Early Atherosclerosis in Obese Juveniles Is Associated with Low Serum Levels of Adiponectin

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Context: There is growing evidence that adiponectin, the most abundant adipocytokine of adipose tissue cells, plays a crucial role in advanced atherosclerosis.

Objective: The objective of the study was to evaluate the role of adiponectin in early atherosclerosis.

Design: One hundred forty obese juveniles (mean age, 13.5 ± 4.4 yr) and 100 age-matched, healthy, normal-weight controls from the STYrian Juvenile Obesity Study were investigated. We measured adipocytokines, inflammatory biomarkers, parameters of insulin resistance, and lipid subfractions. Intima-media thickness (IMT) of common carotid arteries was determined by ultrasonography. Furthermore, lipometric measurements were performed in obese juveniles to determine the topographic distribution of sc adipose tissue (SAT).

Results: Compared with controls, the group of obese juveniles exhibited a significantly increased IMT ($P < 0.001$) and elevated high-sensitive C-reactive protein ($P < 0.001$), indicating early stages of atherosclerosis. Serum levels of adiponectin were highly significantly negatively correlated with carotid IMT, even after controlling for common cardiovascular risk factors ($P < 0.001$; r = −0.34). Furthermore, adiponectin was positively correlated with high-density lipoprotein-free cholesterol and serum apolipoprotein-A1 and negatively with triglycerides, insulin resistance, uric acid, and serum transaminases. By a multiple regression analysis, adiponectin was shown to be the strongest predictive variable for carotid IMT. Finally, adiponectin was found positively correlated with SAT thickness of the rear and inner thigh in boys and negatively with the SAT thickness of the neck in girls.

Conclusion: In summary, our study describes an influence of SAT topography on adiponectin serum levels and provides first evidence that incipient atherosclerosis is associated with low serum levels of this adipocytokine. (*J Clin Endocrinol Metab* **90:** 4792–4796, 2005)

BESIDES SERVING AS energy storage, adipose tissue constitutes a highly active endocrine organ (1). Adiponectin, a cytokine that is exclusively and abundantly expressed in adipose tissue (2), was initially found to be decreased in obesity (3). Later on, studies revealed that hypoadiponectinemia is also associated with insulin resistance (4), type 2 diabetes (5), dyslipidemia (6), and hypertension (7). Furthermore, there is growing evidence that adiponectin has a protective effect against atherosclerosis due to antiinflammatory and antiatherogenic features (8). This is in line with observations that adiponectin levels are decreased in adults afflicted with advanced stages of atherosclerosis, such as coronary artery disease (9), and in subjects with endothelial dysfunction (10, 11). However, the significance of adiponectin in early atherosclerosis is still unknown. Therefore, we analyzed serum adiponectin levels in obese juveniles with reference to the fact that we observed in a foregoing study already increased carotid intima-media thickness (IMT) paralleled by a subclinical inflammation detected by an increased high-sensitive C-reactive protein (hs-CRP) in obese kids aged around 13 yr (12). The study participants were additionally examined for cardiovascular risk factors, such as insulin resistance, dyslipidemia, oxidized low-density lipoprotein (oxLDL), and other adipocytokines as well as further relevant parameters, *e.g.* leptin, resistin, and homocysteine, to explore possible relationships between adiponectin and metabolic abnormalities in juvenile obesity (13–17). Finally, the distribution of sc adipose tissue (SAT) and percent as well as total body fat were evaluated by means of a lipometer device, and correlated with the other data.

Subjects and Methods

Subjects

Study participants were derived from the STYrian Juvenile OBesity Study (STYJOBS), which is designed to investigate early atherosclerosis and metabolic disorders in obese juveniles. Study participants were recruited by public advertisement in local newspapers and on television. The inclusion criterion for the obese probands was juvenile obesity [if aged under 18 yr: body mass index (BMI) > 97th percentile;

if aged over 18 yr: BMI > 30 kg/m²] (18), and exclusion criteria were endocrine diseases (*e.g.* hypothyreosis) and infectious diseases. Controls were volunteers partially recruited from the Department of Pediatric Surgery, at which they underwent minor elective surgery (*e.g.* herniotomia). Blood samples were collected before surgery, and they had to be normal weighted (<18 yr, BMI around 50th percentile; above 18 yr, BMI < 25 kg/m²) and free of infectious or endocrine diseases. One hundred forty obese juveniles (mean age 13.5 ± 4.4 yr) and 100 normal-weight, age- and sex-matched, healthy controls were investigated. The study was approved by the Ethical Committee of the Medical University of Graz. Blood collection and ultrasonography were performed after written informed consent was given by the probands if aged over 18 yr or by their parents if they were under 18 yr old. At the time of blood collection, the probands were fasting. Venous puncture was performed in a standard procedure (cubital vein approach with butterfly), and blood samples were immediately centrifuged at 3500 rpm at ambient temperature and stored at −80 C until analysis.

Laboratory analysis

Adiponectin, leptin, and resistin were determined by ELISA (Biovendor Laboratory Medicine, Inc., Brno, Czech Republic) according to manufacturer's instructions. Intra- and interassay coefficients of variation for all ELISAs in our study were less than 10%. Cholesterol and triglycerides were measured by means of an electrochemiluminiscence assay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany), and lipoproteins were separated by a combined ultracentrifugation-precipitation method (β-quantification). Blood lipids were analyzed as outlined elsewhere (19). Soluble CD 40 ligand (sCD40L), and oxLDL were measured by commercially available ELISA (human sCD40L instant ELISA; Bender Medsystems BMS239 Instruments, Vienna, Austria; Mercodia oxLDL competitive ELISA, Uppsala, Sweden). The hs-CRP was measured with a particle-enhanced immunoturbidimetric assay [Tina-quant C-reactive protein latex ultrasensitive assay (Roche Diagnostics)]. Homocysteine was analyzed by triple quadrupole mass spectometry (API 2000 LC/MS/MS system; Applied Biosystems, Foster City, CA) using a 3.3 × 0.46 cm HPLC column (SUPELCO LC-CN). Plasma insulin was measured by ELISA (Mercodia), and plasma glucose was measured by the glucose hexokinase method on a Hitachi 917 chemical analyzer (Tokyo, Japan). Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as the product of the fasting plasma insulin value (in microunits per milliliter) and the fasting plasma glucose value (in millimoles per liter) divided by 22.5 (20). HOMA-IR, a representative value for insulin resistance, ordinarily ranges from 0 to 15. The transaminases aspartate aminotransferase (AST)/glutamic oxaloacetic transaminase (GOT), alanine aminotransferase (ALT)/glutamic pyruvic transaminase (GPT), and γ-glutamyl transpeptidase were measured by routine laboratory methods on a Hitachi 917 chemical analyzer.

Carotid artery ultrasound

The ultrasound protocol involved scanning of the bulbous near the common carotid artery on both sides with a 12- to 5-MHz broadband linear transducer on a HDI 5000 (ATL, Bothell, WA). All scans were performed by the same investigator. Longitudinal images directed through the center of the artery were taken at each vessel site. Measurements were made from stored digital images by an experienced reader. The carotid IMT was assessed at the far wall as the distance between the interface of the lumen and intima and the interface between the media and adventitia. The maximal IMT was recorded at each of the vessel segments and averaged for the left and right sides. The lumen diameter was calculated as the interadventitial diameter minus twice the maximum far wall IMT. All diameters were measured during diastole to avoid image blurring due to systolic arterial wall motion and minimize the influence of blood pressure.

Lipometry

Measurements of SAT thickness were performed by means of a patented optical device (EU patent no. 0516251) on 15 anatomically well-defined body sites distributed from neck to calf on the right and left side of all obese juveniles and then averaged for both body sides. The sensor head of the lipometer, which is held perpendicular to the measurement site, consists of light-emitting diodes (lambda = 660 nm, light intensity 3.000 millicandela) as light sources and a photodetector, which measures the corresponding light intensities that are backscattered in the SAT. Calibration and evaluation were done using computer tomography as the reference (21). Percent and total body fat were calculated from the lipometer-derived data. Total body electrical conductivity was initially used as a reference method for estimating percentage total body fat (22).

Statistics

Statistical analysis was performed by SPSS (version 11.5; SPSS, Inc., Chicago, IL). Data were expressed as mean ± 1 SD. Distributions of continuous variables were examined for skewness and curtosis and were logarithmically transformed, where appropriate. Associations between adiponectin and other variables were determined by simple linear regression analysis for continuous, and Student's *t* test for categorical variables. Partial correlation analysis of adiponectin and other variables with controlling for possible confounders was applied. Multiple regression analysis was performed to determine predictive variables for carotid IMT. A value of $P < 0.05$ was considered statistically significant.

Results

The clinical and laboratory characteristics of the study probands are summarized in Table 1. Adiponectin serum concentrations were higher in females in the controls (13.46 *vs.* 12.78 μg/ml; $P = 0.30$) and the obese cohort (11.01 *vs.* 10.43 μg/ml; $P = 0.58$), but this difference was not statistically significant. Adiponectin was reduced in obese juveniles, compared with controls ($P = 0.009$; Table 1), and in a correlation analysis including all study subjects, adiponectin was found negatively correlated with BMI ($P = 0.01$; r = −0.21) and BMI-SD score ($P = 0.013$; r = −0.16) (18). The results of further unadjusted correlation analysis of adiponectin serum concentrations (including the values of all 240 study participants) with several other parameters measured are listed in Table 2. All of the results in Table 2 remained statistically significant even after adjustment for age, sex, and BMI. The highly significant negative correlation between adiponectin and carotid IMT ($P < 0.001$; r = −0.34)

TABLE 1. Clinical and laboratory characteristics of the study subjects from STYJOBS

Variable	Controls	Obese juveniles
Individuals (n)	100	140
Female/male	44/56	73/67
Age (yr)	14.4 ± 4.4	13.5 ± 4.4
Age range (yr)	5–25	5–25
Body length (m)	1.6 ± 0.1	1.6 ± 0.1
Body weight (kg)	50.1 ± 15.5	79.4 ± 22.9[a]
BMI (kg/m²)	19.4 ± 3.2	30.9 ± 5.4[a]
BMI-SDS	0.3 ± 1.2	6.0 ± 2.4[a]
Cholesterol (mmol/liter)	4.22 ± 0.74	4.26 ± 0.65
HOMA-IR	1.7 ± 1.3	5.9 ± 4.8[a]
SBP (mm Hg)	118.9 ± 13.2	128.8 ± 16.6[a]
DBP (mm Hg)	64.5 ± 7.7	69.9 ± 10.9[b]
Carotid IMT (cm)	0.053 ± 0.1	0.068 ± 0.1[a]
Creatinine (μmol/liter)	62.78 ± 17.68	65.42 ± 13.26
hs-CRP (ng/ml)	1.0 ± 1.4	3.9 ± 4.7[a]
Adiponectin (μg/ml)	12.8 ± 6.4	10.8 ± 4.9[b]
Resistin (ng/ml)	3.6 ± 1.1	3.9 ± 1.4
Leptin (ng/ml)	11.8 ± 11.3	31.8 ± 14.5[a]

BMI-SDS, BMI SD score; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] $P < 0.001$ (obese *vs.* controls analyzed by Student's *t* test); [b] $P < 0.01$.

TABLE 2. Correlation analysis of adiponectin serum levels of all study participants with several other parameters

Variable	P	r value
ALT/GPT	0.007	−0.23
AST/GOT	0.021	−0.20
Carotid IMT	<0.001	−0.34
HOMA-IR	<0.001	−0.34
Triglycerides	0.04	−0.14
Uric acid	0.001	−0.28
HDL-cholesterol	0.006	0.21
HDL-cholesterolester	0.005	0.22
HDL-free cholesterol	<0.001	0.33
HDL-phospholipids	0.001	0.27
Serum apolipoprotein-A1	<0.001	0.34

is depicted in Fig. 1. This correlation remained statistically significant, even after controlling for BMI, HOMA-IR, cholesterol, triglycerides, blood pressure, hs-CRP, gender, and age ($P = 0.001$; r = −0.32). Furthermore, a multiple regression analysis using the carotid IMT as the dependent variable and BMI, HOMA-IR, cholesterol, triglycerides, blood pressure, hs-CRP, gender, age, and adiponectin as independent variables identified adiponectin as the strongest predictive variable for carotid IMT ($P = 0.002$).

Concerning lipid metabolism, adiponectin was found positively correlated with high-density lipoprotein (HDL)-cholesterol ($P = 0.006$; r = 0.21), HDL-cholesterol ester ($P = 0.005$; r = 0.22), HDL-free cholesterol ($P < 0.001$; r = 0.33), HDL-phospholipids ($P = 0.001$; r = 0.27), and serum apolipoprotein-A1 ($P < 0.001$; r = 0.34). A negative correlation was seen with triglycerides ($P = 0.04$; r = −0.14). No significant correlations of adiponectin were observed with LDL or very low-density lipoprotein subfractions, free fatty acids, lipoprotein (a), or apolipoproteins other than apolipoprotein-A1 (data not shown).

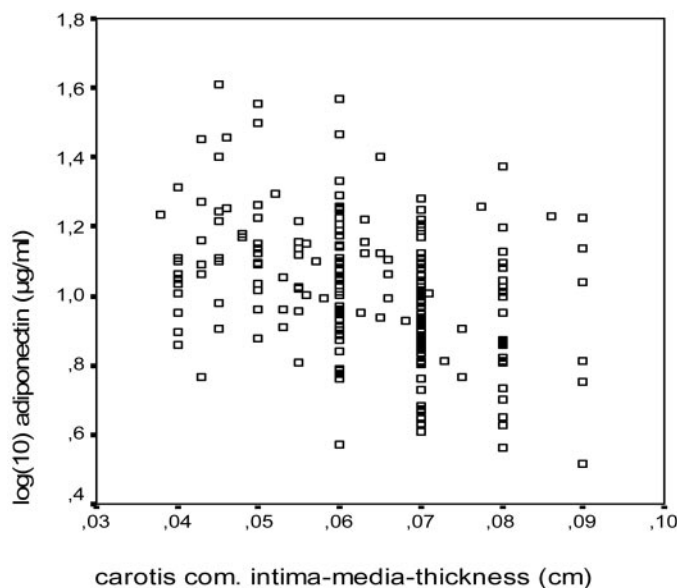Beside the correlations as mentioned above, adiponectin

FIG. 1. Adiponectin negatively correlates with carotid IMT ($P < 0.001$; r = −0.34), even after controlling for BMI, HOMA-IR, cholesterol, triglycerides, blood pressure, hs-CRP, gender, and age ($P = 0.001$; r = −0.32).

was found negatively correlated with HOMA-IR ($P < 0.001$; r = −0.34), which was elevated in the obese juveniles (Table 1), indicating a beginning type 2 diabetes mellitus in these young patients. Significantly negative correlations of adiponectin were also seen with uric acid ($P = 0.001$; r = −0.28) and the liver enzymes ALT/GPT ($P = 0.007$; r = −0.23) and AST/GOT ($P = 0.021$; r = −0.2). Inflammatory parameters (sCD40L, hs-CRP, oxLDL) and homocysteine did not significantly correlate with adiponectin (not shown).

Finally, whereas percent and total body fat values of obese juveniles did not correlate with adiponectin (not shown), the topography of SAT was found to significantly influence its serum levels (Table 3) in dependence of gender: obese boys exhibited a significant positive correlation of adiponectin with SAT thickness of the inner ($P = 0.015$; r = 0.29; Fig. 2) and rear thigh ($P = 0.049$; r = 0.24), with obese girls a negative correlation was observed between adiponectin and SAT thickness of the neck ($P = 0.01$; r = −0.30). The SAT thickness of other locations did not significantly correlate with adiponectin (Table 3). Leptin, which was elevated in obese juveniles ($P < 0.001$), and resistin (not elevated) did not significantly correlate with adiponectin (not shown). With the exception of the above-mentioned correlations between adiponectin and SAT thickness, all other statistical analyses did not reveal any significant gender-related differences.

Discussion

Several studies suggest that adiponectin is protective against atherosclerosis, and measurements of adiponectin may be helpful to assess the risk of coronary artery disease (8–11, 23). However, the data concerning an association between decreased adiponectin and increased IMT in obese adults are contradictory (24, 25). Furthermore, the involvement of adiponectin in very early stages of atherosclerosis was not examined so far. Toward this we measured adiponectin and carotid IMT in obese juveniles. Enhanced carotid IMT is an established marker for atherosclerosis (26, 27), and there are observations showing that carotid IMT in obese children is related to flow-mediated dilatation of the brachial artery, which is also a marker of early atherosclerosis (28). We

TABLE 3. Correlation analysis of adiponectin serum levels and SAT-thickness in obese females and obese males

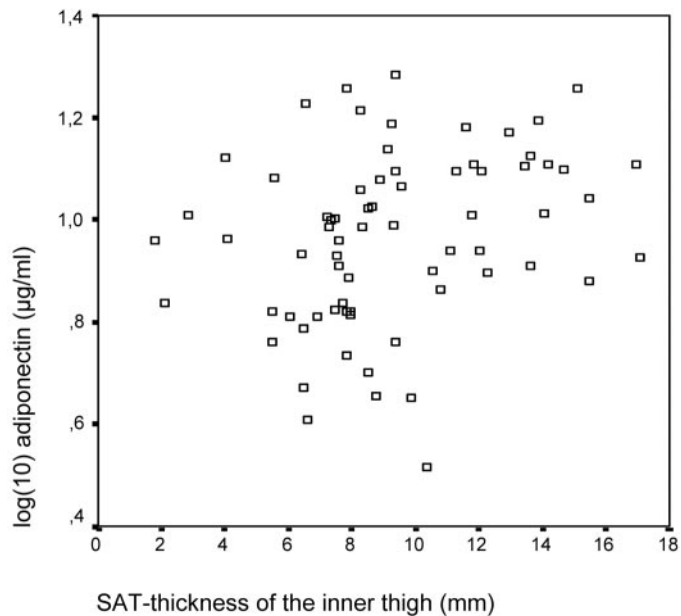| SAT thickness	Obese females	Obese males
Neck	0.01[a]/−0.30	0.49/−0.08
Triceps	0.62/−0.06	0.47/0.09
Biceps	0.08/−0.21	0.25/0.14
Upper back	0.14/−0.17	0.50/−0.08
Front chest	0.07/−0.21	0.78/0.03
Lateral chest	0.50/−0.08	0.41/−0.10
Upper abdomen	0.78/−0.03	0.86/−0.02
Lower abdomen	0.90/−0.02	0.37/0.11
Lower back	0.93/0.01	0.71/0.05
Hip	0.94/−0.01	0.83/0.03
Front thigh	0.21/0.15	0.09/0.20
Lateral thigh	0.11/0.19	0.17/0.17
Rear thigh	0.37/0.11	0.049[a]/0.24
Inner thigh	0.32/0.12	0.015[a]/0.29
Calf	0.97/0.01	0.19/0.16

Data represent *P*/r value.
[a] $P < 0.05$.

FIG. 2. Adiponectin positively correlates with SAT thickness of the inner thigh in obese male juveniles ($P = 0.015$; $r = 0.29$).

reasoned that if adiponectin plays a causative role in the pathophysiology of atherosclerosis, serum levels should be altered in the early phase of this disease. This notion appears to be confirmed by the significant negative correlation between adiponectin and carotid IMT as observed in the obese juveniles. To the best of our knowledge, this is the first observation that earliest stages of atherosclerosis as identified by an increased IMT are associated with hypoadiponectinemia, already in childhood. The observation that adiponectin was the strongest independent variable to predict carotid IMT in a multiple regression analysis strongly argues for a major role of this adipocytokine in early atherosclerosis. The vasoprotective effect of adiponectin is supported by *in vitro* studies showing that adiponectin decreases the expression of adhesion molecules on endothelial cells (29), suppresses foam cell formation by macrophages (30), and inhibits vascular smooth muscle migration (31). Furthermore, it could be shown that adiponectin knock out mice developed atherosclerotic lesions as detected by neointimal formation (32). Nevertheless, the exact pathophysiologic implication of adiponectin in early atherosclerosis as observed in our obese juveniles remains to be clarified by further in-depth investigations.

It has also been reported that adiponectin is positively correlated with HDL-cholesterol and negatively with triglycerides (6, 33). The present results appear to confirm (13–15) and extend these data in juveniles (Table 2). Concerning the correlation among HDL subfractions, triglycerides, and adiponectin, it should be noted that adiponectin increases lipoprotein lipase activity (34) and stimulates fatty acid oxidation (35), which may be related to low adiponectin levels accompanied by dyslipidemia.

Furthermore, we found negative correlations among adiponectin, insulin resistance, and uric acid, which confirms the close relationship between adiponectin and the metabolic syndrome (36), even as early as in childhood.

Although it is well established that adiponectin is negatively correlated with BMI and significantly reduced in obesity, it has been recently suggested that adiponectin is by far stronger related to dyslipidemia and insulin resistance than to the degree of obesity (4, 33). This is supported by our lipometric data derived from the obese juveniles, in whom we observed no significant correlations between adiponectin and total as well as percent body fat. All these findings underline that adiponectin is not associated with the degree of obesity *per se* (33). Nevertheless, adiponectin correlated positively with the SAT thickness of the rear and inner thigh in boys and negatively with the SAT thickness of the neck in girls, suggesting a relationship between fat distribution and adiponectin levels.

Our results also confirm recent findings of an inverse correlation between adiponectin and liver enzymes (37). In this context, decreased adiponectin levels were brought into connection with nonalcoholic hepatic steatosis (38). Putative hepatoprotective effects of adiponectin include the induction of hepatic fatty acid oxidation, inhibition of fatty acid synthesis, and suppression of TNFα production (39).

Taken together, our data identified an influence of SAT topography on adiponectin serum levels and provide first evidence that early atherosclerotic lesions are associated with hypoadiponectinemia. Hence, adiponectin appears to play a significant role in early atherosclerosis. Furthermore, prospective studies are needed to clarify whether adiponectin serum levels are of prognostic value to identify patients at high risk to develop severe vascular disease.

Acknowledgments

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