Endocrine Journal 2007, **54** (2), 221–226

Decreased Plasma Adiponectin is Associated with Insulin Resistance and HDL Cholesterol in Overweight Subjects

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Abstract. The purpose of this study was to investigate plasma adiponectin concentration and its relation with metabolic parameters in overweight and normal weight subjects. The study was carried out in 46 overweight subjects (20 male, 26 female; mean age 39.4 ± 10.2 years) and 48 (19 male, 29 female; mean age 36.1 ± 10.6 years) sex- and age-matched normal weight subjects. Anthropometric measurements were recorded and adiponectin, glucose, insulin, lipid profile, total homocysteine (tHcy) and fibrinogen levels were measured. The insulin resistance index was assessed by homeostasis model assessment for insulin resistance (HOMA-IR). Plasma mean adiponectin concentrations of the overweight subjects were significantly lower than those of normal weight subjects (15.0 ± 4.2 vs 17.3 ± 5.6 ng/ml) ($P<0.05$). In overweight subjects, adiponectin levels negatively correlated with body weight ($r = –0.35$, $P<0.001$), body mass index (BMI) ($r = –0.28$, $P<0.006$), systolic blood pressure ($r = –0.21$, $P<0.04$), fasting insulin ($r = –0.19$, $P<0.01$) and HOMA-IR ($r = –0.20$, $P<0.01$) and positively with high-density lipoprotein cholesterol (HDL-C) ($r = 0.27$, $P<0.009$). Overweight subjects with low HDL-C levels had significantly decreased plasma adiponectin levels compared to those with high HDL-C levels ($P<0.05$). Multiple regression analysis revealed that BMI, HOMA-IR and HDL-C explained 12%, 20% and 15% variance of the adiponectin concentrations. These findings may suggest that circulating adiponectin is associated with insulin resistance and HDL-C levels independent from BMI in overweight subjects.

Key words: Adiponectin, Overweight, Insulin resistance, HDL cholesterol

(*Endocrine Journal* **54**: 221–226, 2007)

OBESITY is an important health problem in all countries. It is a disease that involves several complications and increases the risk of many common diseases including coronary artery disease (CAD), type 2 diabetes mellitus (DM) and hypertension [1].

Adipose tissue is currently thought to be not only a depot for energy storage, but also an active hormone system involved in metabolic control [2]. Adiponectin is one of the hormones secreted from adipocytes [3]. This peptide has various biological functions such as insulin sensitizing, anti-inflammatory and anti-atherogenic properties [4–7]. Clinically, hypoadiponectinemia has been observed in patients with type 2 DM and CAD [5]. Unlike most adipose-derived peptides, previous reports demonstrated that plasma adiponectin levels are decreased in obese subjects [8, 9]. In recent studies, circulating adiponectin levels have been reported to be associated with the metabolic parameters including insulin resistance, lipid profile and body mass index (BMI) [10–12]. In addition to obesity, the inverse association between adiponectin and body weight is reported in extremely lean subjects like patients with anorexia nervosa [13, 14]. Data from these studies support the evidence that hypoadiponectinemia may be associated with obesity. However, there is not enough data regarding the adiponectin levels in a study group consisting only overweight subjects. Therefore, in the present study, we examined plasma adiponectin concentration and its relation to metabolic parameters such as BMI, insulin resistance and lipid parameters in non-diabetic overweight and normal weight subjects.

Received: January 30, 2006
Accepted: November 10, 2006
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Patients and Methods

Fortysix overweight subjects (20 male, 26 female; mean age: 39.4 ± 10.2 years) and fortyeight (19 male, 29 female; mean age: 36.1 ± 10.6 years) sex- and age-matched normal weight subjects were enrolled in the study. Patients did not have hepatic or renal dysfunction, chronic inflammatory and clinically significant infectious diseases. None of the subjects had DM, hypertension and no subjects were taking any medication. Anthropometric measurements including height, body weight and BMI were recorded. All blood samples were taken after 12 hours of fasting period from an antecubital vein and was seperated and frozen at –70°C until analyzed. Serum levels of total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured using Abbott-Aeroset (Chicago-USA) autoanalyzer with original kits. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald equation. We categorized serum HDL-C concentrations into two levels: high (>35 mg/dl for men, >40 mg/dl for women) and low (<35 mg/dl for men, <40 mg/dl for women) according to the recommendations of National Cholesterol Education Program [15]. Serum total homocysteine (tHcy) levels were measured with HPLC using Chromsystems kits with fluorescence detector. Serum fibrinogen measurement was performed by Sismax 7000 auto analyzer with Clauss clotting methods. Plasma adiponectin levels were determined by using ELISA methods. (Kit: B-Bridge International, Inc., CA, USA). Insulin resistance was estimated by using the homeostatic model assessment for insulin resistance (HOMA-IR) index, calculated as (serum glucose level (mg/dl)/18.1) × insulin level (μIU/ml)/22.5 [16].

The regional ethics committee approved the study protocol and informed consents were obtained from all subjects.

Statistical analysis was performed using SPSS version 11.0 for Windows (Statistical Package for Social Science, Chicago, IL, USA). All data were expressed as mean ± SD. Comparisons of the groups were examined by Student's t test. Pearson correlation test was used to determine the relationship between adiponectin and the other continuous variables. Partial correlation test was used to adjust for BMI. The independent determinants of plasma adiponectin were determined using multiple linear regression analysis. *P* value <0.05 was considered statistically significant for all analyses.

Results

The main clinical and biochemical characteristics of the subjects that comprised this study are shown in Table 1. No differences were found between overweight and normal weight subjects with respect to age and gender.

Overweight subjects had significantly reduced HDL-C levels (45.3 ± 10.5 vs 52.0 ± 12.9 mg/dl, P<0.009) and increased TG levels (126.1 ± 74.2 vs 100.2 ± 42.7 mg/dl, P<0.05) compared to normal weight subjects. Serum T-C, LDL-C, vitamin B_{12} and folic acid levels were similar between the groups (P>0.05). Overweight subjects also showed significantly higher BMI (28.7 ± 3.0 vs 21.6 ± 1.9 kg/m^2, P<0.0001), systolic blood pressure (127.5 ± 14.6 vs 115.7 ± 18.1 mmHg, P<0.05), fasting insulin (11.4 ± 4.9 vs 5.77 ± 2.2 μIU/ml, P<0.01) and HOMA-IR index (2.7 ± 1.2 vs 1.3 ± 0.4, P<0.01) compared to normal weight subjects.

Circulating adiponectin level was slightly higher in women than in men but this difference did not reach a statistical significance in all subjects (16.7 ± 5.6 vs

Table 1. Clinical and biochemical characteristics of subjects

	Overweight subjects (n = 46)	Normal weight subjects (n = 48)	P value
Age (years)	39.4 ± 10.2	36.1 ± 10.6	NS
Gender (F/M)	26/20	29/19	NS
Smoker/non-smoker	30/16	34/14	NS
Height (cm)	165.2 ± 10.5	164.8 ± 8.4	NS
Weight (kg)	77.7 ± 11.8	59.6 ± 8.5	<0.0001
BMI (kg/m^2)	28.7 ± 3.0	21.6 ± 1.9	<0.0001
SBP (mmHg)	127.5 ± 14.6	115.7 ± 18.1	<0.05
DBP (mmHg)	76.3 ± 13.5	76.3 ± 12.1	NS
T-C (mg/dl)	178.4 ± 36.1	177.1 ± 33.2	NS
LDL-C (mg/dl)	109.8 ± 28.8	105.4 ± 28.6	NS
HDL-C (mg/dl)	45.3 ± 10.5	52.0 ± 12.9	<0.009
Triglycerides (mg/dl)	126.1 ± 74.2	100.2 ± 42.7	<0.05
Fasting glucose (mg/dl)	91.7 ± 9.7	90.3 ± 8.1	NS
Fasting insulin (μIU/ml)	11.4 ± 4.9	5.7 ± 2.2	<0.01
HOMA-IR	2.7 ± 1.2	1.3 ± 0.4	<0.01
tHcy (μmol/L)	15.4 ± 9.1	13.8 ± 8.6	NS
Fibrinogen (mg/dl)	338.7 ± 110.6	325.8 ± 117.8	NS
Adiponectin (ng/ml)	15.0 ± 4.2	17.3 ± 5.6	<0.05

Data are expressed as mean ± SD; NS; not significant, SBP, systolic blood pressure; DBP, diastolic blood pressure; T-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; tHcy, total homocysteine.

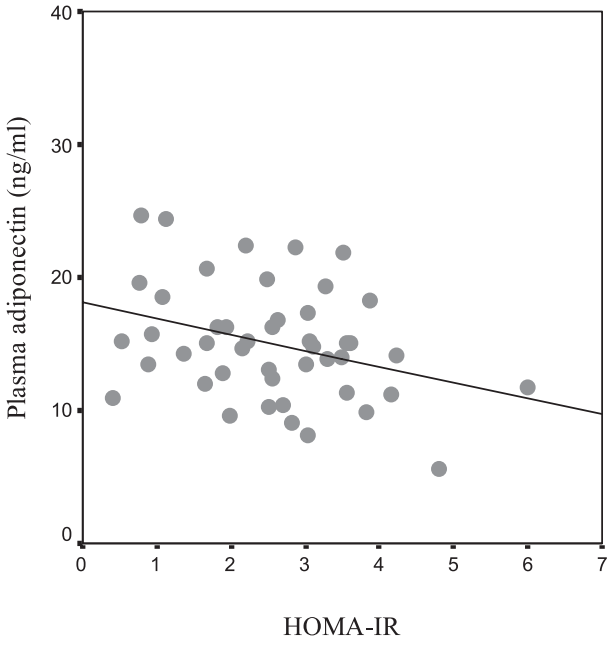

Fig. 1. Relation of plasma adiponectin to HOMA-IR

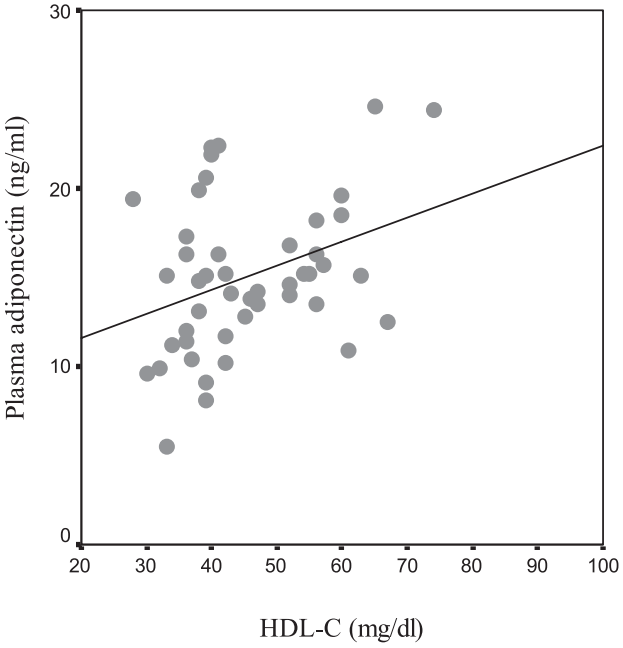

Fig. 2. Relation of plasma adiponectin to HDL-C

15.8 ± 4.2 ng/ml, P>0.05). There were no differences between the adiponectin levels of smokers and those of non-smokers (17.0 ± 6.4 vs 17.3 ± 4.2 ng/ml, P>0.05) in all subjects. Plasma mean adiponectin concentrations of the overweight subjects were significantly lower than those of normal weight subjects (15.0 ± 4.2 vs 17.3 ± 5.6 ng/ml, P<0.05).

Circulating adiponectin levels correlated negatively with body weight (r = –0.35, P<0.001), BMI (r = –0.28, P<0.006), systolic blood pressure (r = –0.21, P<0.04), fasting insulin (r = –0.19, P<0.01) and HOMA-IR index (r = –0.20, P<0.01) (Fig. 1) and positively with HDL-C (r = 0.27, P<0.009) (Fig. 2) in overweight subjects. The associations between adiponectin levels and HOMA-IR and HDL-C remained significant after the adjustment for BMI (P<0.009). There was not a significant correlation between adiponectin levels and age (r = 0.15, P = 0.35), gender (r = –0.17, P = 0.09), fasting glucose (r = –0.13, P = 0.21), diastolic blood pressure (r = 0.02, P = 0.80), T-C (r = 0.07, P = 0.48), LDL-C (r = 0.36, P = 0.73), TG (r = –0.18, P = 0.85), tHcy (r = 0.03, P = 0.77) and fibrinogen levels (r = –0.01, P = 0.88) in overweight subjects.

Plasma adiponectin levels did not correlate with LDL-C/HDL-C ratio (r = –0.14, P = 0.10). But there was a significant negative correlation with adiponectin levels and T-C/HDL-C ratio (r = –0.27, P<0.03).

When the overweight subjects were divided into two groups according to low and high HDL-C levels, 20 subjects were in the low HDL-C group and 26 in the high HDL-C group. The overweight subjects with low

Table 2. Comparison of the overweight subjects according to HDL-C level

	Overweight subjects with low HDL-C	Overweight subjects with high HDL-C	P value
Number	20	26	—
Age (years)	43.6 ± 8.7	39.1 ± 11.4	NS
Gender (F/M)	14/6	17/9	NS
BMI (kg/m^2)	29.1 ± 2.9	28.5 ± 3.2	NS
HDL-C (mg/dl)	36.4 ± 2.9	51.8 ± 10.0	<0.0001
HOMA-IR	2.7 ± 0.7	2.6 ± 1.4	NS
Adiponectin (ng/ml)	13.4 ± 4.2	16.1 ± 3.8	<0.05

Data are expressed as mean ± SD; NS; not significant, BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

Table 3. Multivariate regression analysis for adiponectin

Parameters	β	t	P
BMI	–0.19	–0.29	0.01
HDL-C	0.18	2.10	0.001
HOMA-IR	–0.45	–0.57	0.008
Fasting insulin	–0.02	–0.82	0.11
Systolic blood pressure	–0.01	–0.66	0.24

HDL-C levels showed significantly lower levels of adiponectin compared to overweight subjects with high HDL-C ($P<0.05$) (Table 2).

Multiple stepwise linear regression analysis was performed using adiponectin as the dependent variable and this analysis revealed that BMI, HOMA-IR and HDL-C are the predictors of circulating adiponectin levels and explained 12%, 20% and 15% variance of the adiponectin concentrations (Table 3).

Discussion

Adiponectin is the only adipose-secreted protein known that is inversely related with obesity. A strong relationship has been suggested between hypoadiponectinemia and increased BMI [6]. In consistent with this data, our overweight subjects had decreased plasma adiponectin levels compared to normal weight subjects. Moreover, in the regression analysis, BMI was one of the major determinants of plasma adiponectin.

Some studies [17–19] have found sex-related difference in plasma adiponectin level, higher adiponectin levels in women than men, but not all [20, 21]. Whether plasma adiponectin concentrations are gender-dependent remains to be elucidated. Plasma adiponectin levels were slightly higher in women than in men but this difference did not reach a statistical significance in our subjects.

Here, we also investigated the associations of adiponectin with metabolic parameters like insulin resistance. Several studies support the hypothesis that adiponectin serves as an insulin sensitizer by decreasing hepatic glucose output and regulating glucose homeostasis [6]. In a study of normal and obese women showed that adiponectin is related with insulin resistance [22]. Another study has found that plasma adiponectin is negatively correlated with glucose, insulin and HOMA-IR [17]. Shand *et al.* [7] reported decreased adiponectin levels in overweight and obese subjects and suggested adiponectin to be an important marker in insulin resistance and obesity. Low levels of adiponectin were also found in insulin-resistant subjects regardless of whether they are obese [23]. However, whether decreased adiponectin levels could be a result of increased insulin resistance or an etiological factor for insulin resistance is still not known. On the other hand, Silha *et al.* [24] has reported that adiponectin did not significantly correlate with insulin resistance measured by HOMA-IR index. They argued that their small number of subjects might be responsible from this result. Our results are in agreement with other studies that found association between adiponectin and insulin resistance. Also, insulin resistance remained as a determinant for adiponectin levels in the regression analysis in our study. In the present study, there was a significant relationship between plasma adiponectin, insulin and insulin resistance but adiponectin did not correlate with fasting glucose. In a recent study of healthy male subjects [11], plasma adiponectin concentrations have been suggested to predict subsequent changes in insulin resistance. Further studies with a larger number are needed to better understand in which way decreased adiponectin levels are associated with insulin resistance.

Plasma tHcy and fibrinogen concentrations have been suggested to be emerging risk factors for atherosclerotic vascular disease [25, 26]. But we did not find any relationship between adiponectin levels and tHcy and fibrinogen as independent cardiovascular risk factors in overweight subjects. It seems that adiponectin has no effect on atherogenesis via direct mechanisms related with tHcy and fibrinogen.

We also assessed the association of adiponectin with lipid parameters. Recent clinical studies have shown adiponectin levels to correlate with serum lipids including LDL-C, HDL-C and TG [19, 27, 28]. Rothenbacher *et al.* [29] demonstrated that adiponectin was strongly correlated with lipoproteins in particular HDL-C in patients with CAD. The association of adiponectin and HDL-C levels was also shown in normal weight Japanese population [17] and in overweight and obese subjects [30]. In our study, overweight subjects had increased TG levels and low HDL-C levels compared to normal weight subjects. A significant negative correlation was found between plasma adiponectin concentration and HDL-C level that is consistent with other studies. On the other hand, an important observation in our study was the negative significant correlation between adiponectin level and the ratio of T-C/HDL-C although no significant correlation was found between adiponectin and T-C levels. Moreover, in multiple linear regression analysis, HDL-C was one of the independent determinants of plasma adiponectin levels. This result demonstrated that in overweight subjects, plasma adiponectin level may modulate HDL-C levels independent of BMI. Another interesting point of the present study was that overweight

subjects with low HDL-C levels had the lowest plasma adiponectin levels. In other words, plasma adiponectin levels decrease as HDL-C levels decrease. Therefore, adiponectin could perform the anti-atherogenic effects via increasing HDL-C levels beyond the contribution of BMI in the development of atherosclerotic process. Regarding this relationship between adiponectin and HDL-C, it has been suggested in a previous study [31] that the possible mechanism may partly be explained with peroxisome proliferator-activated receptor-α (PPAR-α) which effects the genes associated with HDL-C metabolism since adiponectin stimulates PPAR-α ligand activities both in skeletal muscle and liver which results increased synthesis of HDL-C. However, we think further studies with a larger numbers would be required to investigate causal factors for the relationship between circulating adiponectin and HDL-C.

In conclusion, obesity has been known as an important risk factor for CAD and type 2 DM. We found that even overweight subjects not only obese subjects had low adiponectin concentrations compared to normal weight subjects. Our finding that hypoadiponectinemia and its association with insulin resistance and HDL-C levels in overweight subjects support the evidence that adiponectin may have anti-atherosclerotic role through improving insulin resistance and lipid profile especially HDL-C. An existence of a linkage between adipocytes and lipoproteins like HDL-C could play a role in the pathogenesis of atherosclerosis in overweight subjects. Therefore, we suggest that overweight subjects should be carefully evaluated as in the obese subjects for the cardiovascular risk.

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