Circulating Adiponectin and Resistin Levels in Relation to Metabolic Factors, Inflammatory Markers, and Vascular Reactivity in Diabetic Patients and Subjects at Risk for Diabetes

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OBJECTIVE — Adiponectin and resistin, two recently discovered adipocyte-secreted hormones, may link obesity with insulin resistance and/or metabolic and cardiovascular risk factors. We performed a cross-sectional study to investigate the association of adiponectin and resistin with inflammatory markers, hyperlipidemia, and vascular reactivity and an interventional study to investigate whether atorvastatin mediates its beneficial effects by altering adiponectin or resistin levels.

RESEARCH DESIGN AND METHODS — Associations among vascular reactivity, inflammatory markers, resistin, and adiponectin were assessed cross-sectionally using fasting blood samples obtained from 77 subjects who had diabetes or were at high risk to develop diabetes. The effect of atorvastatin on adiponectin and resistin levels was investigated in a 12-week–long randomized, double-blind, placebo-controlled study.

RESULTS — In the cross-sectional study, we confirm prior positive correlations of adiponectin with HDL and negative correlations with BMI, triglycerides, C-reactive protein (CRP), and plasma activator inhibitor (PAI)-1 and report a negative correlation with tissue plasminogen activator. The positive association with HDL and the negative association with PAI-1 remained significant after adjusting for sex and BMI. We also confirm prior findings of a negative correlation of resistin with HDL and report for the first time a positive correlation with CRP. All of these associations remained significant after adjusting for sex and BMI. No associations of adiponectin or resistin with any aspects of vascular reactivity were detected. In the interventional study, atorvastatin decreased lipid and CRP levels, but adiponectin and resistin were not specifically altered.

CONCLUSIONS — We conclude that adiponectin is significantly associated with inflammatory markers, in part, through an underlying association with obesity, whereas resistin's associations with inflammatory markers appear to be independent of BMI. Lipid profile and inflammatory marker changes produced by atorvastatin cannot be attributed to changes of either adiponectin or resistin.

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Abbreviations: ACH%, acetylcholine chloride with percentage increase over baseline of endothelium-dependent vasodilation; CRP, C-reactive protein; ET1, endothelin-1; ICAM, intracellular adhesion molecule; NID, nitroglycerin-induced dilation; NNP%, sodium nitroprusside with percentage increase over baseline of endothelium-independent vasodilation; PAI, plasma activator inhibitor; TNF-α, tumor necrosis factor-α; tPA, tissue plasminogen activator.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Obesity and insulin resistance are associated with cardiovascular risk factors, including altered levels of inflammatory markers and endothelial dysfunction (1). Two recently identified adipocyte-secreted hormones, adiponectin and resistin, are thought to link obesity with insulin resistance and cardiovascular risk (1–7). Adiponectin, a recently discovered 244–amino acid, adipose-specific protein (2), is found in high concentrations in the peripheral circulation (3), and its circulating levels are decreased in obesity and type 2 diabetes (4). Adiponectin levels are inversely associated with central or overall adiposity, as well as hyperlipidemia and insulin resistance independently of BMI (5,6). Resistin levels have been reported to be markedly elevated in obese mice and to be decreased by insulin sensitizers, such as rosiglitazone and other thiazolidinediones, and by the administration of antiresistin antiserum, which also leads to a significant decrease in blood glucose (7). These initial findings in mice were challenged by subsequent observations, however, demonstrating increased or decreased resistin levels in obesity as well as variable responses to thiazolidinediones (8,9) and a null association between circulating resistin and insulin resistance in humans (10,11). Interestingly, although resistin has structural similarities to proteins involved in inflammatory processes (12), circulating resistin levels have never been studied in relation to inflammatory markers in humans. In contrast, adiponectin has been associated with markers of inflammation, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) (13,14), but associations with several other inflammatory markers remain to be studied.

Thus, we have studied cross-sectionally whether adiponectin is inversely associated and if resistin is

positively associated with inflammatory markers, hyperlipidemia, and vascular reactivity. We also studied, in the context of a 12-week–long, double-blind, randomized, placebo-controlled clinical trial, whether atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, which reduces total cholesterol, LDL (15), and triglycerides (16), increases HDL levels (17), and may mediate improved insulin sensitivity (18), affects these outcomes by altering adiponectin and/or resistin levels.

RESEARCH DESIGN AND METHODS

The present study included 77 previously studied subjects (19) who had diabetes with no serious long-term complications (defined as macroalbuminuria, severe neuropathy, and/or peripheral vascular disease associated with foot ulceration or other lower-extremity amputations) or were considered at higher risk to develop type 2 diabetes than the general population (a positive family history and a normal 75-g oral glucose tolerance test, subjects with at least one first-degree relative with type 2 diabetes, or subjects with impaired glucose tolerance), using previously described criteria (20). The study protocol was approved by the institutional review boards at the Joslin Diabetes Center and the Beth Israel Deaconess Medical Center. After being informed on the purpose and procedures of the study, all subjects signed an informed consent form. Subjects were evaluated at an initial screening visit, which involved a full medical history and physical examination including blood pressure, weight, height, waist-to-hip ratio, fundoscopy, and evaluation for clinical signs of neuropathy. Subjects were excluded if they had a known history of cardiovascular disease, stroke or transient ischemic attack, uncontrolled hypertension, liver disease, renal disease, severe dyslipidemia (triglycerides >600 mg/dl or cholesterol >350 mg/dl), or any other serious chronic disease requiring active treatment. Women of child-bearing potential not using an effective form of nonhormonal birth control and subjects taking lipid-lowering agents during the last 3 months, glucocorticoids, antineoplastic agents, psychoactive agents, or bronchodilators on a regular basis were also excluded.

Cross-sectional study

Blood samples were obtained after an overnight fast (~10 h) and a 24-h period free of alcohol or vigorous exercise. Subjects were asked not to take their diabetes medications (sulfonylureas or metformin) for 12 h before each visit. Those subjects using insulin were requested to hold the rapid-acting insulin the morning of each visit. Blood samples were drawn from an antecubital vein with a 19-gauge needle without venous stasis, and the sera were stored at −70°C.

Interventional study

The effect of atorvastatin on adiponectin and resistin levels was investigated in a randomized, double-blind, placebo-controlled study. The 77 subjects described above in the cross-sectional study were randomized in a double-blind manner to receive either 20 mg of atorvastatin daily or the matching placebo for 12 weeks. The subjects were asked to continue with their prior medications, diet plan, and physical activity level in a constant manner for the duration of the study. Subjects were evaluated at baseline and reevaluated after a 12-week treatment period at an exit visit with repeat laboratory evaluations. Vascular reactivity testing was also done at baseline and repeated at 12 weeks. To evaluate the association of serum adiponectin levels, serum resistin levels, and markers of vascular inflammation, fasting blood samples were obtained at baseline and at 12 weeks.

Hormone measurements

Blood samples were analyzed for HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, endothelin-1 (ET1), CRP, tumor necrosis factor-α (TNF-α), intracellular adhesion molecule (ICAM), plasma activator inhibitor (PAI)-1, tissue plasminogen activator (tPA), adiponectin, and resistin. Plasma total cholesterol, HDL cholesterol, and triglycerides were measured using the Synchron CX analyzer (Beckman/Coulter) as previously described (21). LDL cholesterol was calculated from these results. Hormone concentrations were measured using commercially available methods (10) as follows: adiponectin radioimmunoassay (Linco Research, St. Charles, MO) (sensitivity 2 μg/ml; intra-assay coefficient of variation [CV] 1.78–6.21%), human resistin (BioVendor, Brno, Czech Republic) (0.2 ng/ml; 3.4–5.2%), soluble ICAM (R & D Systems, Minneapolis, MN) (0.35 ng/ml; 3.3–4.8%), and ET1 (R & D Systems) (1.0 pg/ml; 4.2–4.6%) were measured in plasma by the enzyme-linked immunosorbent assay method. TNF-α (Immulite DPC) (8.1 pg/ml; 2.6–3.6%) and CRP (Immulite DPC) (0.01 mg/dl; 4.2–6.4%) were measured by chemiluminescent immunoassay. PAI-1 (Diagnostica Stago, France) (1.0 ng/ml; 5.48–6.53%) and tPA (Diagnostica Stago) (1.0 ng/ml; 4.49–4.54%) were also measured by the enzyme-linked immunosorbent assay method. To minimize variability, hormone levels were measured in one assay for all subjects participating in the cross-sectional study and in one assay for each subject in the interventional studies.

Vascular reactivity tests

The vascular reactivity of the forearm skin microcirculation was evaluated by laser Doppler perfusion imaging measurements before and after iontophoresis of acetylcholine chloride ([ACH%], percent increase over baseline of endothelium-dependent vasodilation) and sodium nitroprusside ([NNP%], percent increase over baseline of endothelium-independent vasodilation) and as previously described (22). To assess the endothelium-dependent reactivity in the macrocirculation, the flow-mediated brachial artery dilation was measured by using a high-resolution ultrasound with a 10.0-MHz linear array transducer and an HDI Ultramark 9 system (Advanced Technology Laboratories, Bothel, WA). Reactive hyperemia was produced by inflating a pneumatic tourniquet to 50 mmHg above the systolic pressure for 5 min distal to the brachial artery, and the flow at rest and reactive flow were measured. All measurements were in accordance with recently published guidelines (23). Endothelium-independent vasodilation in the macrocirculation (nitroglycerin-induced dilation [NID]) was assessed by studying brachial artery diameter changes 5 min after the administration of 400 μg of sublingual nitroglycerine (19). This test was performed 15 min after the reactive hyperemia test and after obtaining a new baseline reading.

Data analysis

Data were summarized using standard procedures. Any missing values due to insufficient sample or values outside the assay range were excluded from the analysis

Table 1—*Baseline characteristics of the subjects*

	At risk of type 2 diabetes	Diabetic patients
Total patients	37	40
Age (years)	49 ± 12	53 ± 13
Men	20 (54)	23 (58)
With first-degree relative (normal glucose tolerance)	25 (68)	—
With impaired glucose tolerance	12 (32)	—
Type 1/type 2 diabetes	—	20/20
Diabetes duration (years)	—	8 ± 12
BMI (kg/m^2)	29.5 ± 5.8	29.8 ± 9.4
Fasting glucose (mg/dl)	90 ± 11	178 ± 79
HbA_{1c} (%)	5.4 ± 0.4	8.0 ± 1.6
Total cholesterol (mg/dl)	206 ± 40	205 ± 42
LDL (mg/dl)	125 ± 31	124 ± 35
HDL (mg/dl)	59 ± 19	60 ± 14
Triglycerides (mg/dl)	118 ± 78	102 ± 75
Diabetes treatment		
Diet	—	1 (3)
Oral agents	—	15 (37)
Insulin	—	24 (60)
Resting brachial artery diameter (mm)	3.4 ± 0.7	3.6 ± 0.7
FMD	5.8 (4.0–9.3)	5.0 (3.2–7.8)
NID	15.2 (11.4–20.9)	13.4 (10.1–17.1)
ACH%	158 ± 77	149 ± 77
NNP%	88 ± 49	93 ± 44

Data are mean ± SD, *n* (%), or median (25–75 percentiles). FMD, flow-mediated dilation percentage increase over baseline (endothelium-dependent reactivity of macrocirculation).

of this specific variable only. In the cross-sectional study, we performed both Spearman's and Pearson's correlation analysis, and we report herein the Spearman's correlation coefficients that are more conservative. Then we performed bivariate and multivariate regression analyses. We evaluated for potential associations among serum adiponectin levels and serum resistin levels (dependent variables) and BMI, metabolic markers (lipid profile), inflammatory parameters (ICAM, ET1, TNF-α, CRP, PAI-1, tPA), as well as vascular reactivity, all expressed as continuous variables. In the multivariate analysis models, we evaluated the same independent variables after controlling for potential confounding by sex, sex and BMI, and sex, BMI, and HbA_{1c}. Logarithmic transformation was used to normalize nonnormally distributed dependent variables.

In the interventional study, we assessed the differences in adiponectin and resistin levels, lipid levels and inflammatory marker levels, as well as BMI using a paired *t* test for parametrically distributed data and the Wilcoxon matched-pair signed-rank test for nonparametrically distributed data to compare baseline data and data at the end of the study. The *t* test was used to compare the baseline characteristics between those receiving active treatments and those receiving placebo.

SPSS 8.0 software (SPSS, Chicago, IL) was used for statistical analysis. A *P* value <0.025 (two tailed) was considered statistically significant for all analyses (Bonferroni correction). Descriptive statistics are presented as mean ± SE.

RESULTS

Cross-sectional study

Baseline characteristics of the study population are presented in Table 1. Spearman correlations, including all subjects, among adiponectin and the metabolic markers, inflammatory markers, and vascular reactivity, confirmed prior findings of the positive correlation with HDL ($r = 0.42$, $P < 0.01$) and the negative correlations with triglycerides ($r = -0.35$, $P < 0.01$), CRP ($r = -0.21$, $P = 0.026$), PAI-1 ($r = -0.39$, $P < 0.01$), and BMI ($r = -0.32$, $P < 0.01$). Additionally, we discovered the negative correlation of adiponectin with tPA ($r = -0.30$, $P < 0.01$) (Table 2). We found no correlation of adiponectin with vascular reactivity or glucose levels. Spearman correlations, including all subjects, among resistin and the metabolic markers, inflammatory markers, and vascular reactivity, confirmed prior findings of a negative correlation with HDL ($r = -0.23$, $P < 0.01$) and positive correlation with CRP ($r = 0.25$, $P < 0.01$) (Table 2). Resistin was not associated with any other study variable, including glucose.

We then performed bivariate regression analyses of adiponectin and of resistin with metabolic factors, inflammatory markers, and vascular reactivity considered as independent variables (Tables 3 and 4). We found a positive correlation of adiponectin with HDL and a negative correlation of adiponectin with triglycerides, CRP, PAI-1, and tPA (Table 3). In addition, there was no association among adiponectin and total cholesterol, LDL, ICAM, ET1, TNF-α, and the vascular reactivity measurements (flow at rest, flow-mediated brachial artery dilation, NID, ACH%, and NNP%). To adjust for potential confounders, we then performed multivariate regression analyses, adjusting for successively introduced covariates: sex, then sex and BMI, and finally sex, BMI, and HbA_{1c}. With adjustment for sex, all of the positive and negative correlations found with the bivariate analyses remained significant. However, after adjusting for both sex and BMI, only the positive association with HDL and the negative association for PAI-1 remained significant (Table 3), indicating that adiponectin may mediate the effect of obesity on triglycerides, CRP, and tPA. Finally, we found a positive correlation of resistin with CRP and a negative correlation with HDL (Table 4), and these associations remained significant after adjusting for sex, BMI, and HbA_{1c}, indicating that the effect of resistin is independent of obesity and glycemic control. We also ran these correlations of adiponectin and resistin with metabolic markers, inflammatory markers, and vascular reactivity, excluding the type 1 diabetic subjects. We found a similar positive correlation of adiponectin with HDL ($r = 0.40$, $P < 0.01$), a negative correlation with PAI-1 ($r = -0.33$, $P < 0.01$), and a negative correlation with BMI ($r = -0.25$, $P < 0.025$). However, the other significant correlations found in the

Table 2—*Spearman correlation coefficients among adiponectin, resistin, metabolic and inflammatory markers, and vascular reactivity in subjects at risk of diabetes and in subjects with type 1 and type 2 diabetes*

	Adiponectin	Resistin	Total cholesterol	HDL	LDL	Triglycerides	ICAM	ET1	TNF-α	CRP	PAI-1	tPA	BMI	FR	FMD	NID	ACH%
Adiponectin																	
Resistin	−0.004																
Total cholesterol	−0.001	−0.01															
HDL	0.42*	−0.23*	0.33*														
LDL	−0.06	0.11	0.92*	0.12													
Triglycerides	−0.35*	0.02	0.25*	−0.43*	0.18												
ICAM	0.13	0.06	−0.18	−0.22	−0.15	0.07											
ET1	0.17	0.12	−0.03	−0.09	−0.03	−0.02	0.37*										
TNF-α	−0.07	0.02	−0.03	−0.03	−0.06	0.17	0.001	0.07									
CRP	−0.21†	0.25*	0.04	−0.19	0.07	0.16	0.14	0.35*	0.26*								
PAI-1	−0.39*	0.08	0.07	−0.41*	0.06	0.52*	0.14	0.15	0.29*	0.28*							
tPA	−0.30*	0.07	0.03	−0.40*	0.002	0.51*	0.13	0.21	0.27*	0.36*	0.72*						
BMI	−0.32*	0.13	−0.07	−0.40*	−0.01	0.32*	0.24‡	0.25	0.26*	0.60*	0.48*	0.48*					
FR	−0.12	0.15	−0.11	−0.35*	−0.03	0.16	0.21	0.41*	0.15	0.29*	0.21‡	0.27*	0.21‡				
FMD	−0.01	−0.14	0.01	0.19	−0.05	−0.06	−0.11	−0.16	−0.04	−0.23‡	−0.19	−0.34*	−0.13	−0.55*			
NID	−0.05	−0.25‡	0.07	0.13	−0.04	0.15	−0.24	−0.06	−0.14	−0.27*	0.001	−0.05	0.06	−0.50*	0.57*		
ACH%	−0.05	−0.03	0.11	0.13	0.11	−0.09	−0.19	0.02	0.04	0.04	−0.02	−0.03	−0.01	−0.13	−0.11	−0.01	
NNP%	0.10	0.06	−0.04	0.11	−0.04	−0.06	−0.13	0.10	−0.05	0.04	−0.03	−0.12	0.10	−0.12	−0.05	−0.05	0.52*

FMD, flow-mediated dilation percent increase over baseline (endothelium-dependent reactivity of macrocirculation); FR, resting brachal artery diameter (mm). *$P < 0.01$; †$P = 0.026$; ‡$P < 0.025$.

entire group did not remain significant (triglycerides [$r = -0.11$] and CRP [$r = -0.17$]), which was probably due to the smaller *n*. None of the previously significant correlations of HDL, CRP, and NID with resistin remained significant when we ran these correlations excluding the type 1 diabetic subjects from the entire group.

Finally, we ran all correlations in the entire study sample after statistically controlling for type 1 versus type 2 diabetes status. The previously nonsignificant associations remained unchanged. The significant associations were as follows after controlling for diabetes status: *1*) adiponectin versus HDL ($r = 0.27$, $P < 0.01$), versus triglycerides ($r = -0.07$, $P = 0.45$), versus tPA ($r = -0.09$, $P = 0.32$), versus BMI ($r = -0.18$, $P = 0.04$), and versus PAI-1 ($r = -0.022$, $P < 0.026$) and *2*) resistin versus HDL ($r = -0.27$, $P < 0.01$), versus CRP ($r = 0.23$, $P < 0.026$), and versus NID ($r = -0.20$, $P = 0.05$), which remained essentially unchanged.

Interventional study

Both atorvastatin and placebo treatment resulted in a decrease in total cholesterol and LDL levels, but the decrease in the atorvastatin group was much greater (Table 5). CRP levels also decreased significantly in the atorvastatin group but did not change significantly in the placebo group. Serum adiponectin levels did not change significantly in either the placebo or active treatment group, and serum resistin levels decreased significantly but to the same extent in both groups (Table 5), indicating that atorvastatin has no specific effect on these two hormones. Similar results were obtained when diabetic and nondiabetic subjects were considered separately.

CONCLUSIONS

— Accumulating evidence from animal and human studies shows that adiponectin plays an important role in insulin sensitivity (24–28), inflammation (29), atherogenesis (30,31), lipid metabolism (6,24), and thus influences hyperlipidemia and CAD (29). The association between adiponectin and insulin sensitivity has been established in animal models in which adiponectin administration reversed insulin resistance in lipoatrophic mice (25). Adiponectin levels are significantly lower in humans with type 2 diabetes or insulin

Table 3—*Bivariate and multivariate regression analyses of serum adiponectin levels on metabolic factors, inflammatory markers, and vascular reactivity

Parameters	β1	β2	β3	β4
Metabolic factors				
Total cholesterol (mg/dl)	0.03	0.02	−0.05	−0.05
LDL cholesterol (mg/dl)	−0.04	−0.04	−0.09	−0.08
HDL cholesterol (mg/dl)	0.37†	0.40†	0.31‡	0.31†
Triglycerides (mg/dl)	−0.22‡	−0.22‡	−0.17	−0.17
Inflammatory markers				
ICAM (ng/ml)	0.17	0.19	0.21	0.19
ET1 (pg/ml)	0.15	0.15	0.24	0.21
TNF-α (pg/ml)	−0.13	−0.14	−0.06	−0.05
CRP (mg/dl)*	−0.22‡	−0.25†	−0.07	−0.20
PAI-1 (ng/ml)	−0.36†	−0.36†	−0.24‡	−0.21
tPA (ng/ml)	−0.26†	−0.26†	−0.15	−0.15
Vascular reactivity				
FR	−0.11	−0.14	−0.002	−0.02
FMD	0.004	−0.003	−0.02	0.004
NID	−0.03	−0.05	−0.04	0.01
ACH%	−0.09	−0.12	−0.12	−0.10
NNP%	0.01	0.003	0.04	0.05

β1, bivariate standardized linear regression coefficient; β2, multivariate standardized linear regression coefficient adjusted for sex; β3, multivariate standardized linear regression coefficient adjusted for sex and BMI; β4, multivariate standardized linear regression coefficient adjusted for sex, BMI, and HbA_{1c}. FMD, flow-mediated dilation percentage increase over baseline (endothelium-dependent reactivity of macrocirculation); FR, resting brachial artery diameter (in millimeters). *Logarithmic transformation performed before analysis. †$P < 0.01$; ‡$P < 0.025$.

resistance (32) and increase in subjects treated with thiazolidinediones (33,34), suggesting that adiponectin plays a role in the thiazolidinedione effect of improving insulin sensitivity and decreasing inflammation. In addition, adiponectin may play a critical role in suppressing the inflammatory response that is associated with atherogenesis, endothelial dysfunction, and ultimately vascular disease (29). In vitro mechanistic studies in human aortic endothelial cells have shown that human recombinant adiponectin in a dose-dependent manner suppresses endothelial expression of adhesion molecules, proliferation of vascular smooth muscle cells, and the transformation of macrophages to foam cells (30). Adiponectin also significantly inhibits macrophage phagocytic activity and suppresses lipopolysaccharide-induced production of TNF-α (29). Animal studies in apolipoprotein E–deficient mice demonstrated that adiponectin suppressed the expression of adhesion molecules, scavenger receptors, and TNF-α levels, which cumulatively resulted in reduced in vivo atherosclerosis (35). Finally, it has recently been reported that circulating adiponectin correlates inversely with serum levels of certain inflammatory markers, such as CRP (13). We searched for novel associations between circulating adiponectin and tPA, in addition to confirming known associations with HDL, triglycerides, and PAI-1. Adiponectin's association with HDL and PAI-1 was independent of BMI, which suggests adiponectin may mediate some effects of adiposity, but whether central obesity or other unrecognized pathways might play a regulatory role remains to be elucidated by future studies.

We found that in subjects with diabetes or at risk of developing diabetes, adiponectin is negatively correlated with BMI, triglycerides, CRP, PAI-1, and tPA, suggesting that adiponectin may act as an anti-inflammatory mediator with respect to CRP, PAI-1, and tPA. These findings are consistent with prior data that adiponectin levels correlate negatively with inflammation and endothelial dysfunction (12). In addition to adiponectin's negative association with CRP (13), a molecule known to promote atherogenesis via monocytes and endothelial cells (36), we provide the first description of a negative association between adiponectin and tPA, a molecule known to play a role

Table 4—*Bivariate and multivariate regression analyses of serum resistin levels on metabolic factors, inflammatory markers, and vascular reactivity

Parameters	β1	β2	β3	β4
Metabolic factors				
Total cholesterol (mg/dl)	−0.004	−0.01	0.02	0.02
LDL cholesterol (mg/dl)	0.11	0.11	0.13	0.13
HDL cholesterol (mg/dl)	−0.28†	−0.33†	−0.33‡	−0.33†
Triglycerides (mg/dl)	0.03	0.04	0.01	0.01
Inflammatory markers				
ICAM (ng/ml)	−0.02	−0.01	−0.06	−0.05
ET1 (pg/ml)	0.22	0.22	0.23	0.25
TNF-α (pg/ml)	0.01	0.01	−0.02	−0.01
CRP (mg/dl)*	0.28†	0.29†	0.38†	0.39†
PAI-1 (ng/ml)	0.12	0.13	0.10	0.13
tPA (ng/ml)	0.08	0.08	0.03	0.03
Vascular reactivity				
FR	0.17	0.22	0.18	0.17
FMD	−0.13	−0.13	−0.12	−0.12
NID	−0.17	−0.17	−0.18	−0.17
ACH%	0.06	0.07	0.07	0.08
NNP%	0.07	0.06	0.05	0.05

β1, bivariate standardized linear regression coefficient; β2, multivariate standardized linear regression coefficient adjusted for sex; β3, multivariate standardized linear regression coefficient adjusted for sex and BMI; β4, multivariate standardized linear regression coefficient adjusted for sex, BMI, and HbA_{1c}. FMD, flow-mediated dilation percentage increase over baseline (endothelium-dependent reactivity of macrocirculation); FR, resting brachial artery diameter (in millimeters). *Logarithmic transformation performed before analysis; †$P < 0.01$; ‡$P < 0.025$.

Table 5—*Results of changes in response to atorvastatin or placebo*

	Atorvastatin		Placebo†	
	Before treatment	After treatment	Before treatment	After treatment
Adiponectin (μg/ml)	21.7 ± 2.3	21.4 ± 2.2	25.2 ± 3.5	28.2 ± 4.1
Resistin (ng/ml)	8.1 ± 0.8	6.8 ± 0.6*	8.1 ± 0.8	6.7 ± 0.6‡
BMI (kg/m^2)	29.5 ± 1.3	29.3 ± 1.2	28.8 ± 1.1	28.9 ± 1.0
Total cholesterol (mg/dl)	199.8 ± 7.0	150.7 ± 5.8†	211.9 ± 7.0	199.5 ± 5.3†
HDL (mg/dl)	58.8 ± 2.3	56.9 ± 2.3	61.9 ± 3.3	59.3 ± 2.9
LDL (mg/dl)	120.4 ± 5.9	76.7 ± 4.9†	127.0 ± 5.6	118.4 ± 4.6†
Triglycerides (mg/dl)	114.3 ± 15.0	99.3 ± 14.5	110.2 ± 13.0	116.2 ± 12.9
ICAM (ng/ml)	240.3 ± 9.2	244.8 ± 8.6	219.3 ± 16.9	236.6 ± 13.3
ET1 (pg/ml)	0.76 ± 0.05	0.70 ± 0.04	0.66 ± 0.08	0.68 ± 0.07
TNF-α (pg/ml)	3.5 ± 0.3	3.1 ± 0.3	2.7 ± 0.4	3.3 ± 0.4
CRP (mg/dl)	0.32 ± 0.05	0.25 ± 0.04*	0.30 ± 0.05	0.26 ± 0.04
PAI-1 (ng/ml)	28.8 ± 4.0	22.6 ± 3.3	21.1 ± 3.0	24.9 ± 4.3
tPA (ng/ml)	7.7 ± 0.7	7.2 ± 0.7	6.6 ± 0.6	6.4 ± 0.6

Data are mean ±SE. Atorvastatin, $n = 34$; placebo, $n = 33$. *$P < 0.025$; †$P < 0.01$; ‡$P = 0.03$.

in impaired fibrinolysis in humans (37). The negative correlation of adiponectin to PAI-1, which is also associated with insulin resistance and the metabolic syndrome (38,39), provides another possible mechanism for adiponectin in affecting the metabolic syndrome–induced morbidity and mortality. Further analysis of adiponectin adjusting for type of diabetes showed slightly different associations with tPA. These findings need to be confirmed in larger studies.

Resistin, which has recently been proposed to play a role in obesity-mediated insulin resistance (7), has a structure similar to that of proteins that are involved in inflammatory processes (12). More specifically, resistin is identical to FIZZ3 (found in inflammatory zone 3), and resistin-like molecules, such as RELM-α and RELM-β, are identical with FIZZ1 and FIZZ2, respectively. Patterns of expression of FIZZ proteins are very similar to those reported for resistin and RELMs (8,12). In addition, the pattern of expression and physiological functions proposed for these proteins resemble those of other well-known proinflammatory cytokines, such as interleukin-6 and TNF-α, both of which are involved in cardiovascular obesity-related outcomes (40). These findings suggest that resistin/FIZZ3 and RELMs/FIZZ1 and FIZZ2 may be involved in the inflammatory processes associated with obesity (41), but the role of resistin in vascular reactivity or potential associations with inflammatory markers have not been previously studied. In addition to the known negative correlation between serum resistin and HDL, we report a positive correlation of serum resistin to CRP, and these correlations remained significant after adjusting for type of diabetes, which suggests that the type of diabetes does not influence the associations between resistin levels and these variables. The positive association to CRP also remained significant despite adjustments for sex and BMI, suggesting that resistin's proinflammatory properties may be independent of overall obesity. Larger studies are needed to confirm and extend these finding in healthy and diabetic subjects.

We did not find any correlations between vascular reactivity and adiponectin or resistin in this study. There are two published studies reporting conflicting results regarding adiponectin and vascular function (42,43). More specifically, a recent report showing that hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation (42) conflicts with our findings of no association between adiponectin and any vascular reactivity. Furthermore, the second recently published report stated that adiponectin is associated with endothelium-independent vasodilation, but not endothelium-dependent vasodilation (43). Based on our findings and the findings from these two other groups, we do not feel there is a well-established and reproducible association between vascular reactivity and either adiponectin or resistin levels.

Another topic we addressed in this study was whether statin treatment alters circulating adiponectin and resistin levels. The current understanding of statin efficacy in decreasing the relative risk of major coronary events by 30% has been attributed to several mechanisms, including beneficial effects on plasma lipoprotein levels, endothelial function, plaque architecture and stability, thrombosis, and inflammation, which are seen in addition to and independent of decreased LDL (44–48). Whereas it is enticing to explain some of the vascular and inflammatory effects mediated by atorvastatin possibly via alterations in adiponectin or resistin levels, data from the interventional part of the study show that atorvastatin does not significantly alter serum adiponectin or resistin levels when compared with placebo. These data indicate that other pathways may mediate atorvastatin's effects on insulin resistance and inflammatory processes.

In summary, the findings of this study indicate that adiponectin may have a wide-ranging role in metabolism and inflammation by being associated not only with lipoprotein levels but also inflammatory markers and that some of these associations reflect an underlying association with obesity, whereas others are independent of obesity. However, resistin's associations with inflammatory markers appear to be independent of BMI, suggesting that resistin may have a direct proinflammatory role or mediate its effects via yet to be discovered obesity-

independent mechanisms. Finally, neither vascular reactivity nor lipid profile changes and inflammatory changes produced by therapy with atorvastatin can be attributed to alterations of either adiponectin or resistin levels. Further studies to confirm and extend these observations as well as to elucidate the underlying mechanisms are clearly needed.

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