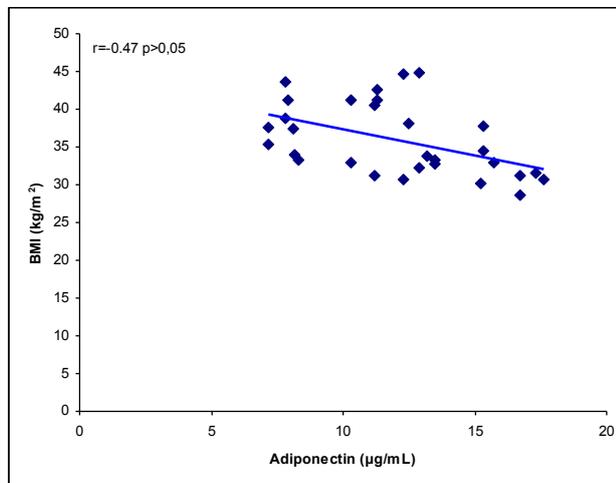


Figure 2

The distribution of serum adiponectin against the BMI in obese patients

When comparing the adiponectin values with the glycosilated hemoglobin, we obtained, in group I, the following results: the adiponectin mean values were: 11.61 ± 7.55 $\mu\text{g/mL}$ and the values of the glycosilated hemoglobin were $9.25 \pm 2.22\%$. The distribution is negative correlated, statistically significant ($r = -0.34$; $p < 0.01$) (Figure 3).

The adiponectin distribution compared with HbA1c, in the second group, the correlation was negative and statistically not significant ($r = -0.29$; $p > 0.05$).

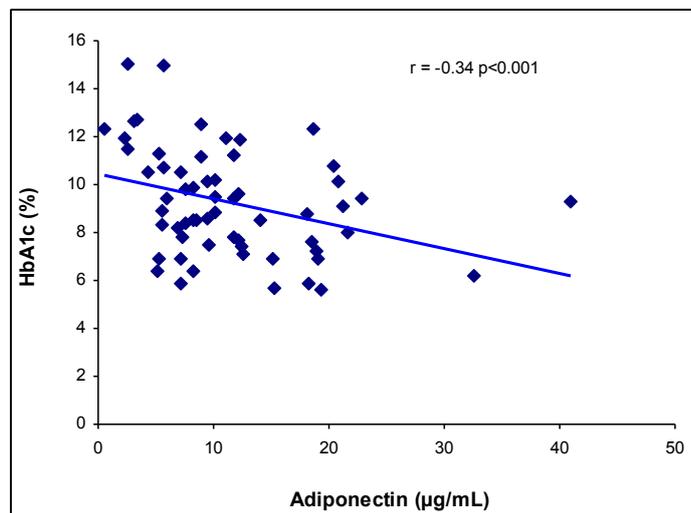


Figure 3

The distribution of the adiponectin values against the HbA1c in group I (diabetes mellitus).

Regarding the adiponectin values versus HbA1c in the control group, we obtained a negative correlation tendency. The low values of adiponectin were accompanied by high values of HbA1c. Even if it is not statistically significant, this glucidic parameter can express the postprandial glycemic increases that can not be identified through the determination of the fasting glycemia. It can indicate a tendency of the subjects to diabetes mellitus, being necessary a follow up evaluation.

As expected, HbA1C was significantly higher (9.25%), in type 2 diabetes mellitus patients (group 1) versus the other 2 groups. However an interesting observation is that of higher levels of HbA1C in the obese group (5.79%) versus the control group (4.86%). Although the differences are not significant, they suggest the presence of subclinical blood glycemia disregulation (probably a postprandial higher level of blood glucose) which was not evaluated in our study.

In conclusion, analyzing the adiponectin distribution as compared to the glucidic metabolic disorders, in the studied groups, there were obtained the following results: in the diabetic group, there was found a linear negative correlation against HbA1c; in the obese patients group and the control group there was not registered any correlation between the parameters studied. Due to the fact that adiponectin was negative correlated with HbA1c, we can state that adiponectin can be used as a marker for the control of the antidiabetic treatment. The adiponectin values were higher in the diabetic patients, with values of the HbA1c closer to normal.

Regarding the parameters of the lipid metabolism correlated with adiponectin, we obtained the following data: in group I: adiponectin versus total cholesterol $12.01 \pm 3.25 \mu\text{g/mL}$ vs. $5.53 \pm 0.97 \text{mmol/L}$ ($r = -0.009$, $p > 0.05$); adiponectin vs. HDL-cholesterol ($r = 0.42$, $p < 0.001$) (figure 4); adiponectin vs. LDL-cholesterol ($r = -0.20$, $p > 0.05$); adiponectin vs. triglycerides ($r = 0.12$, $p > 0.05$).

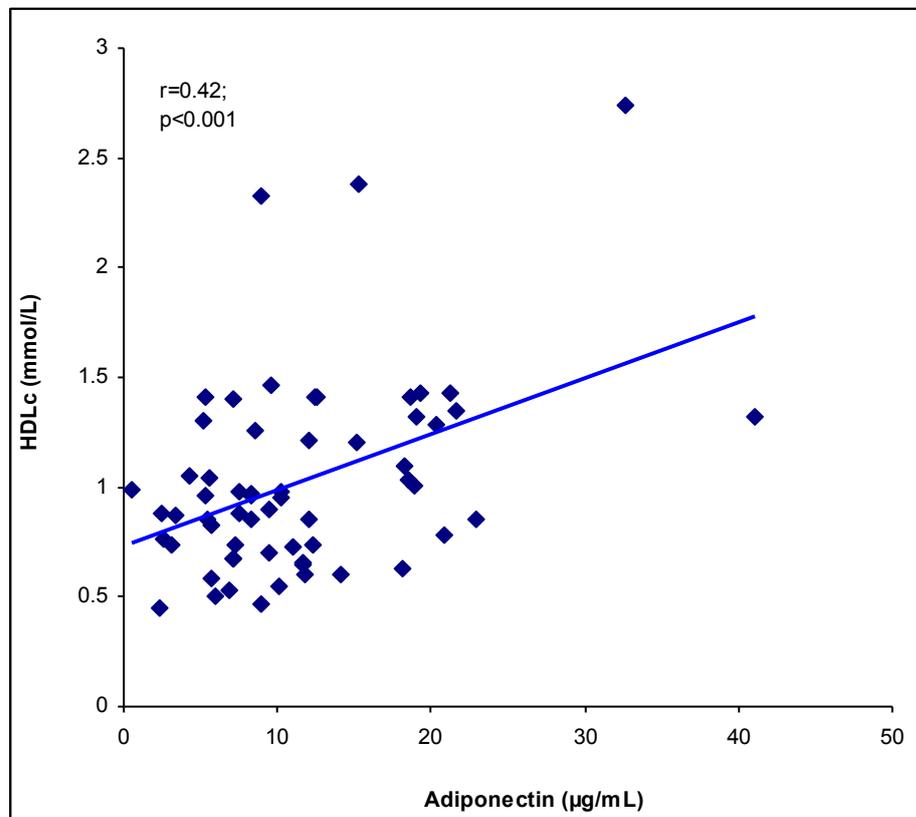


Figure 4

The distribution of serum adiponectin against HDLc in diabetic patients

Following the same comparison of adiponectin with the lipid metabolism parameters, in group II (obese group), we obtained a positive correlation with HDLc, ($r=0.70$, $p<0.001$), (Figure 5).

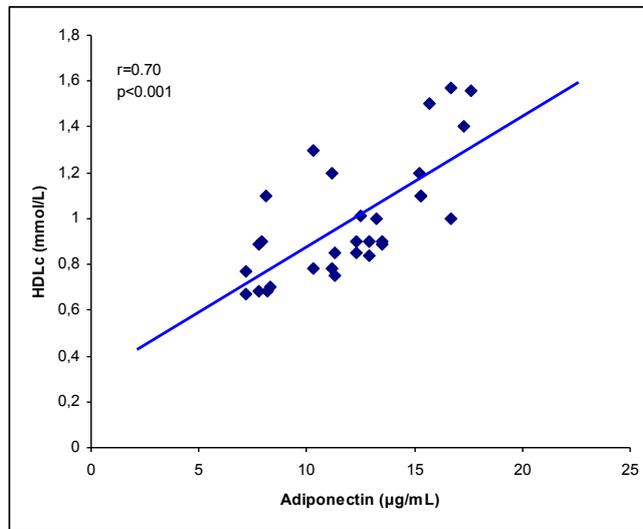


Figure 5

The distribution of serum adiponectin as compared to HDLc in obese patients

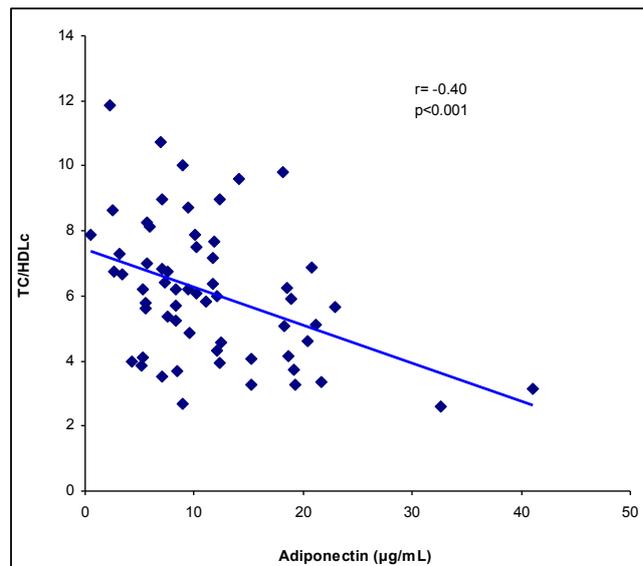


Figure 6

Distribution of serum adiponectin as compared to the TC/HDLc in diabetic patients

TC=total cholesterol

Statistically significant correlations, were obtained in the case of both diabetic and obese groups of patients, in the correlation of adiponectin versus the ratio TC/HDLc, ($r=-0.40$, $p=0.001$; $r=-0.67$ $p<0.001$) (Figures 6-7) and LDLc/HDLc($r=-0.41$, $p=0.001$; $r=-0.65$, $p<0.0001$) (Figures 8-9).

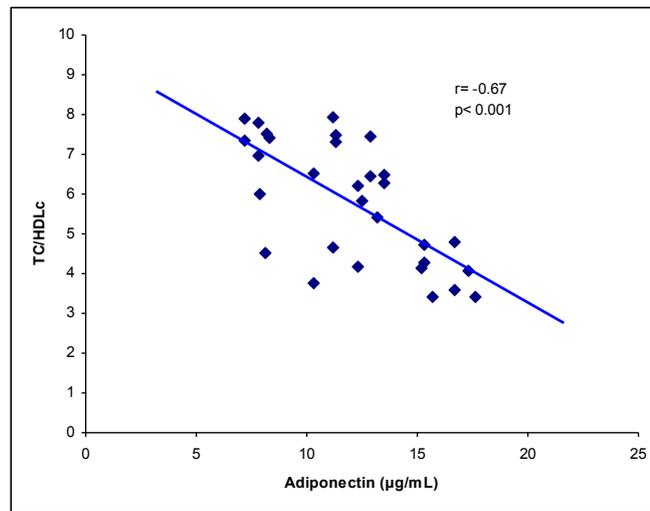


Figure 7

Distribution of serum adiponectin as compared to the TC/HDLc in obese patients

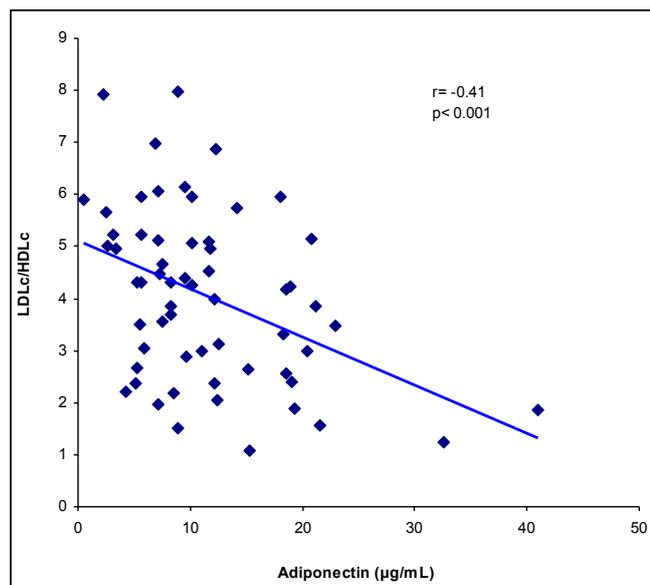


Figure 8

Distribution of serum adiponectin as compared to the LDLc/HDLc in diabetic patients

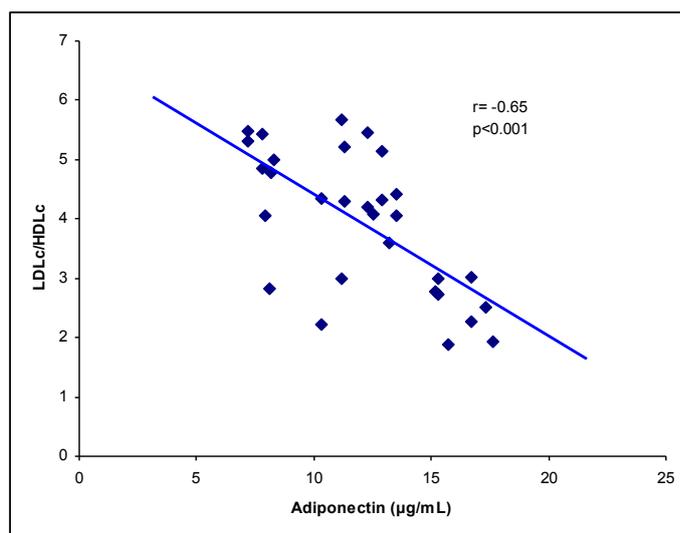


Figure 9

Distribution of serum adiponectin as compared to the LDLc/HDLc in obese patients

The adiponectin distribution for the control group, compared to the lipid metabolism parameters, showed that adiponectin was not linearly correlated to: HDLc ($r=0.11$, $p>0.05$), triglycerides ($r=0.04$, $p>0.05$); LDLc ($r=0.03$, $p>0.05$); total cholesterol ($r=0.14$, $p>0.05$); the ratio TC/HDLc ($r=-0.09$, $p>0.05$) and the ratio LDLc/HDLc ($r=-0.09$, $p>0.05$).

The correlation between obesity, hypertension and dyslipidemia previously reported [10]. Even though, the scientists continued to consider each of them as a different disease without establishing the etiopathogenic relations between these conditions.

In this study, we analyzed the correlation of adiponectin with obesity, diabetes and with the main lipoproteine fractions (total cholesterol, HDLc, LDLc and tryglicerides)

In diabetic patients (group I), the values of cholesterol were significantly higher versus the control ($p<0.0001$). For all other plasma lipoproteins (total cholesterol, HDLc, LDLc and tryglicerides) a significant positive correlation ($p<0.001$) has been found. These data are in agreement with other similar studies carried out by various research groups [21,25,19].

Other studies [21] regarding the lipid metabolism, presented the same results.

Numerous studies proved that adiponectin has a central role in lipid and carbohydrates metabolism. It was shown that the adiponectin infusion in mice, leads to the lowering of the liver expression of the enzymes

implicated in gluconeogenesis, inhibiting the glucose production. More than that, it was shown that adiponectin has anti-inflammatory effects [7,8].

It was also proven that saturated fatty acids increase the insulin resistance and unsaturated fatty acids have a protective effect in developing these metabolic disturbances [5,8,15]. Some studies investigated the effects of the diet composition on the adiponectin expression and its receptors. It was shown that a diet rich in calories lowers the serum adiponectin.

The hypoadiponectinemia was correlated with the incidence of cardiac ischemia, fatal in patients with chronic cardiac insufficiency. It was suggested that low concentrations of adiponectin are a marker of microangiopathy in diabetic patients.

Recent discoveries suggest that the adiponectin level could be useful for the coronary disease risk evaluation. It was described the fact that adiponectin is a PDGF (platelets derived growth factor)-linked protein and inhibits the vascular smooth muscle cells [14]. High levels of adiponectin suppress the atherosclerosis development in apoE deficient mice. The mechanism through which hyperlipemia (total cholesterol, HDLc, LDLc and triglycerides) and low plasma adiponectin levels have cumulative effects for the cardiovascular pathology development is not fully understood [14].

In our study we found negative correlations of serum adiponectin versus BMI in group I (diabetic patients) and group II (obese patients), but we didn't find correlations of serum adiponectin with BMI in the control group. This could be explained by the fact that the control group included only normoponderal subjects.

After comparing the serum concentrations of adiponectin with lipid metabolism parameters, we obtained a positive correlation in all the studied groups, in regard to the HDLc level, suggesting that adiponectin has a protective role on the cardiovascular system. When comparing serum adiponectin with serum triglycerides, the correlation was negative.

We obtained negative correlations of serum adiponectin with HbA1c, in all the studied groups, including the control, reason for us to state that adiponectin can be used as marker in diagnosing and monitoring the diabetic patients.

Conclusions

In the last decades it was given a great importance to the endocrine function of the adipose tissue and, the adipokines production, as well as to the role of this tissue in the inflammatory reaction added to metabolic functions. In our study, the circulating serum adiponectin levels showed

significant lower values for the diabetic and obesity groups versus the control group.

In contrast, serum adiponectin was positively correlated to the HDLc (a lipoprotein with antioxidant properties), showing that adiponectin has an anti-inflammatory and protective effect in various tissues like liver, skeletal muscles and in the pancreatic β cells. A low HDLc and a low adiponectin level can predict the decompensation of blood glucose regulations in obese individuals and the protective character of adiponectin, both in the diabetes and obesity groups of patients.

Finally, because in diabetic patients, the adiponectin values were negatively correlated to the HbA1c level (%), the serum adiponectin level can be a potential marker for the metabolic monitoring of diabetic patients.

References

- 1.*** ADA - Dyslipidemia Management in Adults With Diabetes. *Diabetes Care* 2004 vol 24 Suppl 1
- 2.*** National Heart, Lung and Blood Institute in cooperation with The national Institute of diabetes and Digestive and Kidney Diseases, Clinical Guidelines on the Identification, Evaluation and Treatment of overweight and obesity in Adults, the evidence report, *NIH publication* 1998, september No. 98-4083.
- 3.Beaser RS, Joslin's Diabetes Deskbook, A guide for primary care providers, second edition, Lippincott Williams & Wilkins, 2007, 68-75.
- 4.Berg AH, Combs TP, Du X, Brownlle M., Scherer PE., The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med*, 2001, 7(8):947-953
- 5.Blüher M, Unger R, Rassoul F., Richter V., Paschke R., Relation between glycaemic control, hyperinsulinaemia and plasma concentrations of soluble adhesion molecules in patients with impaired glucose tolerance or type II diabetes. *Diabetologia* 2002;45:201-216.
- 6.Boutin Ph., Dina C., Vasseur F., Dubois S., Corset L., Séron K., Bekris L., Cabellon J., Neve B., Vasseur-Delannoy V., Chikri M., Charles MA., Clement K., Lernmark A., Froguel Ph., GAD2 on Chromosome 10p12 is a candidate gene for human obesity, *Plos Biol* 2003 3:361-371
- 7.Bullen JW Jr, Bluher S., Kelesidis T., Mantzoros CS., Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. *Am J Physiol Endocrinol Metab* 2007, 292(4):E1079-E1086
- 8.Bullo M, Salas-Salvado J, Garcia-Lorda P., Adiponectin expression and adipose tissue lipolytic activity in lean and obese women. *Obesity Surgery* 2005;15:382-386
- 9.Corbetta S, Bulfamante G, Cortelazzi D., Barresi V., Cetin I., Mantovani G., Bondioni S., Beck-Peccoz P., Spada A., Adiponectin expression in human fetal tissues during mid- and late gestation, *J Clin Endocrinol Metab*, 2005; 90:2397-2402
10. Cucuianu M., Brudașcă I., Contribuții al medicinei Clujene la studiul unor mecanisme implicate în patogeneza sindromului metabolic. *Clujul Medical* 2008, vol.LXXXI nr. 1, 7-17.
11. De Oliveira C., de Mattos ABM., Biz C., Oyama LM., Ribeiro EB., Oller do Nascimento CM., High-fat diet and glucocorticoid treatment cause hyperglycemia associated with adiponectin receptor alterations. *Lipids in Health Disease* 2011;10:11-24
12. Dray C, Valet P, Castan-Laurell I. Adipokines: quelles nouvelles. *Obes* 2008;3:33-41
13. Fischbach F., A manual of laboratory and diagnostic tests, 7th ed. Lippincott Williams & Wilkins, 2004, 426, 532-533.

14. Fortuño A., Rodriguez A., Gómez-Ambrosi J., Frühbeck G., Diez J., Adipose tissue as an endocrine organ: role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. *J. Physiol. Biochem.* 2003;59(1):51-60
15. International Diabetes Federation. The IDF Consensus Worldwide Definition of Metabolic Syndrome 2006.
16. Junqueira LC, Carneiro J., Histologie, tratat și atlas, ediția a 11-a, Ed Medicală Callisto, București, 2008, 123-127.
17. Kadawaki T., Yamauchi T., Adiponectin and adiponectin receptors. *Endocrine Reviews*, 2005;26(3):439-451
18. Katsiogiannis S, Kapsogeorgou EK, Manoussakis MN, Skopouli FN. Salivary gland epithelial cells: a new source of the immunoregulatory hormone adiponectin. *Arthritis Rheum* 2006, 54:2295-2299
19. Li J., Liao C., Su H., Peng Q., Zhang Z., Yan S., Yang Q., The corelationship among adiponectin, high sensityve C-reactive protein and triacylglycerol level in healthy young persons. *Lipids Health Dis* 2011;10:109
20. Lu J-Y, Huang K-C, Chang L-C., Huang Y-S., Chi Y-C., Su T-C., Chen C-L., Yang W-S., Adiponectin: a biomarker of obesity-induced insulin resistance in adipose tissue and beyond. *J Biomed Sci* 2008;15:565-576.
21. Nishida M, Funahashi T, Shimomura I., Pathophysiological significance of adiponectin. *Med Mol Morphol* 2007; 40:55-67
22. Piñeiro R., Iglesias MJ., Gallego R., Raghay K., Eiras S., Rubio J., Diéquez C., Gualilo O., González-Juanatey JR, Lago F., Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett* 2005, 579:5163-5169
23. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in adults (Adult Treatment Panel III), final report, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institute of Health, *NIH Publication No. 02-5215*, September, 2002
24. Trayhurn P., Beattie JH., Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proccedings of the Nutrition Society.* 2001; 60:329-339.
25. Ukkola O., Santaniemi M., Adiponectin: a link between excess adiposity and associated comorbidities? *J Mol Med* 2002; 80:696-702
26. Voet DJ, Voet JG, Pratt CW. Principles of Biochemistry 3rd edition. Wiley & Sons, Inc. 2008, 711-714, 806
27. World Health Organization. Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part I: Diagnosis and Classification of Diabetes Mellitus (PDF) 1999.
28. Yamauchi T, Kamon J, Minokoshi Z, Ito Y., Waki H., Uchida S., Yamashita S., Noda M., Kita S., Ueki K., Eto K., Akanuma Y., Froguel P., Foufelle F., Ferre P., Carling D., Kimura S., Nagai R., Kahn BB., Kadowaki T., Adiponectin stimulated glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinaze. *Nat Med.* 2002, 8(11):1288-1295
29. Yokota T, Meka CS, Medina KL., Igarashi H., Comp PC., Takahashi M., Nishida M., Oritani K., Miyagawa J-I., Funahashi T., Tomiyama Y., Matsuzawa Y., Kinkade PW., Paracrine regulation of fat cell formation in bone marrow cultures via adiponectin and prostaglandins *J Clin Invest* 2002, 109:1303-1310

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Erratum

Regarding the article titled “The optimization of prolonged release multiparticulate tablets with betahistine dihydrochloride – Part II”, by Radu Cazacincu et al., published in Farmacia volume 60(1), 2012, it has to be noted that citric acid should be disregarded everywhere it appears in the article.