

RELATIONSHIP BETWEEN ADIPONECTIN AND CERTAIN METABOLIC PARAMETERS IN DIABETIC AND CARDIOVASCULAR DISEASE PATIENTS

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The clinical observation showed the association of the cardiovascular condition and diabetes with high blood pressure, dyslipidemia and atherosclerosis. The white adipose tissue can be seen as an endocrine organ that secretes several soluble factors, called adipocytokines or adipokines, like: fatty acids, cytokines (TNF- α , IL-6), adipocytokines (adiponectin, leptin, resistin, and more recently, visfatin). 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 adiponectin with obesity, diabetes and dyslipidemia. We studied a total number of 120 subjects. These were divided into three groups, depending on their metabolic conditions. Group I – 60 patients diagnosed with type 2 diabetes, group II – 40 patients diagnosed with cardiovascular disease 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, $t = 9.13$; $p < 0.001$.

Key words: adiponectin, diabetes mellitus, dyslipidemia, obesity.

INTRODUCTION

The adipose tissue is distributed all over the organism and can be considered one of the biggest organs of the body, 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 cardiovascular diseases, diabetes and dyslipidemia. The biomolecules secreted by the adipose tissue could explain the relationship between obesity, insulin-resistance and the dysfunction of pancreatic β -cells [14,16].

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 the 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 [9,11,12]. Obese patients, type 2 diabetic, insulin resistant, dyslipidemic 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 [3,4,11]. 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 goal 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 120 subjects. These were divided in three group, depending on the fundamental condition. Group I – 60 patients with type 2 diabetes, group II – 40 patients with cardiovascular diseases and a control group – 20 normal weight, healthy voluntaries. (Table I)

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

Group II included 40 cardiovascular diseased patients, without diabetes. The inclusion criteria was based on the high blood pressure, cardiac ischemia

according to the recommendations of the European Society of Cardiology 2007.

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	22/18	10/10
Age (years)	60.7 \pm 11.55	59.8 \pm 12	41 \pm 11.17
BMI (kg/m^2)	29.03 \pm 4.3	26.11 \pm 5.02	23.91 \pm 3.44

The control group included subjects that were clinically healthy and had normal weight values (BMI<25 kg/m^2). [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. 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 laboratory of the Biochemistry Department 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, spectrophotometrical methods using the analysis kit from Diagnosticum Hungary, being processed on 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 with glucose-6 phosphate using the analysis kit from Spin React Spain processed on 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 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. To determine the correlation, we calculated 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, $p < 0.05$.

In all the groups, including the control one, we determined the adiponectin levels.

RESULTS AND DISCUSSION

Comparing the serum concentrations of adiponectin with the BMI, for the whole diabetic 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, overweight and obese.

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 second group, the adiponectin values were significantly lower when compared to the control group, $t = 6.99$; $p < 0.0001$.

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

	BMI (Kg/m ²)	Adiponectin (µg/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	< 25	20,92 ± 7,37	5,18 ± 0,51
	25 – 29,9	14,97 ± 6,59	5,61 ± 0,79
	≥ 30	9,60 ± 2,63	5,6 ± 0,41
Control group	< 25	33,99 ± 11,62	4,86 ± 0,41

Table II. The characteristics of lipid metabolic profile in the studied groups.

Plasma parameters	Group I (n=60)	Group II (n=40)	Control group (n=20)
Cholesterol (mmol/L)	5.53±0.97	4,81±0,53	4,13±0,35
LDLc (mmol/L)	3.62±0.81	2,93±0,69	2,17±0,42
HDLc (mmol/L)	1.02±0.44	1,25±0,34	1,51±0,22
Triglycerides (mmol/L)	1.94±0.96	1,47±0,54	0,92±0,31
Cholesterol/HDLc	6.1±2.11	4,12±1,16	2,78±0,49
LDLc/HDLc	4.05±1.65	2,55±1,03	1,48±0,43

Regarding the adiponectin distribution against BMI in diabetic subjects, this was negatively correlated and statistically significant ($r = -0.47$; $p < 0,001$) (figure 1).

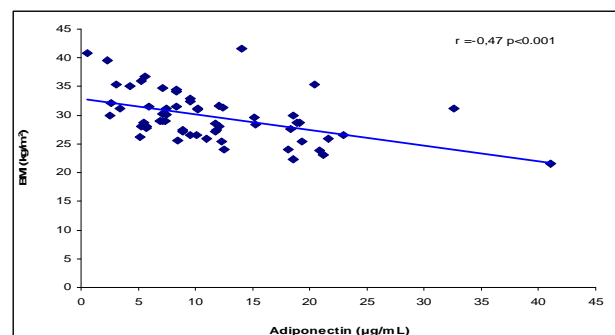


Figure 1. The distribution of adiponectin against the BMI in diabetic patients

The same negative correlations has been found between adiponectin and BMI in the group 2 (cardiovascular diseased individuals), and statistically significant (figure 2) ($r = -0.54$; $p < 0.001$). As expected, the adiponectin distribution in the control group (normal weight

subjects) wasn't correlated with BMI ($r=-0.008$; $p>0.05$).

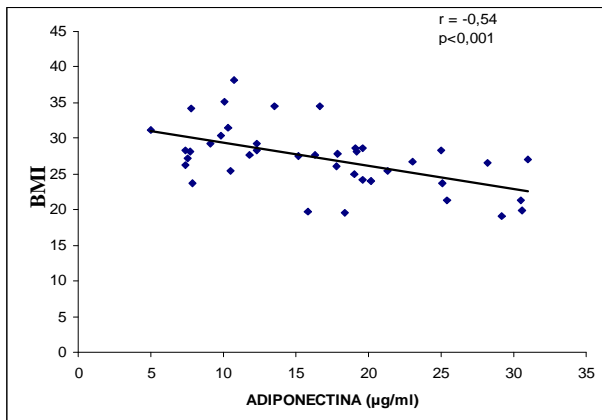


Figure 2. The distribution of adiponectin against the BMI in cardiovascular diseased patients

When comparing the adiponectin values with the glycosilated hemoglobin, we obtained, in group I, the following results: the adiponectin mean values were: $11.61 \pm 7.55 \mu\text{g/mL}$ 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 as compared with HbA1c, in the second group subjects there wasn't any correlation ($r=-0.11$; $p>0,05$).

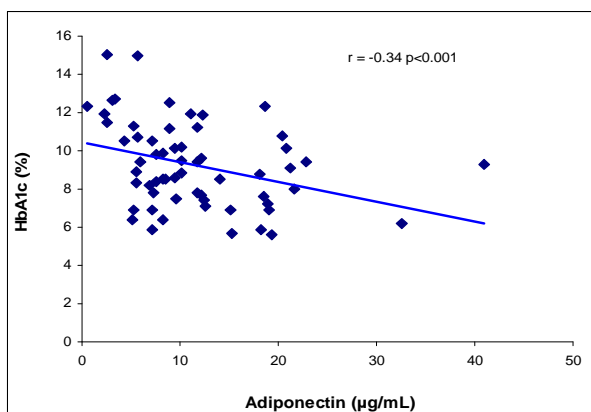


Figure 3. The distribution of the adiponectin values against the HbA1c in group I (diabetes mellitus)

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 ($p<0.0001$). However an interesting observation is that of higher levels of HbA1C in the cardiovascular group (5.49%) *versus* the control group (4.86%) ($p<0.001$). These differences suggest the presence of subclinical blood glycemia disregulation (probably a postprandial higher level of blood glucose) which however was not evaluated in our study (Figure 4).

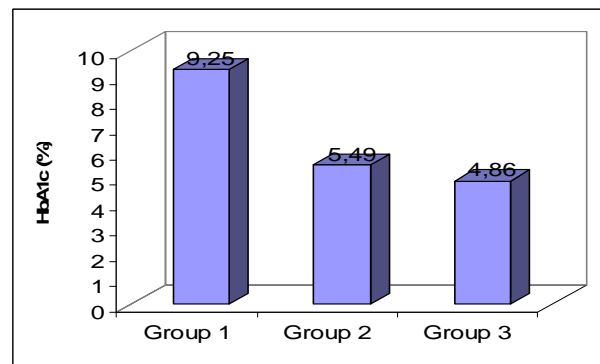


Figure 4. Mean values of HbA1c

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 cardiovascular diseased patients group and the control there was no linearly correlation between the parameters studied. Due to the fact that adiponectin was negative correlated with HbA1c, in diabetic patients, we can state that adiponectin could 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 5); adiponectin vs. LDL-

cholesterol ($r = -0.20$, $p > 0.05$); adiponectin vs. triglycerides ($r = 0.12$, $p > 0.05$).

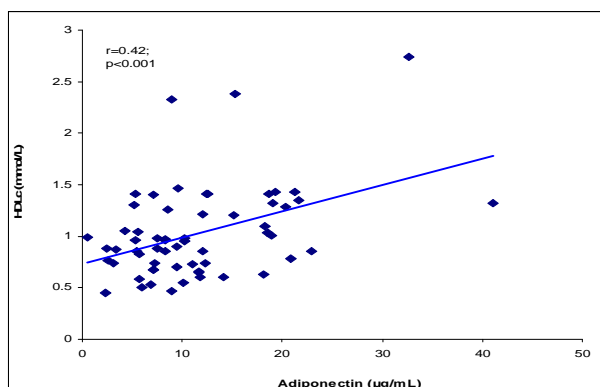


Figure 5. The distribution of adiponectin against HDLc in diabetic patients

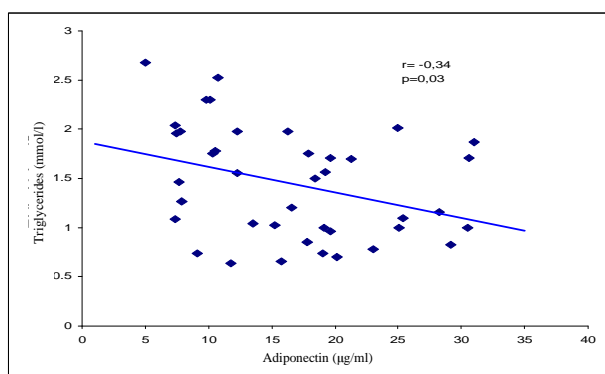


Figure 6. The distribution of adiponectin as compared to triglycerides in cardiovascular diseased patients

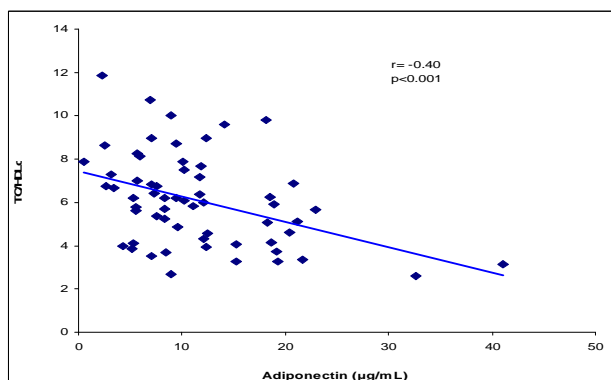


Figure 7. Distribution of adiponectin as compared to the TC/HDLc in diabetic patients. TC=total cholesterol

Following the same comparison of adiponectin with the lipid metabolism parameters, in group II (cardiovascular group), we obtained a negative correlation with serum triglycerides, statistically significant, ($r = -0.34$, $p < 0.05$), (figure 6). With the other lipidic metabolism parameters there wasn't obtained any correlation.

Statistically significant correlations, were obtained in the case of diabetic group of patients, in the correlation of adiponectin versus the ratio TC/HDLc, ($r = -0.40$, $p = 0.001$) (figure 7) and LDLc/HDLc ($r = -0.41$, $p = 0.001$) (figure 8).

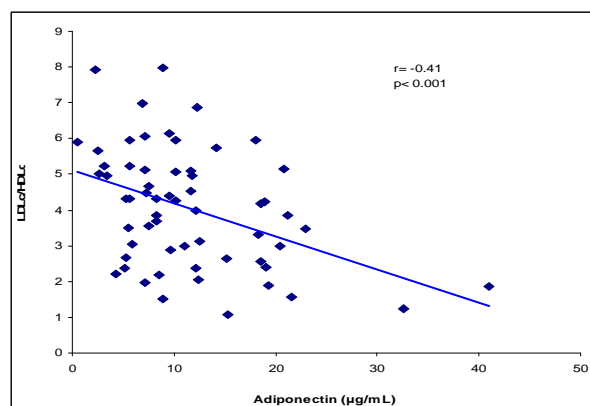


Figure 8. Distribution of adiponectin as compared to the LDLc/HDLc in diabetic patients

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 cardiovascular diseases, diabetes mellitus, 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 cardiovascular diseases, diabetes and with the main lipoprotein fractions (total cholesterol, HDLc, LDLc and triglycerides)

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 triglycerides) 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.

The mechanism through which the hyperlipemia and the low plasma adiponectin

have cumulated effects in the development of the cardiovascular pathology it is not fully elucidated. [14]

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 [7,8]. More than that, it was shown that adiponectin has anti-inflammatory effects.

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 tryglicerides) and low plasma adiponectin levels have cumulative effects for cardiovascular pathology development, it is not fully understood [14].

In our study we found negative correlations of adiponectin versus BMI in group I (diabetic patients) and group II (cardiovascular diseased patients), but we didn't find correlations of adiponectin with BMI in the control group. This could be explained by the fact of the control group included only normoponderal subjects. These results show the effect of body fat on the values of serum adiponectin.

After comparing the serum concentrations of adiponectin with lipid metabolism parameters, we obtained a positive correlation in diabetic patients, compared to the HDLc level and between

adiponectin and the TC/HDL and HDL/LDL, negative correlation, suggesting that adiponectin has a protective role on the cardiovascular system. In patients with cardiovascular diseases, we found negative correlation of adiponectin against triglycerides.

The recent discoveries suggest that the adiponectin values could help to the evaluation of the coronary disease risk, it was described the fact that adiponectin as a binding protein of the PDGF (plateletes derived growth factor) and inhibates the proliferation and migration of the smooth muscular cells. [14,27]

We obtained negative correlations of adiponectin in comparing HbA1c, in all the group, including the control, reason for us to state that adiponectin could be used as marker in diagnosing the diabetic patients.

CONCLUSIONS

In the last decades it was given a great importance to the endocrine function of the adipose tissue, the adipokines production as well as to the role of this tissue in the inflammatory reaction added to metabolic function.

In our study, circulating adiponectin levels showed significant lower values in the diabetic and cardiovascular diseased groups *versus* the control group.

The lowest adiponectin value was found in obese diabetic patients followed by the patients with cardiovascular disease and obesity, fact that certifies the implication of obesity in the etipatogenicity of the two conditions.

The cardiovascular protective effect of adiponectin is proven through the positive relation between this cytokine and HDLc in diabetic patients and control group, HDLc being recognized as a cardiovascular protector.

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

It could be predicted that in the future there could be developed adiponectin treatments due to its antiatherosclerotic effects.

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