Serum adiponectin concentrations and their relationship with plasma lipids in obese diabetic and non-diabetic Caucasians

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Abstract

OBJECTIVES: Adiponectin is a novel plasma protein produced exclusively in adipocytes. Despite early data, its relationship with obesity and diabetes has been recently questioned. Since plasma lipids influence diabetes and obesity, of concern is whether any associations between plasma lipids and adiponectin exist.

DESIGN AND METHODS: The aim of this study was to measure adiponectin levels and to investigate their associations with plasma cholesterol fractions and triglycerides in 73 obese non-diabetic subjects (44 women and 29 men), and 43 obese diabetic subjects (28 women and 15 men), aged 52.7±11.2 and 53.1±11 years, respectively, and matched for age, sex and BMI. The WHO definitions of obesity and diabetes were used. Adiponectin was determined by an enzyme-linked immunosorbent assay.

RESULTS: No correlations between adiponectin and total and LDL cholesterol levels were shown (for the whole cohort: r=0.0130; p=0.8899, and r=0.0807; p=0.3958, respectively). A positive correlation between HDL cholesterol levels and adiponectin occured predominantly in obese women without diabetes (r=0.4531; p=0.0023), resulting in an overall statistical trend in the whole cohort (r=0.2243; p=0.0164). A negative correlation between serum adiponectin and triglycerides was found (r=–0.3413; p=0.0002).

CONCLUSION: Adiponectin correlated only with TG and partially with HDL but not with LDL and total cholesterol in the study group of obese diabetic and obese non diabetic subjects. In view of these results we suggest that the role of adiponectin in human metabolism is unclear and merits further investigation.

ORIGINAL ARTICLE

INTRODUCTION

The endocrine function of adipose tissue plays an important role in the pathogenesis of obesity and type 2 diabetes mellitus. Contemporary, adipose tissue is no more understood as an inactive reservoir of energy but rather, as a complicated endocrine organ with rich neuroendocrine regulatory pathways. Termed adipocytokines, endocrine substances secreted by this tissue have been investigated in obese and diabetic humans, with adiponectin being the most extensively examined. In clinical practice, plasma lipids and adiponectin are substances which may be influenced by diabetes, and thus their measurements may help manage diabetic patients. Nonetheless, whereas plasma lipids are the cornerstone of a modern approach to diabetes, the role of adiponectin is still poorly understood, and arouses controversy. Discovered in the mid-1990s by four different groups of researchers, adiponectin is also referred to as Acrp30, AdipoQ, ApM1, and GBP28 (Scherer *et al*., 1995; Hu *et al*., 1996; Maeda *et al*., 1996; Nakano *et al*., 1996). It is the most abundant adipocytokine, and it is produced solely in the adipose tissue (Scherer *et al*., 1995; Stefan and Stumvoll, 2002). It circulates in the blood at high concentrations, accounting for approximately 0.01% of the total plasma protein (Fruebis *et al*., 2001; Berg *et al*., 2002). Its plasma concentration has been found to be decreased in patients with obesity, type 2 diabetes, or coronary artery disease, and inversely correlated with insulin resistance in both non-obese and obese subjects as well as in patients with type 2 diabetes mellitus (Pellme *et al*., 2003, Weyer *et al*., 2001; Kern *et al*., 2003, Piestrzeniewicz *et al*., 2007). Moreover, in a few studies the treatment of diabetic animals with adiponectin has been shown to improve insulin sensitivity and lower plasma free fatty acid levels (Fruebis *et al*., 2001; Berg *et al*., 2001). The associations between adiponectin and the endocrine system have been investigated: as shown in animal studies, adiponectin might be dependent on a pituitary adenylate cyclase activating peptide (PACAP 38), although the interactions in animals can not be distributed to humans in all cases (Ozkan *et al*., 2005, Bik *et al*., 2007). Two receptors for adiponectin, termed AdipoR1 and AdipoR2, have been cloned; AdipoR1 is highly expressed in skeletal muscles, and AdipoR2 is expressed mainly in the liver (Yamauchi *et al*., 2003).

In spite of all the data mentioned above, some latest papers have questioned the relationship between adiponectin and insulin sensitivity or obesity, suggesting that the role of adiponectin in human metabolism remains to be established (Nassis *et al*, 2005; Kaser *et al*., 2005; Bacha *et al*., 2005; Staiger *et al*., 2005; Owecki *et al*., 2007). In view of these contoversial reports, since adiponectin has been previously associated with an impaired lipid profile, the aim of our study was to measure adiponectin concentrations in non-diabetic and diabetic humans with a similar range of trunkal obesity, and to examine whether they were related to the levels of plasma cholesterol and triglicerydes.

SUBJECTS AND METHODS

The study group consisted of 73 obese non-diabetic subjects (44 women and 29 men), and 43 obese and diabetic subjects (28 women and 15 men), recruited by local advertising. Their age was 52.7±11.2, and 53.1±11.0 years, respectively. Obesity was defined according to the WHO criterion (BMI, >30 kg/m^2). All diabetic and non-diabetic subjects had hypertension, well controlled on medication with ACE-inhibitors. None of the subjects was treated for hyperlipaemia or had a history of previous antihyperlipaemic treatment. In all non-diabetics, a normal glucose tolerance was confirmed in the standard oral glucose tolerance test: 75 grams of glucose was administered orally and the plasma glucose concentration was measured in 2 hours. In the diabetes group, all subjects presented with type 2 diabetes mellitus. Diabetes was defined according to WHO criterion (fasting glucose equal or more than 126 mg/dL, or 6.99 mmol/L, on two various days). All subjects were treated with oral sulfonylureas and diabetes was controlled sufficiently: that fasting plasma glucose was close to the values found in the non diabetic subgroup was the condition of entering into the study. None of the subjects had a history of alcohol overconsumption. None was completely sedentary, or involved in athletics. All subjects were examined in the morning (at 08:00 a.m.) after an overnight fast. Waist and hip circumferences where measured. Repeated bioimpedance tests were performed at the same time after an overnight fast (08:00 a.m.). Exercise, and alcohol or caffeine consumption was banned 24 hrs prior to the bioimpedance test. A venous blood sample was obtained for the measurement of plasma levels of glucose, total plasma cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and triglycerides (TG) at the hospital's routine chemistry laboratory. Serum levels of adiponectin were determined in the Department of Clinical Biochemistry of the Poznań University of Medical Sciences using commercial ELISA kit (R&D Systems Inc., MN, USA; microplater reader Sunrise Tekan, Switzerland), and were expressed as nanograms per milliliter. Adiponectin was measured according to the manufacturer's recommended protocol, with a sensitivity of 0.246 ng/ml. An intra-assay and inter-assay coefficients of variation were 4.27% and 5.88%, respectively.

The values are given as the mean ± SD, median. Mann-Whitney test was used for statistical comparisons and Spearman's test for analyses of correlations. For all statistical procedures, Statistica 7.1 computer software (STATSOFT, U.S.A.) was used.

The study was approved by the ethics committee of the Poznań University of Medical Sciences. All subjects gave informed consent to participate.

RESULTS

The clinical data of diabetic and non-diabetic subjects are shown in Table 1. Diabetic patients showed higher levels of glycosylated haemoglobin. Except for that, the study groups were of similar age, and their anthropometric characteristics, percent body fat, fasting plasma glucose and plasma lipids, as well as serum adiponectin concentrations did not differ. For both sexes compared separately, no differences were found, either, except small differences of LDL cholesterol in women. Tables 2 and 3 present the same values for men and women separately.

To investigate the influence of adiponectin on serum concentrations of HDL, LDL and total cholesterol, as well as triglycerides, correlations between those lipids and adiponectin were calculated as follows: for all subjects grouped together, for diabetics only and for non-diabetics only. In order to evaluate the influence of sex, we also estimated all correlations for females and males separately.

In a simple regression analysis performed in the whole cohort, serum levels of adiponectin were correlated with levels of HDL and TG (r=0.2243; p=0.0164, and r=–0.3413; p=0.0002, respectively), and not correlated with TC and LDL (r=0.0130; p=0.8899, and r=0.0807; p=0.3958, respectively). Data shown on Figure 1. Similar results were found in non-diabetics: r=0.0535; p=0.6532, r=0.3206; p=0.0060, r=0.0403; p=0.7389 and r=–0.2701; p=0.0208 for TC, HDL, LDL and TG, respectively. In diabetics, serum adiponectin did not correlate with the levels of TC, HDL and LDL, whereas a correlation with TG was found (r=0.0035; p=0.9820, r=0.0583; p=0.7139, r=0.2514; p=0.1083, and r=–0.4374; p=0.0034, respectively).

Women. In diabetic women, serum levels of adiponectin did not correlate with levels of TC, HDL, LDL and TG (r=–0.0156; p=0.9372, r=–01411; p=0.4828, r=0.2783; p=0.1599, and r=–0.3449; p=0.0722, respectively). In non-diabetic women, however, serum adiponectin positively correlated with HDL levels (r=0.4531; p=0.0023), whereas it did not correlate with other lipids (r=0.1119; p=0.4695, r=0.0328; p=0.8345, and r=–0.1837; p=0.2327, for TC, LDL and TG, respectively). In all women assessed together, serum levels of adiponectin were not correlated with TC and LDL (r=0.0166; p=0.8897, r=0.0612; p=0.6150, respectively). In contrast, adiponectin correlated with HDL and TG (r=0.2557; p=0.0327, r=–0.2721; p=0.0208, respectively) in this group.

Men. No correlations between adiponectin and lipids were found in either of men subgroups. The results for TC, HDL, LDL and TG were respectively: in diabetic men: r=–0.0571; p=0.8397, r=0.1519; p=0.5889, r=–0.1435; p=0.6099, and r=–0.1571; p=0.5760; in non-diabetic men: r=0.0256; p=0.8950, r=0.1158; p=0.5497, r=0.0359; p=0.8560, and r=–0.3503; p=0.0625. Furthermore, in all men assessed together adiponectin levels were not correlated with the levels of TC, HDL, LDL, but they correlated with TG (r=0.0073; p=0.9627, r=0.1129; p=0.4654, r=–0.0229; p=0.8840, and r=–0.3583; p=0.0169, respectively).

DISCUSSION

This clinical study was designed to evaluate the association between plasma lipid levels and concentrations of adiponectin in obese Caucasian men and women. We investigated two groups of obese patients, in whom the presence of type 2 diabetes was the only differentiating factor. However, we decided to examine only diabetic subjects with a correct fasting plasma glucose achieved on medication. One may argue about this limitation, which is in contrast to many other studies. This approach

Table 1. Both groups of non diabetic and diabetic subjects compared. Values are compared with Mann-Whitney test and expressed as mean±SD, median. FPG: fasting plasma glucose.

	Non-diabetics	Diabetics	p-value
Sample	73	43	
Age (years)	52.7±11.2, 53.0	53.1±11.0, 55.0	0.6837
BMI (kg/m^2)	38.21±8.22, 34.80	37.60±6.46, 36.30	0.6869
Waist (cm)	113.99±17.66, 110.50	115.09±11.55, 114.00	0.2642
Hip (cm)	122.01±16.27, 119	119.88±14.82, 115.00	0.5966
FPG (mmol/L)	5.49±0.68, 5.50	5.95±1.51, 5.38	0.8643
HbA1c	5.7±0.7, 5.7	7.4±1.6, 7.2	0.0156
Total cholesterol (mmol/L)	5.21±1.11, 5.11	5.32±1.12, 5.16	0.3849
HDL cholesterol (mmol/L)	1.19±0.40, 1.11	1.10±0.32, 1.11	0.2970
LDL cholesterol (mmol/L)	3.10±0.86, 3.00	3.36±1.05, 3.30	0.1130
Triglycerides (mmol/L)	1.75±0.99, 1.70	1.94±0.99, 1.77	0.2787
Adiponectin (ng/mL)	6044.07±4399.91, 5617.60	5089.17±4066.40, 3864.10	0.1372

Table 2. Non diabetic and diabetic men compared. Values are compared with Mann-Whitney test and expressed as mean±SD, median. FPG: fasting plasma glucose.

	Non-diabetic men	Diabetic men	p-value
Sample	29	15	
Age (years)	51.6±10.1, 53.0	52±10.35, 55.0	0.6737
BMI (kg/m^2)	36.22±7.02, 33.30	35.50±5.18, 33.90	0.9802
Waist (cm)	118.1±17.44, 112.0	117.47±13.24, 114.00	0.6199
Hip (cm)	116.1±14.68, 110.0	116.27±14.19, 111.00	0.6734
FPG (mmol/L)	5.58±0.62, 5.63	5.50±0.63, 5.56	0.8934
HbA1c	5.7±0.6, 5.8	7.0±0.8, 7.1	0.0236
Total cholesterol (mmol/L)	5.42±1.30, 5.29	5.00±1.19, 5.02	0.3280
HDL cholesterol (mmol/L)	1.05±0.36, 1.02	1.01±0.33, 1.03	0.7474
LDL cholesterol (mmol/L)	3.05±0.91, 3.09	2.91±0.92, 2.90	0.8183
Triglycerides (mmol/L)	2.22±1.16, 2.17	2.33±1.06, 2.32	0.6117
Adiponectin (ng/mL)	4658.73±2180.93, 4472.60	4701.07±5977.20, 2600.10	0.0651

Table 3. Non diabetic and diabetic women compared. Values are compared with Mann-Whitney test and expressed as mean±SD, median. FPG: fasting plasma glucose.

	Non-diabetic women	Diabetic women	p-value
Sample	44	28	
Age (years)	51.7±12.1, 52.0	53.8±11.4, 54.5	0.6754
BMI (kg/m^2)	39.52±8.76, 37.45	38.73±6.87, 36.50	0.9355
Waist (cm)	111.21±17.47, 109.00	113.82±10.58, 114.00	0.2709
Hip (cm)	126.00±16.23, 125.00	121.82±15.04, 120.00	0.2892
FPG (mmol/L)	5.42±0.71, 5.40	6.10±1.72, 5.20	0.6469
HbA1c	5.07±0.95, 4.94	5.49±1.06, 5.27	0.0734
Total cholesterol (mmol/L)	5.7±0.7, 5.6	7.7±1.5, 7.4	0.0069
HDL cholesterol (mmol/L)	1.28±0.40, 1.18	1.14±0.32, 1.13	0.2345
LDL cholesterol (mmol/L)	3.13±0.83, 2.90	3.61±1.06, 3.50	0.0267
Triglycerides (mmol/L)	1.44±0.72, 1.38	1.72±0.90, 1.69	0.1878
Adiponectin (ng/mL)	6957.13±5212.56, 6070.60	5297.08±2658.67, 4945.15	0.3290

diminished our sample but gave us the opportunity to rule out the influence of imbalanced diabetes on a secretion of adiponectin. In other words, we analyzed a strictly limited group of obese diabetic and euglycemic individuals, with the diabetic subgroup well balanced on medication. This way of investigation gave us astonishing results: with some exceptions in the subgroups, no strong correlations between plasma lipids and adiponectin were found. Also, because gender may be a confounding factor, we studied both men and women, and evaluated them separately. Including only women and only men into the analyses yielded comparable results as including all individuals.

In contrast to our results, previous research papers have demonstrated correlations between plasma lipids and adiponectin (Cnop *et al.*, 2003; Pajvani and Scherer, 2003, Bik *et al.*, 2006). In their study of an adolescent population, Martin *et al.* have suggested that the relationships between adiponectin and HDL and triglycerides are present in both lean and nonlean adolescents and are strengthened with increasing adiposity (Martin *et al.*, 2005). Although higher adiponectin levels and an

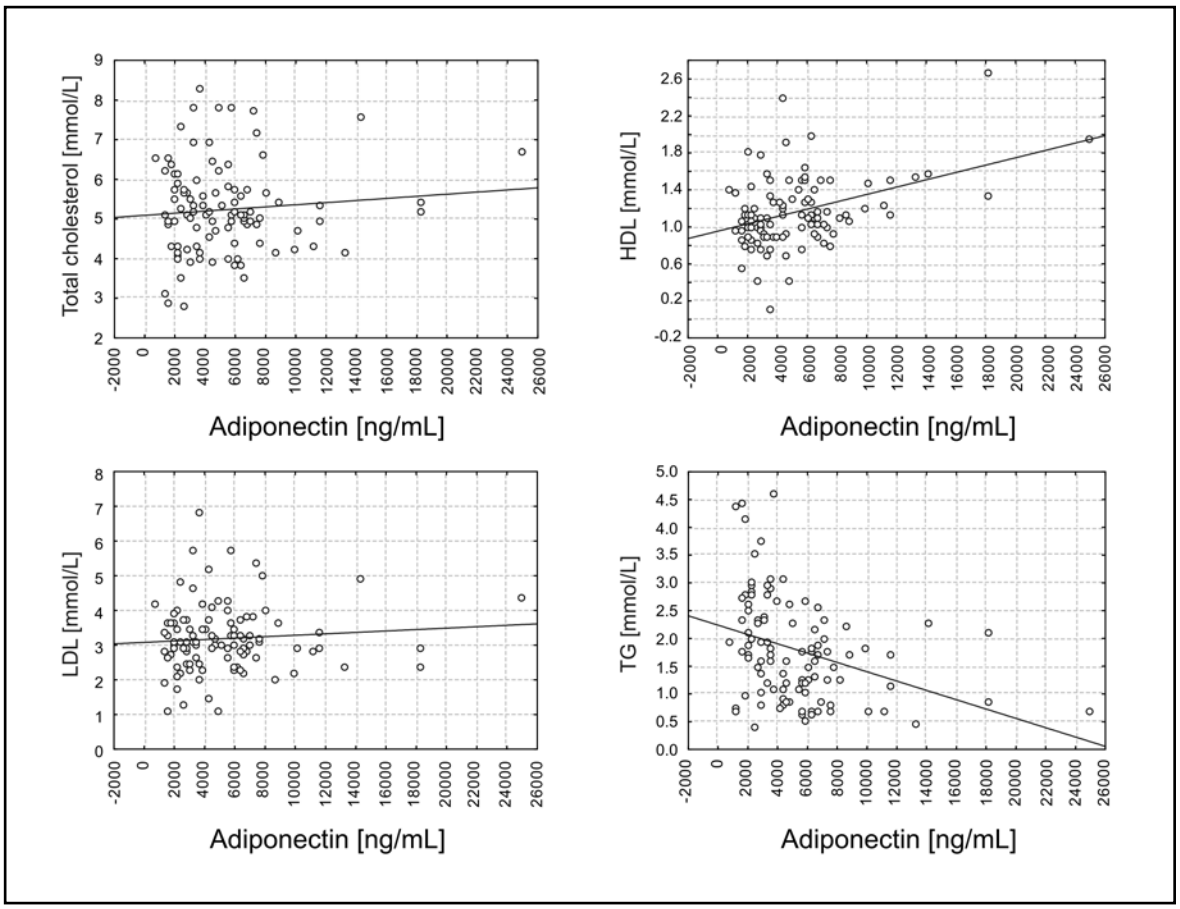

Figure 1. Correlations between plasma adiponectin and total, HDL, LDL cholesterol and triglycerides in all subjects grouped together.

advantegous lipid profile has been associated with a large lower body fat deposition (Buemann *et al*., 2006), others have demonstrated that plasma adiponectin level correlates with serum lipids independently of fat mass (Baratta *et al*.). Interestingly, in the latter study plasma adiponectin was correlated with body mass index in nonobese subjects only but not in obese subjects, whereas it was correlated with high density lipoprotein cholesterol and triglycerides in both obese and nonobese subjects. The authors conclude that their data strongly suggest that adiponectin levels directly regulate lipid metabolism and that this effect is independent from the patient fat mass. Furthermore, the authors advocate that baseline adiponectin level measurements could be useful in identifying obese patients at high risk of dyslipidemia and cardiovascular disease. Consequently, obese individuals with the lowest adiponectin levels should be considered at high risk for cardiovascular disease and adiponectin treatment should be highly recommended in these patients. Evidence to the contrary was shown in another study of 925 diabetic women, where adiponectin levels were not associated with LDL or total cholesterol, whereas they were strongly and positively associated with HDL and strongly inversely associated with triglycerides. (Mantzoros *et al*., 2005)

As briefly discussed above, contradictory reports on the role of adiponectin in obesity and on the relationship between adiponectin and plasma lipids exist. In view of that, we aimed to re-evaluate the relationship between adiponectin and plasma lipids. To avoid the confusing influence of low body mass on the whole cohort which have commonly occured in other studies, we performed our study solely in obese humans. In this setting, we were able to compare diabetic to non-diabetic patients, all of them with the same degree of trunkal obesity.

At first glance, our results seem confusing because they deviate from many others and do not support the common concept of a strong relationship between adiponectin and cholesterol levels. (Cnop *et al*., 2003). Although we observed a weak correlation between adiponectin and HDL levels in the whole cohort and a stronger one in non diabetics, this correlation was merely imposed by non-diabetic women. After the subjects have been divided into subgroups with respect to their sex and the presence of diabetes, a correlation between adiponectin and HDL was only present in non-diabetic women and absent in all other subgroups. Furthermore, the presence of diabetes mellitus weakened the positive correlation between HDL and adiponectin to non significant values in women, whereas this phenomenon did not

occur in men as no correlation in either men subgroup was found. Also, with respect to total cholesterol and LDL cholesterol, the latter being the crucial risk factor for obesity and diabetes related morbidity and mortality, no correlations with serum adiponectin were found. In contrast, we observed an inverse correlation between serum adiponectin and triglycerides in the whole cohort and in most of subgroups. The clinical value of this finding, however, is of concern, since LDL and TC being much better predictors of mortality and morbidity proved to be of no associations with adiponectin levels in this study.

Our results should be discussed bearing in mind the unsolved "adiponectin paradox": adipose tissue is the only source of adiponectin, but decreased concentrations of adiponectin have been reported in humans and animals with increased fat amounts. This relationship is paradoxical, whatever explanation would be proposed. In simple words, the less fat tissue, the more adiponectin is produced by this tissue in the body. Following this rule, in cases lacking fat tissue completely, adiponectin concentrations would be extremely high – but the question of the source of its secretion would remain unsolved even then.

Interestingly, an increasing number of other clinical studies question the role of adiponectin in human pathology *in vivo*. For example, Abbasi *et al*. demonstrated that plasma adiponectin concentrations did not increase in association with moderate weight loss in insulin-resistant, obese women. Thus, neither weight loss, per se, nor enhanced insulin sensitivity resulted in a change in plasma adiponectin concentrations (Abbasi *et al*., 2004). Also, the association between adiponectin and incident coronary heart disease risk has been recently doubted. According to a large British study, adiponectin did not predict coronary heart disease events in unadjusted or adjusted analyses despite its association with insulin resistance and diabetes (Lawlor *et al*., 2005). Furthermore, the role of adiponectin production for the circulating protein concentration in humans is unclear. A reduced adiponectin secretion rate per tissue unit is probably counterbalanced by the increased total body fat amounts in obesity and insulin resistance (Hoffstedt *et al*., 2004).

Adiponectin has been proposed to be one of biochemical markers in obesity and diabetes, or at least a candidate for such a marker. We agree that clinicians need simple and available tools to assess the metabolic status of the obese patient and that researchers should search these tools. However, in view of our results and the controversies presented above, we suggest that the role of adiponectin in the clinical control of obesity and diabetes should be questioned as no strong relationship between adiponectin and plasma cholesterol has been demonstrated. Health care professionals must be aware that a lot of proteins may be involved in the pathogenesis of diabetes and obesity but only very few of them *really* correlate with treatment results and the clinical picture of these disorders. This should also be considered in the terms of cost and effectiveness of treatment, especially as we face an epidemic of obesity and diabetes in Europe.

In conclusion, as we demonstrate in this paper in a human cohort *in vivo*, there is no correlation between adiponectin and total and LDL cholesterol levels in obese subjects with and without type 2 diabetes mellitus. Second, a positive correlation between HDL cholesterol levels and adiponectin occured only in obese women without diabetes, resulting in an overall statistical trend in the whole cohort with respect to HDL. Third, an inverse correlation between serum adiponectin and triglycerides was found, but the clinical significance of this finding remains to be established.

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