Plasma adiponectin and E-selectin concentrations in patients with coronary heart disease and newly diagnosed disturbances of glucose metabolism

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Abstract

Purpose: Adiponectin is a fat derived hormone, which enhances insulin sensitivity. In experimental studies adiponectin was shown to have antiatherogenic properties by suppressing endothelial expression of adhesion molecules. Therefore, the aim of the study was to evaluate plasma adiponectin and E-selectin concentrations in patients with coronary artery disease and impaired glucose metabolism and evaluation of their relationship with selected anthropometric, biochemical and clinical parameters.

Material and methods: The study group consisted of 62 patients with coronary heart disease, without previous diagnosis of diabetes mellitus (mean age 48.6±6.0 years; mean BMI 28.6±3.13 kg/m^2). In the studied group the OGTT with glucose and insulin estimation was performed and insulin resistance index (HOMA-IR) was calculated. In the fasting state, the plasma adiponectin, soluble form of E-selectin, HbA1c and lipid parameters were estimated.

Results: Adiponectin concentration was not different in patients with type 2 diabetes mellitus and impaired glucose tolerance (n=36) in comparison to the group with normal glucose tolerance (n=26). There was also no difference in adiponectin concentration in relation to atherosclerosis progression. There was no significant correlation between adiponectin and calculated insulin resistance index, while there was marked inverse correlation between adiponectin and BMI (r=-0.30; p=0.018), body weight (r=-0.33; p=0.008), E-selectin (r=-0.263; p=0.039), TG concentration (r=-0.27; p=0.036), duration of coronary heart disease (r=-0.33; p=0.009) and borderline significance with ejection fraction (r=-0.268; p=0.06).

Conclusions: Our study supports the hypothesis that adiponectin could be recognised as a protective protein for the development of atherosclerosis.

Key words: adiponectin, E-selectin, coronary heart disease.

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Introduction

Adiponectin is a protein of 30kD, synthesized predominantly by adipose tissue [1]. In recent years, a function of adiponectin was associated mainly with the insulin resistance. The data provided showed, that adiponectin concentration positively correlated with insulin sensitivity measured by the euglycemic clamp, as well as with the activity of insulin receptor [2]. Also, adiponectin function is connected with lipid metabolism and dyslipidemia. It was shown that adiponectin is negatively related to HDL-cholesterol and positively to triglycerides (TG) concentration [3]. Low adiponectin concentration was observed in obesity [4,5], type 2 diabetes [3], coronary heart disease (CHD) [6], and in hypertension [7]. In addition, the experimental studies showed, that adiponectin had not only metabolic, but also antiatherogenic and antiinflammatory effect [8,9]. There was observed, that adiponectin inhibited atherogenesis probably by a influence on the proinflammatory cytokine secretion and by a inhibition of the endothelial expression of adhesion molecules [9].

Epidemiological studies show, that cardiovascular diseases are the main cause of premature mortality among type 2 diabetic patients [10]. In type 2 diabetes the accelerated atherogenesis is observed and diabetes per se is considered as the independent risk factor of CHD [11]. Our previous studies indicated, that in obese patients, with normal glucose metabolism, the concentration of sICAM-1 was significantly increased and correlated with the insulin resistance and with concentration of proinflammatory cytokines, like tumor necrosis factor-α (TNF-α) [12]. Furthermore, in patients with type 2 diabetes or impaired glucose tolerance (IGT) and CHD the increased concentration

Table 1. **The clinical characteristics of studied group with coronary heart disease (CHD)**

	N (%)
Age (years)	48.6 (±6.0)
BMI (kg/m^2)	28.6 (±3.13)
Hypertension	21 (33%)
History of myocardial infarction	37 (57%)
Family history of CHD	32 (52%)
Smoking	32 (52%)

of E-selectin and VCAM-1 concentration was also noticed [13]. There are several studies concerning adiponectin concentrations in patients with type 2 diabetes mellitus and CHD. For instance, low adiponectin concentration was observed in type 2 diabetic patients with CHD in Japanese population [3].

The aim of the present study was the evaluation of adiponectin concentration in patients with newly diagnosed type 2 diabetes mellitus or IGT and CHD in comparison to the group without disturbances of glucose metabolism. We also aimed to asses the relationship between adiponectin concentration and E-selectin and selected anthropometric, biochemical and clinical parameters.

Material and methods

Sixty two male patients, without history of type 2 diabetes mellitus, with stable CHD were recruited for the study. The patient was considered to have CHD if he had history of myocardial infarction or the diagnosis was based on the result of coronary angiography. In the studied group 57% of the patients had history of myocardial infarction, 52% were smokers. Clinical characteristic of the study population is presented in *Tab. 1*. The consent for the study was obtained from all participants, and the protocol was approved by Ethics Committee of Medical University in Białystok.

In all subjects the standard oral glucose tolerance test (OGTT) after 75 g oral glucose was performed. Glucose and insulin concentrations were measured at 0 min, 60 min and 120 min during the OGTT. Type 2 diabetes mellitus or IGT was diagnosed in accordance of the WHO guidelines from 1999. Plasma glucose was measured immediately by the oxidase method on automatic glucose analyzer (YSI START PLUS 2300) and samples for plasma insulin estimation were frozen in -20°C, until assayed. Plasma insulin concentration was measured using IRMA method (Polatom, Świerk, Poland).

Before the OGTT, blood samples were drawn also for plasma measurements of adiponectin (RIA, Linco Research Inc., USA), selectin E (ELISA, R&D System, USA), HbA1c (HPLC-BIO-RAD, Germany), cholesterol, HDL-cholesterol and TG concentrations (enzymatic method-ANALCO-CBG, Poland). Insulin sensitivity was assessed by indirect indexes: insulin resistance index – HOMA-IR (Homeostasis Model Assessments) based on fasting glucose and insulin concentration [14] and by oral glucose tolerance (IS-OGTT) test according to Matsuda and De Fronzo [15].

Table 2. **Plasma glucose and insulin concentrations during oral glucose tolerance test and indices of insulin resistance in studied patients**

	Patients with type 2 diabetes and IGT n=36	Patients with normal glucose tolerance n=26
Glucose 0 min (mg/dl)	95.2±14.9	85.6±10.6*
Glucose 60 min (mg/dl)	193.1±41.0	139.0±30.4*
Glucose 120 min (mg/dl)	173.5±33.5	107.5±19.6*
Insulin 0 min (mU/l)	11.6± 8.09	8.9±8.6
Insulin 60 min (mU/l)	85.3±82.0	106.1±68.0
Insulin 120 min (mU/l)	92.4±82.4	48.0±46.4 p=0.05
HOMA-IR	2.04±2.36	2.76±2.00
IS-OGTT	4.22±2.4	8.13±5.02*

*p<0.05 patients with type 2 diabetes and IGT in comparison to the group with normal glucose tolerance

Statistical analysis was performed by using STATISTICA Stat-Soft 5.0 program. The comparison of data between the groups was done with the Student t-test. To analyze factors correlated with adiponectin, Pearson's correlation index was used.

Results

In the studied group, 6 of the patients were diagnosed to have type 2 diabetes and 30 patients to have IGT, basing on the results of the oral glucose tolerance test. In whole group, 58% of patients presented disturbances of glucose metabolism. Plasma glucose concentrations during OGTT was statistically significantly higher among patients with disturbances of glucose metabolism (0 min; $p<0.01$, 60 min; $p<0.001$, 120 min; $p<0.001$) (*Tab. 2*). Also, the insulin sensitivity index calculated from the plasma glucose and plasma insulin level during oral glucose tolerance test was significantly lower in this group ($p=0.0004$) (*Tab. 2*). HOMA-IR did not differ between studied groups.

Plasma adiponectin concentrations in patients with diabetes and IGT were not significantly different compared with patients with normal glucose tolerance (*Tab. 3*). Also, when the groups with type 2 diabetes and IGT were considered separately, there were no differences in adiponectin concentration between examined groups (type 2 diabetes – 5.41±0.38 μg/ml, IGT – 6.01±0.81 μg/ml, patients with normal glucose tolerance – 6.22±0.86 μg/ml). There was also no difference in adiponectin concentration in relation to atherosclerosis progression. However, the group of patients with disturbances of glucose metabolism had significantly higher BMI ($p=0.01$), (*Tab. 3*).

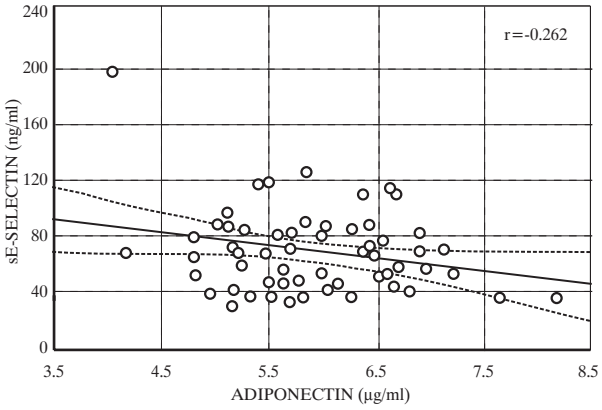
E-selectin concentration was significantly higher in patients with type 2 diabetes mellitus and IGT ($p=0.014$) (*Tab. 3*). There were negative statistically significant correlations between plasma adiponectin level and BMI ($r=-0.30$; $p=0.018$), E-selectin level ($r=-0.26$; $p=0.039$) (*Fig. 1*), duration of ischemic heart disease ($r=-0.33$, $p=0.009$), TG concentration ($r=-0.27$; $p=0.036$) and of borderline significance with ejection fraction ($r=-0.27$; $p=0.06$).

Table 3. **Adiponectin, E-selectin plasma concentrations and selected clinical and metabolic parameters in studied group**

	Patients with type 2 diabetes and IGT n=36	Patients with normal glucose tolerance n=26
Adiponectin (μg/ml)	6.0±0.86	5.91±0.78
E-selectin (ng/ml)	76.2±32.4	58.4±22.3*
Age (years)	47.0±5.75	46.6±6.45
BMI (kg/m^2)	29.5±2.88	27.5±3.2*
HbA1c (%)	5.6±0.49	5.36±0.56
Total cholesterol (mg/dl)	195.6±39.4	210.7±27.1
LDL cholesterol (mg/dl)	127.0±34.7	140.8±24.9
HDL cholesterol (mg/dl)	32.6±11.3	33.5±12.7
TG (mg/dl)	179.2±100.8	177.2±96.0

*p<0.05 patients with type 2 diabetes and IGT in comparison to the group with normal glucose tolerance

Figure 1. **Correlation between plasma adiponectin and E-selectin concentration in studied groups**



Discussion

In our observation, we found IGT in more than 50% of patients with CHD, without previous history of type 2 diabetes mellitus. Similar results were obtained in our study with large cohort of patients with CHD [16], what supports the notion that the disturbances of glucose metabolism are considered to be an independent risk factor in the arteriosclerosis development. In the present study we did not observe any differences of adiponectin concentrations between group of male patients with impaired glucose metabolism and CHD in comparison to the group with normal glucose tolerance. It should be pointed out, that in the present study the comparison was done among group of male patients with CHD according to appearance of impaired glucose tolerance. Hotta et al. showed statistically significant lower plasma adiponectin level in patients with type 2 diabetes and CHD, than in patients with diabetes without CHD [3]. We also noticed that plasma adiponectin concentration was also lower in patients with diabetes, but probably because of the small number of patients with type 2 diabetes (n=6), this association did not reach statistical significance (p=0.11). Yaturu et al. found a statistically significant decrease in adiponectin level in the patients with prediabetes defined as a IGT, and the patients with type 2 diabetes in comparison to the controls [17]. Furthermore, in the prospective study of 745 male patients with type 2 diabetes, high plasma adiponectin level was associated with a significantly lower risk of the cardiovascular events in 5-years observation [18]. Authors suggested that the increased adiponectin levels are associated with a moderately decreased CHD risk in the diabetic men. In contrast, the results from British Women's Heart and Health Study did not show the association of adiponectin with future risk of CHD in women [19]. However, other investigators, found a lower adiponectin concentration in the patients with CHD comparing to control group, in groups of patients without diabetes [5,20]. The latest data showed, that also in type 1 diabetes, the higher adiponectin level was associated with a lower risk of CHD [21]. The review of the data showed the connection of hypoadiponectinaemia and CHD [3,5,17,18,20]. Additionally, in this study we also observed the negative correlation between the plasma adiponectin concentration and duration of CHD.

The next question, which needs an explanation is a mechanism of the adiponectin antiatherogenic effect. It is known, that adiponectin is the protein synthesized predominantly by adipose tissue and plays an important role in the glucose and lipids metabolism [22]. As we mentioned at the beginning, adiponectin function is connected mainly with insulin sensitivity. In recent years more attention is paid to adiponectin influence on blood vessels. Studies *in vivo* and *in vitro* showed, that adiponectin concentration correlated with vasodilatation and that this effect was independent of insulin [23,24]. Studies *in vitro* also indicated, that adiponectin had anti-inflammatory effect. Adiponectin inhibits TNF-α stimulated expression of adhesion molecules on endothelial cells and thus prevents the first stages of the development of atherosclerosis [8,25]. In the present study the concentration of soluble form of E-selectin in plasma was measured in all the patients, and it was statistically significantly higher in the group with disturbances of glucose metabolism. Moreover, the investigated adhesion molecule negatively correlated with adiponectin concentration.

In the performed evaluation we observed also a correlation between plasma adiponectin concentration and ejection fraction, of borderline statistical significance. In the previous studies there are only few information about relationship between adiponectin and ejection fraction. In one of the studies, Huang et al. examined the association between those parameters, and they did not observe any correlation between adiponectin and ejection fraction. However, it should be noticed, that they evaluated different group of patients with chronic renal insufficiency treated by peritoneal dialysis and hemodialysis [26].

The obtained results are consistent with clinical data and identify the adiponectin as an important factor, preventing cardiovascular diseases.

Conclusions

Our study supports the hypothesis that adiponectin is a protein with antiatherogenic activities.

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