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Obesity and adiponectin in acute myocardial infarction

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Abstract

Background: *Low plasma concentration of adiponectin, a hormone-like peptide secreted by adipose tissue, is detected in obesity and in coronary artery disease. The aim of the study was to assess the impact of obesity on adiponectin and the relation of adiponectin to the anthropometric parameters and cardiovascular risk factors in men with acute myocardial infarction.*

Methods: *Two groups of patients with first acute myocardial infarction were analyzed: 40 obese and 40 non-obese men. Waist and hip circumferences and waist-to-hip ratio, C-reactive protein (CRP), uric acid, fasting glucose, lipid profile and adiponectin were measured.*

Results: *Mean level of adiponectin was significantly lower in obese than non-obese patients (6.80 μg/ml ± 4.31 vs. 11.18 μg/ml ± 7.19; $p < 0.01$). Adiponectin levels correlated negatively with all anthropometric measurements, the most significantly with waist circumference, with systolic blood pressure, fasting glucose, triglyceride levels, CRP, uric acid and positively with age and HDL-cholesterol. Adiponectin level was significantly associated with HDL-cholesterol, waist circumference and with trigliceryde levels and these independent variables explained 39% of the plasma adiponectin variability.*

Conclusions: *In patients with acute myocardial infarction obesity is related to decreased adiponectin. Low adiponectin level is associated with atherogenic lipid profile and higher levels of inflammatory markers.* (Cardiol J 2007; 14: 29–36)

Key words: obesity, adiponectin, myocardial infarction

Introduction

Excess body fat, particularly abdominal adiposity, not only carries a cluster of cardiovascular risk factors [1] but is itself an independent cardiovascular risk factor [2–4]. Obesity in patients with established coronary artery disease worsens the prognosis [5]. It has been revealed that body mass index (BMI) is associated with acute coronary syndromes [6, 7]. Recent evidence suggests that adipose tissue is both a storage site for fat and an active endocrine and paracrine system. It secretes adipokines, hormone-like peptides which have an impact on glucose and lipid metabolism, the inflammatory process and other bioactivities [8–10]. Adiponectin is regarded as a protective adipokine associated with lower risk of myocardial infarction [11]. A wide range of adiponectin levels (1.9–17.0 μg/ml) has been

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detected in healthy subjects [12]. Decreased plasma adiponectin concentration is detected in obesity [12, 13] and it is associated with cardiovascular risk factors such as insulin resistance, impaired glucose metabolism, arterial hypertension, decreased blood concentration of high-density lipoprotein cholesterol (HDL-CH) and increased concentration of triglycerides (TG) [14–17]. Adiponectin has an impact on the endothelial function, mostly by the modulation of endothelial inflammatory reaction [18, 19]. Hypoadiponectinaemia is detected in patients with coronary artery disease [4, 20] and is related to clinical instability [21]. Studies are currently being carried out in order to elucidate the precise mechanism linking adiponectin and vascular disease, including endothelial dysfunction, atherosclerosis and restenotic change after balloon angioplasty [22–25]. The results may subsequently lead to preventive measures and eventually to a specific treatment.

The aim of the study was to assess the impact of obesity on adiponectin and the relationship between its concentration and the anthropometric parameters and cardiovascular risk factors in men with acute myocardial infarction treated with primary coronary intervention.

Methods

Study population

From the cohort of patients with first acute myocardial infarction which had been successfully treated with primary coronary intervention (TIMI flow grade 3, residual stenosis < 30%) 40 obese men age ≤ 65 years, who admitted to being obese for at least 5 years, were selected for the study group. A further 40 non-obese men, matched to the obese group for age and localisation ofthe myocardial infarction, were included in the study as a control group. Our study was designed for males in order to avoid the impact of sex on the results. It has been reported that there are sex-related differences in the location of adipose tissue, the number of fat cells and fat-cell size and plasma adiponectin concentrations [16, 26, 27].

Insulin therapy before blood sampling for adiponectin measurement was considered a criterion for exclusion. Additional exclusion criteria were applied owing to the unreported in this study requirements for the acquisition of echocardiographic parameters. These conditions were atrial fibrillation, atrio-ventricular or bundle branch block, temporary or permanent stimulation and significant valvular heart disease.

Anthropometric measurements clinical definitions and treatment

Diagnosis of acute myocardial infarction was based on the clinical symptoms, electrocardiographic signs and elevation of myocardial necrotic markers. All patients received aspirin and those who underwent stenting were concomitantly treated with an additional antiplatelet agent. Heparin was infused during the procedure. Glycoprotein IIb/IIIa inhibitor was administered at the physician's discretion.

Body mass index calculated as the body weight divided by the square of the height (kg/m^2) was used as a marker of obesity. Weight and height were measured on the third or fourth day after admission while the subjects were fasting and wearing only their undergarments. Patients were designated as obese where BMI exceeded 30 kg/m^2 and were considered non-obese where BMI was below 25 kg/m^2. Waist circumference, a measure of subcutaneous plus visceral fat, was measured at the widest diameter between the xiphoid process of the sternum and the iliac crest. Hip circumference, representing subcutaneous fat alone, was measured at the widest diameter over the greater trochanters. Waist-to-hip ratio was than calculated. Systolic and diastolic blood pressure was measured before blood sampling.

The study was approved by the Internal Ethics Committee of Medical University of Łódź, and each patient gave informed consent.

Laboratory measurements

Along with several analyses performed from the samples of blood taken on admission to the hospital, C-reactive protein (CRP) and uric acid were assessed. Fasting glucose, lipid profile, and adiponectin were determined from blood drawn on the following day. Plasma TG and total cholesterol (TCH) were measured by enzymatic analytical chemistry. The HDL-cholesterol was precipitated using dextran-sulphate and measured enzymatically. The low-density lipoprotein cholesterol (LDL-CH) was calculated using the Friedewald equation: LDL-CH = TCH – (TG/5) – HDL-CH. Impaired lipid metabolism was diagnosed if at least one of the following disorders was present: hypercholesterolemia (TCH > 200 mg/dl), hypertriglicerydemia (TG > 150 mg/dl), high LDL-CH (LDL-CH > 100 mg/dl) or low HDL-CH (HDL-CH < 40 mg/dl). Plasma glucose concentrations were measured with the oxidise method, uric acid with the colorimetric method and CRP concentrations with an immunotubidimetric assay.

Plasma samples for adiponectin concentration measurements were frozen at –70° until analysis with

Table 1. The clinical characteristics and anthropometric measurements of the study groups.

	Obese (n = 40)	Non-obese (n = 40)	p
Age	53.6 ± 7.39	54.4 ± 6.62	NS
Hypertension	25 (62.5%)	18 (45%)	NS
Systolic blood pressure [mm Hg]	124.1 ± 9.32	119.0 ± 13.2	< 0.05
Diastolic blood pressure [mm Hg]	75.5 ± 6.18	73.1 ± 8.37	NS
Diabetes mellitus	11 (27.5%)	7 (17.5%)	NS
Total cholesterol > 200 mg/dl	27 (67.5%)	26 (65%)	NS
HDL-cholesterol < 40 mg/dl	15 (37.5%)	5 (12.5%)	< 0.01
Triglycerides > 150 mg/dl	24 (60%)	13 (32.5%)	< 0.05
LDL-cholesterol > 100 mg/dl	36 (90%)	34 (85%)	NS
Smoking	25 (62.5%)	27 (67.5%)	NS
Body mass index	32.2 ± 1.96	23.8 ± 1.40	< 0.0001
Waist circumference [cm]	111.9 ± 7.52	88.1 ± 7.09	< 0.0001
Hip circumference [cm]	108.3 ± 6.73	91.4 ± 7.67	< 0.0001
Waist-to-hip ratio	1.03 ± 0.05	0.96 ± 0.3	< 0.001

a sandwich enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

Continuous data were expressed as mean ± ± standard derivation. Variables were log-transformed before statistical analysis if necessary. Comparisons between the obese and non-obese group were analysed with Student's *t*-test or the Mann-Whitney test, as appropriate. Categorical variables were presented as the number and percentage of patients and comparisons between the two groups were analysed with the χ^2 test.

The relationship between adiponectin concentration and the analyzed parameters (clinical, anthropometric and biochemical) were examined using Pearson's or Spearman's correlation coefficient, as appropriate. A multiple stepwise regression analysis was performed to evaluate the independent contribution of anthropometric parameters (BMI, waste circumference and waist-to-hip ratio) to the variance of adiponectin.

The univariate regression analysis included age, systolic and diastolic blood pressure, waist circumference (the best anthropometric predictor of adiponectin distribution), fasting glucose, TCH, HDL-CH, TG, LDL-CH, CRP and uric acid. Independent variables that correlated with adiponectin in the univariate analysis were included in the multiple stepwise regression model. The results are presented as relative risk (RR) and 95% confidence intervals (CI). A p value of < 0.05 was considered to be statistically significant.

Results

The clinical characteristics and anthropometric measurements of the study population are shown in Table 1. The incidence of most cardiovascular risk factors (hypertension, diabetes, smoking and hypercholesterolemia) was similar in the two groups. A significant difference between groups was observed only in the proportion of patients with HDL-CH < 40 mg/dl (37.5% *vs.* 12.5%, $p < 0.01$) and TG > 150 mg/dl (60% *vs.* 32.5%, $p < 0.05$). The value of systolic blood pressure was significantly higher in obese than in non-obese patients (124.1 mm Hg ± ± 9.32 *vs.* 119.0 mm Hg ± 13.2; $p < 0.05$). All the assessed anthropometric measurements (BMI, waist circumference and waist-to-hip ratio) were also significantly higher in obese than non-obese group ($p < 0.0001$). Glycoprotein IIb/IIIa inhibitor was administered to a similar proportion of patients from each group. Pharmacological treatment with aspirin, clopidogrel, statins, beta-blockers, inhibitors of angiotensin II, nitrates and diuretics was similar in the two groups.

Biochemical data in obese and non-obese patients are summarised in Table 2. In obese patients the values of the following parameters were significantly higher than in non-obese: TG (161.3 mg/dl ± ± 59.8 *vs.* 132.9 mg/dl ± 52.1; $p < 0.01$), fasting glucose (110.1 mg/dl ± 14.5 *vs.* 94.8 mg/dl ± 10.3, $p < 0.001$) and CRP (7.95 mg/dl ± 7.29 *vs.* 4.25 mg/dl ± ± 4.85, $p < 0.01$), whereas HDL-CH levels were lower (45.6 mg/dl ± 11.9 *vs.* 51.6 mg/dl ± 12.3, $p < 0.05$).

Table 2. Biochemical parameters in the study groups.

	Obese (n = 40)	Non-obese (n = 40)	p
Fasting glucose [mg/dl]	110.1 ± 14.5	94.8 ± 10.3	< 0.001
Total cholesterol [mg/dl]	224.2 ± 44.0	216.7 ± 40.1	NS
HDL-cholesterol [mg/dl]	45.6 ± 11.9	51.6 ± 12.3	< 0.05
Triglycerides [mg/dl]	161.3 ± 59.8	132.9 ± 52.1	< 0.01
LDL-cholesterol [mg/dl]	146.3 ± 43.1	138.4 ± 42.5	NS
C-reactive protein [mg/dl]	7.95 ± 7.29	4.25 ± 4.84	< 0.01
Uric acid [mg/dl]	6.11 ± 1.48	5.66 ± 1.47	NS

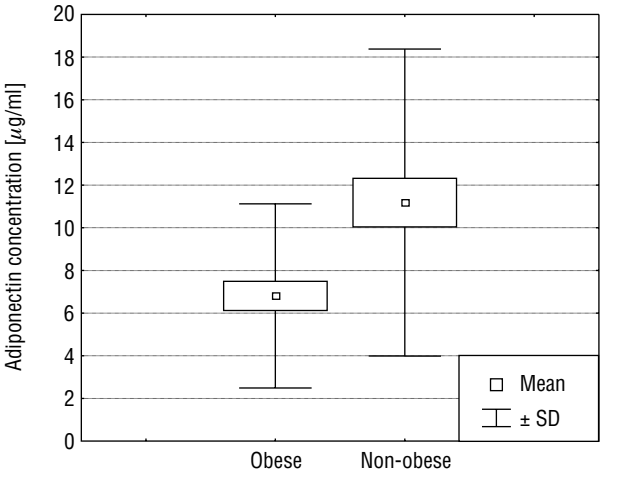

Figure 1. The mean value ot plasma adiponectin concentration in the study groups.

Mean adiponectin level was significantly lower in obese than non-obese group (6.80 μg/ml ± 4.31 *vs.* 11.18 μg/ml ± 7.19; $p < 0.01$) (Fig. 1).

The association of adiponectin with anthropometric measurements is shown in Figure 2. Adiponectin was negatively correlated with all the anthropometric measurements, with the closest correlation observed for waist circumference ($r = -0.52$, $p < 0.0001$). Moreover, multiple stepwise regression analysis revealed that waist circumference was the only independent predictor of adiponectin (RR = = –0.209; 95%CI –0.229 to –0.120, $p < 0.0001$) and could explain 21% of the variation in adiponectin in a model including BMI, waist circumference and waist-to-hip ratio. In the study group as a whole a positive correlation was detected between adiponectin and HDL-CH ($r = 0.57$, $p < 0.0001$) and age ($r = 0.23$, $p < 0.05$), whereas a negative correlation was observed between adiponectin and systolic blood pressure ($r = -0.33$, $p < 0.01$), fasting glucose ($r = -0.47$, $p < 0.0001$), TG ($r = -0.49$, $p < 0.0001$), CRP ($r = -0.45$, $p < 0.0001$) and uric acid ($r = -0.37$, $p < 0.001$) (Table 3). Adiponectin

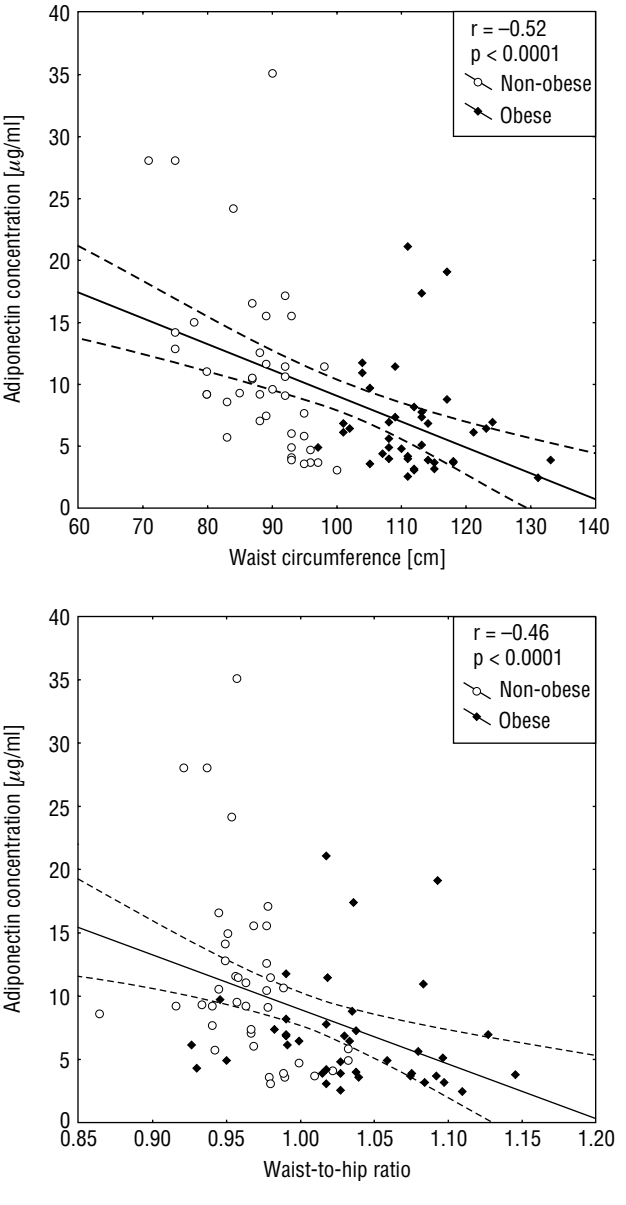

Figure 2. Correlation between plasma adiponectin concentration and anthropometric measurements.

correlated with lipid parameters (HDL-CH and TG) more closely in obese than in non-obese group. The correlation between adiponectin and CRP and

Table 3. Correlation between plasma adiponectin concentration and clinical and biochemical parameters.

	All patients	Obese	Non-obese
Age	r = 0.23 (p < 0.05)	r = 0.29 (NS)	r = 0.17 (NS)
Systolic blood pressure	r = –0.33 (p < 0.01)	r = –0.29 (NS)	r = 0.0004 (NS)
Diastolic blood pressure	r = –0.11 (N S)	r = –0.21 (NS)	r = –0.09 (NS)
Fasting glucose	r = –0.47 (p < 0.0001)	r = –0.46 (p < 0.0001)	r = –0.22 (NS)
Total cholesterol	r = 0.09 (NS)	r = 0.25 (NS)	r = 0.03 (NS)
HDL-cholesterol	r = 0.57 (p < 0.0001)	r = 0.67 (p < 0.0001)	r = 0.42 (p < 0.0001)
Triglycerides	r = –0.49 (p < 0.0001)	r = –0.51 (p < 0.001)	r = –0.39 (p < 0.05)
LDL-cholesterol	r = 0.06 (NS)	r = 0.21 (NS)	r = 0.006 (NS)
C-reactive protein	r = –0.45 (p < 0.0001)	r = –0.55 (p < 0.0001)	r = –0.2 (NS)
Uric acid	r = –0.37 (p < 0.001)	r = –0.33 (p < 0.05)	r = –0.33 (p < 0.05)

between adiponectin and fasting glucose was observed only in the obese group (Table 3).

As shown in Table 4, univariate regression analysis revealed a relation between adiponectin and systolic blood pressure, waist circumference, fasting glucose, HDL-CH, TG, CRP and uric acid. In the multiple stepwise regression analysis, adiponectin concentration was independently associated with HDL-CH, waist circumference and TG and these variabies explained 39% of adiponectin variability (Table 5).

Discussion

Abdominal obesity is an element of the metabolic syndrome, a c1uster of proatherogenic metabolic disorders. There is growing evidence of an association between low adiponectin and the metabolic and cardiovascular complications of obesity. This is why it has been suggested that adiponectin could be a link between excess adiposity and atherosclerotic vascular disease.

Table 4. Univariate regression analysis for plasma adiponectin concentration.

	Relative risk	–95% confidence intervals	+95% confidence intervals	p
Age	0.1769	–0.02233	0.376179	0.081
Systolic blood pressure	–0.143	–0.26011	–0.02592	0.0173
Diastolic blood pressure	–0.075	–0.26579	0.115664	0.4356
Waist circumference	–0.2092	–0.29889	–0.11964	0.0001
Fasting glucose	–0.1654	–0.25435	–0.07652	0.0003
Total cholesterol	0.0048	–0.0289	0.038573	0.7759
HDL-cholesterol	0.2431	0.143146	0.343173	0.0001
Triglycerides	–0.0455	–0.06796	–0.02317	0.0001
LDL-cholesterol	0.0006	–0.03257	0.03382	0.9702
C-reactive protein	–0.3475	–0.55412	–0.14104	0.0012
Uric acid	–1.3693	–2.2751	–0.46363	0.0035

Table 5. The final model of multiple stepwise regression analysis for plasma adiponectin concentration.

	Relative risk	–95% confidence intervals	+95% confidence intervals	p
HDL-cholesterol	0.1493	0.0500	0.2486	0.0037
Waist circumference	–0.1371	–0.2233	–0.0510	0.0021
Triglycerides	–0.0282	–0.0488	–0.0075	0.0080

In this study we have confirmed that in patients with acute myocardial infarction, similary as it has been reported in previous studies in healthy subjects and patients with various stages of coronary artery disease, adiponectin is significantly lower in obese than in non-obese patients and decreased plasma adiponectin levels are more often observed in the former than in the latter [11–13, 15, 16, 20, 28].

Adiponectin has been shown *in vitro* to be secreted particularly from the human visceral adipose tissue [29] and its plasma concentration is influenced to a greater extent by visceral than by subcutaneous adipose tissue [30, 31]. With the aid of computed tomography waist circumference was identified as the best surrogate of visceral adiposity [32]. In our study, although all anthropometric parameters were negatively correlated with adiponectin, the strongest correlation was observed for waist circumference, and multiple regression analysis revealed that waist circumference was the only independent anthropometric predictor of adiponectin level and could explain 21% of adiponectin variation. Some other authors have made different observations. Steiger et al. [28] revealed that adiponectin correlates negatively with waist-to-hip ratio but not with either waist circumference or hip circumference. Waist-to-hip ratio was found to be a better screening measure for cardiovascular risk factors than other anthropometric indicators by Esmaillzadeh et al. [33].

In the group of patients studied here we observed that adiponectin increased with age ($r = 0.23$, $p < 0.001$). This is in agreement with other authors [16, 20] and it has been suggested that androgens may inhibit adiponectin production [26]. The exact effect of androgens on adiponectin is not known. On the grounds of the *in vitro* studies it has been suggested that testosterone may sequester a coactivator ARA70, common to the androgen receptor and the peroxisome proliferator-activated receptor gamma 1 (PPARγ). Such competition may result in the reduced expression of PPARγ-regulated genes such as adiponectin [34].

Several authors have shown the association between low adiponectin plasma concentration and the atherogenic lipoprotein profile. We have revealed a significant difference in adiponectin concentrations as well as in HDL-CH and TG between the groups of obese and non-obese patients. A significant positive correlation, between adiponectin and HDL-CH ($r = 0.57$, $p < 0.0001$) and a lesser negative correlation between adiponectin and TG ($r = –0.49$, $p < 0.0001$) were revealed in our group of patients. This observation is in agreement with the results of previous studies performed in European, American and Japanese populations of healthy individuals [15, 16, 30], patients with coronary artery disease [20] and subjects with obesity [35] and diabetes [36]. Moreover, our observation [15, 35, 37] that the contribution of HDL-CH and TG to the variance of adiponectin is independent of age and BMI is similar to that put forward by other authors.

It has been suggested that the association of high adiponectin with high HDL-CH and low TG could be explained by a direct insulin-sensitising effect of adiponectin on hepatic and muscle lipoprotein metabolism [37]. The negative correlation between adiponectin and uric acid revealed in our study ($r = –0.37$, $p < 0.001$) is stronger than in the male subgroup in the study by Yamamoto et al. ($r = –0.265$, $p < 0.0001$) [15].

Recent studies have established the fundamental role of inflammation in mediating all stages of atherosclerosis [19]. CRP is not only a marker of the chronic inflammatory process but also a molecule known to promote atherogenesis [38]. It has been suggested that in patients with diabetes or at higher risk of developing diabetes adiponectin is involved in the modulation of inflammation, in part through the underlying association with obesity [36]. In our study CRP was significantly higher in the obese patient group than in control group and, in keeping with prior data [39, 40], adiponectin negatively correlated with CRP. We suggest that a strong direct association of adiponectin with CRP in patients with acute myocardial infarction could possibly be explained by the acute state of inflammation underlying plaque rupture and the adhesion of adiponectin to injured vascular walls, a process described by Okamaoto et al. [41].

Study limitations

The time from the onset of acute myocardial infarction to the blood sampling for adiponectin measurements differed in individual patients by between 24 and 72 hours. Serial analysis of adiponectin in the course of acute myocardial infarction performed by Kojima et al. [39] showed that adiponectin significantly declines during the initial 24 hours of acute myocardial infarction but is relatively stable by the following 48 hours and then rises until the seventh day of acute myocardial infarction, although it does not reach the values assessed at admission.

Since plasma insulin levels were not available in our data set, we were not able to examine the impact of this potential intermediate variable.

Conclusions

1. In patients with acute myocardial infarction obesity is related to decreased plasma adiponectin concentration.
2. Waist circumference is a better predictor of plasma adiponectin concentration than body mass index and waist-to-hip ratio.
3. Low adiponectin plasma concentration is associated with atherogenic lipid profile and increased inflammatory reaction.

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