Relationship Between Adiponectin and Glycemic Control, Blood Lipids, and Inflammatory Markers in Men With Type 2 Diabetes

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OBJECTIVE — Adiponectin, synthesized in the adipose tissue, appears to play an important role in hyperglycemia and dyslipidemia, as well as in inflammatory mechanisms, which lead to a markedly increased atherosclerotic risk in diabetic subjects. However, previous studies did not evaluate the complex relationships between adiponectin and the array of metabolic abnormalities commonly observed in diabetes.

RESEARCH DESIGN AND METHODS — To examine the associations between plasma levels of adiponectin and HbA_{1c}, blood lipids, and inflammatory markers, we obtained blood samples from 741 participants in the Health Professionals Follow-up Study with a diagnosis of type 2 diabetes.

RESULTS — Plasma adiponectin levels were positively correlated with HDL cholesterol and negatively correlated with triglycerides, apolipoprotein B-100 ($apoB_{100}$), C-reactive protein (CRP), and fibrinogen. These associations were not appreciably altered after controlling for lifestyle exposures, medical conditions, and obesity-associated variables. A 10-μg/ml higher level of plasma adiponectin was associated with lower HbA_{1c} (−0.21% points, $P = 0.001$), triglycerides (−0.39 mmol/l, $P < 0.001$), $apoB_{100}$ (−0.04 g/l, $P < 0.001$), CRP (−0.51 mg/l, $P = 0.003$), and fibrinogen (−0.53 μmol/l, $P < 0.001$) and higher HDL cholesterol (0.13 mmol/l, $P < 0.001$). Associations between adiponectin and inflammatory markers were furthermore independent of HbA_{1c} and HDL cholesterol, suggesting that the anti-inflammatory properties of adiponectin are not mediated by potential effects on glycemic control and blood lipids. Our results were consistent among obese and nonobese men.

CONCLUSIONS — Our study supports the hypothesis that increased adiponectin levels might be associated with better glycemic control, better lipid profile, and reduced inflammation in diabetic subjects. Measures that increase adiponectin levels might be valuable targets for decreasing the atherosclerotic risk present in diabetes.

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Patients with type 2 diabetes have a markedly increased atherosclerotic risk. The risk of fatal coronary heart disease among diabetic subjects is comparable with that observed in subjects who have had a previous myocardial infarction (1,2). This increased risk has been mainly attributed to hyperglycemia, dyslipidemia, and inflammatory mechanisms (3). Adiponectin, which is solely synthesized in the adipose tissue, appears to play an important role in all of these pathways (4). It has been found to be a major modulator of insulin action and resistance (5) and to predict the development of type 2 diabetes (6–8). Furthermore, it seems to have substantial anti-inflammatory properties (4). Adiponectin is also related to lipid metabolism, particularly higher levels of HDL cholesterol, and lower levels of triglycerides (9). However, previous studies did not evaluate the complex relationships between adiponectin and the array of metabolic abnormalities commonly observed in diabetes. In particular, it remains unresolved whether the potential anti-inflammatory properties of adiponectin are apparent among diabetic subjects and whether effects on glycemia and blood lipids largely mediate them. We therefore examined the relationship between adiponectin levels and HbA_{1c}, blood lipids (HDL, LDL, and non-HDL cholesterol and apolipoprotein B-100 [$apoB_{100}$]), C-reactive protein (CRP), fibrinogen, and other inflammatory markers in diabetic men.

RESEARCH DESIGN AND METHODS

— The Health Professionals Follow-up Study is a prospective cohort study of 51,529 U.S. male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) aged 40–75 years at study initiation in 1986. This cohort is followed through biennially mailed questionnaires focusing on different lifestyle factors and health outcomes.

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Abbreviations: $apoB_{100}$, apolipoprotein B-100; CRP, C-reactive protein; sICAM, soluble intracellular cell adhesion molecule; sTNFR2, soluble fraction of tumor necrosis factor-α receptor 2; sVCAM, soluble vascular cell adhesion molecule; TNF, tumor necrosis factor.

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

In addition, between 1993 and 1994, 18,159 study participants provided blood samples by overnight courier. Among participants who returned blood samples, 741 had a diagnosis of type 2 diabetes at the time of blood draw and reported their weight on the preceding questionnaire. The study was approved by the institutional review boards at the Harvard School of Public Health and the Brigham and Women's Hospital. Completion of the self-administered questionnaire was considered to imply informed consent.

Diabetes confirmation

We sent supplementary questionnaires to all men who reported a diagnosis of diabetes on any of the regular biennial questionnaires to confirm this self-report. In accordance with the criteria of the National Diabetes Data Group (10), confirmation of diabetes required at least one of the following: *1*) an elevated plasma glucose concentration (fasting plasma glucose ≥7.8 mmol/l, random plasma glucose ≥11.1 mmol/l, and/or plasma glucose ≥11.1 mmol/l after ≥2 h during an oral glucose tolerance test) plus at least one classic symptom (excessive thirst, polyuria, weight loss, or hunger); *2*) no symptoms, but at least two elevated plasma glucose concentrations (by the above criteria) on different occasions; or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). We used the National Diabetes Data Group criteria to define diabetes because the majority of our subjects were diagnosed before the release of the American Diabetes Association criteria in 1997 (11). The validity of self-reported diabetes using the supplementary questionnaire has been documented in a subsample of 71 men from the Health Professionals Follow-up Study cohort. Of these, 12 had incomplete medical records, whereas the diagnosis of type 2 diabetes was confirmed in 57 (97%) of the remaining 59 men (12).

Assessment of anthropometric and lifestyle exposures

Participants provided information on their age, weight, smoking status, aspirin use, and physical activity. If the weight was missing, we used the weight reported on the preceding questionnaire instead. We calculated BMI as the ratio of weight (in kilograms) to height (in meters squared). Self-reports of body weight have been shown (13) to be highly correlated with technician-measured weights ($r = 0.97$) in this cohort. Physical activity was computed as metabolic equivalents per week using the duration per week of various forms of exercise, weighting each activity by its intensity level (14). History of cardiovascular disease (angina pectoris, myocardial infarction, coronary bypass surgery or coronary angioplasty, and stroke), high blood pressure, high blood cholesterol, and cancer were determined from self-reports preceding the blood collection. Alcohol intake was estimated with a dietary questionnaire in 1994.

Biochemical analysis

Each interested participant was sent a blood collection kit containing instructions and needed supplies (blood tubes, tourniquet, gauze, Band-Aids, and needles). The participants made arrangements for the blood to be drawn. Blood samples were collected in three 10-ml liquid EDTA blood tubes, placed on ice packs stored in Styrofoam containers, and returned to our laboratory via overnight courier. Over 95% of the samples arrived within 24 h. After receipt, the chilled blood was centrifuged, aliquoted into plasma, erythrocytes, and buffy coat, and stored in continuously monitored nitrogen freezers at a temperature not higher than −130°C. We requested information on the date and time of the blood sample drawing and the time elapsed since the preceding meal to identify nonfasting (<8 h) subjects.

All biomarker assays were carried out on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN). Adiponectin was measured by a competitive radioimmunoassay using a commercial reagent set from Linco Research (St. Louis, MO) with a day-to-day variability at adiponectin concentrations of 3, 6, and 15 ng/ml of 9.2, 6.9, and 9.2%, respectively. HbA_{1c} determination was based on turbidimetric immunoinhibition using hemolyzed whole blood or packed red cells. The day-to-day variability at HbA_{1c} concentrations of 5.5 and 9.1% was 1.9 and 3.0%, respectively. The determination of total cholesterol, triglycerides, and HDL cholesterol concentrations was simultaneously performed using reagents and calibrators from Roche Diagnostics (Indianapolis, IN); coefficients of variation for these measurements were <1.8%. LDL cholesterol was measured by a homogenous direct method from Genzyme (Cambridge, MA). The day-to-day variability at LDL cholesterol concentrations of 2.33, 2.74, and 3.34 mmol/l was <3.1%. Measurement of $apoB_{100}$ was based on the immunonephelometric assay using reagents and calibrators from Wako Chemicals (Richmond, VA), with a day-to-day variability of <5%. We calculated non-HDL cholesterol as the difference between total and HDL cholesterol. CRP was measured via an immunoturbidimetric assay using reagents and calibrators from Denka Seiken (Niigata, Japan). The day-to-day variability of the assay at concentrations of 0.91, 3.07, and 13.38 mg/l were 2.8, 1.6, and 1.1%, respectively. Fibrinogen was measured with an immunoturbidimetric assay using reagents and calibrators from Kamiya Biomedical (Seattle, WA). The day-to-day variability of the assay at concentrations of 4.92, 9.51, and 16.29 μmol/l was 0.9, 1.1, and 1.5%, respectively. Soluble intracellular cell adhesion molecules (sICAMs), soluble vascular cell adhesion molecules (sVCAMs), and plasma soluble fractions of tumor necrosis factor (TNF)-α receptor 2 (sTNFR2s) were measured by enzyme-linked immunosorbent assay from R&D Systems (Minneapolis, MN). The day-to-day variabilities of the assays at concentrations of 64.2, 117, 290, and 453 ng/ml sICAM and at concentrations of 9.8, 24.9, and 49.6 ng/ml sVCAM were 10.1, 7.4, 6.0, and 6.1% and 10.2, 8.5, and 8.9%, respectively. The day-to-day variability of the sTNFR2 assay at concentrations of 89.9, 197, and 444 pg/ml was 5.1, 3.5, and 3.6%, respectively.

Statistical analysis

Spearman correlations and scatter plots were used to evaluate bivariate relationships between plasma levels of adiponectin and of lipids and inflammatory markers. Multivariate linear regression analyses with robust variance were performed to evaluate the association between adiponectin and biomarkers without the need of normal distribution assumptions (15). We adjusted for age, BMI, activity (quartiles of metabolic equivalents), smoking (never, past, and current), aspirin use, history of cardiovascular disease, history of high blood pressure, history of high blood cholesterol, history of cancer, fasting status, alcohol intake (0.0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day), and insulin use.

Table 1 —*Characteristics by quartiles of adiponectin in 741 diabetic men*

Variable	Quartiles of adiponectin				*P* for trend*
	1	2	3	4	
Adiponectin (μg/ml)	7.82 (1.40–10.54)	12.69 (10.55–14.78)	17.54 (14.79–20.49)	27.83 (20.50–63.78)	—
Age (years)	64.1	64.5	65.5	66.1	0.009
BMI (kg/m^2)	28.6	28.0	27.0	25.9	<0.001
Physical activity (MET/week)†	26.1	29.1	31.9	30.4	0.202
Alcohol intake (g/day)‡	8.3	7.0	10.3	11.1	0.014
Currently smoking (%)	5.4	9.2	3.2	7.6	0.866
Aspirin use (%)	47.0	48.1	46.8	52.4	0.319
Insulin use (%)	20.0	22.2	25.3	34.6	0.001
History of CVD (%)	24.3	27.0	29.0	23.8	0.882
History of hypertension (%)	52.4	54.6	54.4	43.2	0.059
History of high blood cholesterol (%)	56.8	48.1	53.2	42.2	0.015
Fasting (%)	56.2	50.8	53.2	55.1	0.950
HbA_{1c} (%)*	7.5	7.5	7.3	7.1	0.008
Total cholesterol (mmol/l)*	5.22	5.39	5.40	5.33	0.447
Triglycerides (mmol/l)*§	2.20	1.93	1.65	1.28	<0.001
LDL cholesterol (mmol/l)*	2.91	3.21	3.25	3.17	0.020
HDL cholesterol (mmol/l)*	0.89	0.99	1.05	1.20	<0.001
Non-HDL cholesterol (mmol/l)*	4.29	4.36	4.30	4.07	0.012
$ApoB_{100}$ (g/l)*	1.06	1.05	1.01	0.94	<0.001
CRP (mg/l)*	2.35	1.93	1.58	1.34	<0.001
Fibrinogen (μmol/l)*	14.64	13.70	13.11	12.98	<0.001
sTNFR2 (pg/ml)*	2,861.8	2,935.7	2,891.4	2,992.9	0.206
sICAM-1 (ng/ml)*	357.97	340.10	345.20	340.57	0.128
sVCAM-1 (ng/ml)*	1,366.45	1,379.03	1,345.56	1,378.88	0.912
Creatinine (μmol/l)*	92.33	92.05	89.69	93.04	0.147

Data are mean and mean (range), unless indicated otherwise. *Biomarkers were log transformed; †644 subjects due to missing values; ‡694 subjects due to missing values; §fasting samples only (n = 399). CVD, cardiovascular disease; MET, metabolic equivalent.

We furthermore tested for effect modifications by obesity status, with adjustment for potential confounders. All statistical analyses were performed using SAS statistical software version 8 (SAS Institute, Cary, NC).

RESULTS — Among the study population of 741 diabetic men, higher plasma adiponectin levels were associated with higher age, higher physical activity, higher alcohol consumption, and lower BMI (Table 1). Furthermore, men with relatively high adiponectin levels were more likely to use insulin and were less likely to have a history of high blood cholesterol. Although HDL and LDL cholesterol were positively associated with adiponectin levels, the opposite was observed for HbA_{1c}, triglycerides, non-HDL cholesterol, $apoB_{100}$, CRP, and fibrinogen. Adiponectin levels were not significantly associated with creatinine levels. One hundred twenty-three subjects (26%) had a history of cardiovascular disease. One-half of the subjects reported aspirin use, and 31% used at least six aspirin tablets per week. We calculated Spearman correlation coefficients to further elucidate the associations between adiponectin and blood lipids and inflammatory markers (Table 2). Adiponectin was positively correlated with HDL cholesterol (r = 0.42) and negatively correlated with triglycerides (r = −0.38). Significant correlations (at $P < 0.01$) were also found between adiponectin and HbA_{1c}, $apoB_{100}$, CRP, and fibrinogen, although correlation coefficients were relatively weak (<0.20).

Figure 1 presents scatter plots between log-transformed adiponectin and HDL cholesterol, triglycerides, $apoB_{100}$, HbA_{1c}, CRP, and fibrinogen levels. We observed a positive association between adiponectin and HDL cholesterol and a negative association between adiponectin and triglycerides, $apoB_{100}$, HbA_{1c}, CRP, and fibrinogen. All biomarkers monotonically increased or decreased with increasing adiponectin, thus no indications for nonmonotonic associations between these variables were present.

We used multivariate linear regression to estimate the change in blood lipids and inflammatory markers required for an increase in adiponectin by 10 μg/ml (61% compared with the mean level of 16.5 μg/ml), adjusting for age, physical activity, smoking, and other covariates, including BMI (Table 3). A 10-μg/ml increase in plasma adiponectin was associated with a 0.21% point decrease in HbA_{1c}, a 0.39-mmol/l decrease in triglycerides (−18% as compared with the mean level), a 0.13-mmol/l increase in HDL cholesterol (14%), and significant reductions in $apoB_{100}$ (−0.04 g/l, −4%), CRP (−0.51 mg/l, −15%), fibrinogen (−0.53 μmol/l, −4%), and sICAM (−7.56 ng/ml, −2%). These associations remained significant after further adjustment for the waist-to-hip ratio in a subset of men who reported their waist and hip circumferences in 1996 (n = 667), except in the case for sICAM. Furthermore, adjustment for HDL cholesterol, CRP, and fibrinogen

Table 2—*Spearman correlation between adiponectin and blood lipids, HbA_{1c}, and inflammatory markers in 741 diabetic men*

	Adiponectin	Total cholesterol	Triglycerides*	HDL cholesterol	LDL cholesterol	Non-HDL cholesterol	$ApoB_{100}$
Adiponectin	1	0.04	**−0.38**	**0.42**	0.09	−0.08	**−0.19**
Total cholesterol	—	1	**0.21**	**0.30**	**0.87**	**0.95**	**0.86**
Triglycerides*	—	—	1	**−0.52**	−0.05	**0.37**	**0.43**
HDL cholesterol	—	—	—	1	**0.29**	0.03	−0.09
LDL cholesterol	—	—	—	—	1	**0.84**	**0.77**
Non-HDL cholesterol	—	—	—	—	—	1	**0.94**
$ApoB_{100}$	—	—	—	—	—	—	1

	Adiponectin	HbA_{1c}	CRP	Fibrinogen	sTNFR2	sICAM-1	sVCAM-1
Adiponectin	1	−0.09	**−0.18**	**−0.18**	0.03	−0.10	<0.01
HbA_{1c}	—	1	**0.12**	**0.09**	<0.01	**0.12**	−0.03
CRP	—	—	1	**0.45**	**0.30**	**0.31**	0.09
Fibrinogen	—	—	—	1	**0.25**	**0.15**	**0.11**
sTNFR2	—	—	—	—	1	**0.44**	**0.58**
sICAM-1	—	—	—	—	—	1	**0.50**
sVCAM-1	—	—	—	—	—	—	1

Values at $P < 0.01$ are in boldface. *Fasting samples only ($n = 399$).

only slightly attenuated the association for triglycerides ($\beta = -0.22$, $P < 0.001$). Adiponectin remained positively associated with HDL cholesterol after additional adjustment for CRP and fibrinogen ($\beta = 0.13$, $P < 0.001$). The association between adiponectin and $apoB_{100}$ was only slightly attenuated after controlling for HDL cholesterol ($\beta = 0.04$, $P < 0.001$). Similarly, adiponectin remained significantly associated with CRP and fibrinogen, controlling for HDL cholesterol and HbA_{1c}. Regression parameter estimates (β) for an increase in adiponectin of 10 μg/ml predicting CRP and fibrinogen were −0.42 ($P = 0.019$) and −0.36 ($P = 0.035$), respectively.

We further evaluated whether the observed associations were modified by obesity status. The associations were relatively consistent across obesity strata, and interaction terms were all nonsignificant (CRP, $P = 0.191$; fibrinogen, $P = 0.657$; triglycerides, $P = 0.966$; $apoB_{100}$, $P = 0.221$; and HDL cholesterol, $P = 0.999$).

CONCLUSIONS — We found that among men with type 2 diabetes, high plasma levels of adiponectin were positively associated with HDL cholesterol and inversely associated with HbA_{1c}, triglycerides, $apoB_{100}$, CRP, and fibrinogen. These associations were independent of lifestyle factors and of anthropometric characteristics. Associations between adiponectin and CRP as well as fibrinogen were furthermore independent of HbA_{1c} and HDL cholesterol, which suggests that adiponectin may have anti-inflammatory properties in diabetic subjects that are not mediated by its potential effects on glycemic control and blood lipids.

Our observation that adiponectin levels may be associated with the status of glycemic control among diabetic men is supported by previous studies that found adiponectin to be a major modulator of insulin action and resistance. Plasma levels of adiponectin are significantly lower in humans with insulin resistance or type 2 diabetes (5) and predict the development of type 2 diabetes (6–8). Strong correlations between adiponectin and measures of insulin sensitivity have been well established in humans (4). The connection between adiponectin levels and insulin resistance have been furthermore confirmed by data obtained from animal models, wherein adiponectin treatment reversed insulin resistance in lipoatrophic mice (16), increased hepatic glucose uptake (17), and stimulated muscular fatty acid oxidation (18). Furthermore, thiazolidinedione treatment increased plasma adiponectin levels in normal and diabetic subjects (19–22), which supports the thought that adiponectin plays a role in the systemic insulin-sensitizing and anti-inflammatory properties of the thiazolidinediones. Similarly, increased plasma adiponectin may underlie the improvement of insulin resistance with sulfonylureas (23).

Our data suggest that decreased adiponectin levels may be associated with an atherogenic lipoprotein profile. A 10-μg/ml increase in adiponectin was associated with substantially higher HDL cholesterol and lower triglycerides and $apoB_{100}$. Similar associations between adiponectin and HDL and triglycerides were observed among nondiabetic (24–31) and diabetic (32,33) subjects. Inverse associations between adiponectin and $apoB_{100}$ were also observed in one (24) but not in another (25) study. The mechanisms by which adiponectin may affect blood lipids are largely unknown. Effects of adiponectin on hepatic lipase activity, which is increased in central obesity and insulin resistance, are suspected (25). However, our observed associations were largely independent from BMI and waist-to-hip ratio. Similarly, adiponectin was found to be associated with HDL cholesterol and triglycerides independent from abdominal fat area measured by computed tomography scan (25), visceral and extremity fat (26), BMI and body fat mass (24,29–32), or waist circumference (33). This suggests that although adiponectin might in part mediate effects of body fat on lipoproteins, other unrecognized pathways controlling its production

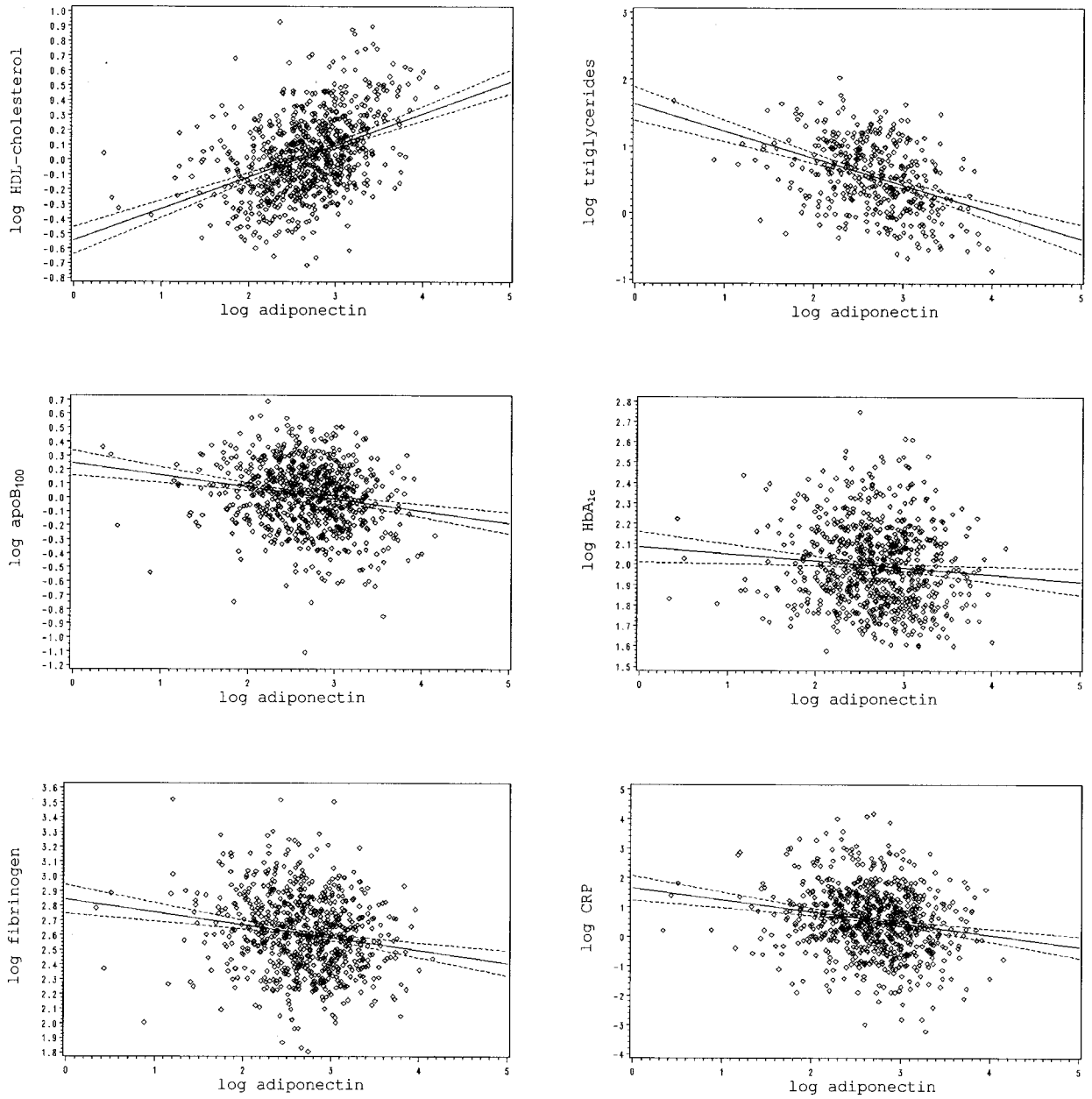

Figure 1— *Relationship between log-transformed plasma adiponectin levels and plasma lipids and inflammatory markers as determined by linear regression.*

might be important as well. Furthermore, the associations were largely independent of fasting insulin concentration (32,33) and indexes of insulin resistance assessed by the homeostasis model assessment (29,31), the euglycemic-hyperinsulinemic clamp, and the oral glucose tolerance test (30). This suggests that mechanisms other than effects on insulin resistance and hepatic lipase activity most likely mediate the association between adiponectin and blood lipids.

Our finding that plasma adiponectin levels may be negatively associated with levels of CRP and fibrinogen is supported by previous reports (28,29,34–37) that indicate potential anti-inflammatory properties of adiponectin. Anti-inflammatory effects of adiponectin might be mediated indirectly by its effects on glycemic control and blood lipids. Hyperglycemia acutely increases circulating cytokine concentrations (38,39). HDL cholesterol downregulates expression of adhesive molecules on the surface of vascular endothelium (40) and inhibits platelet aggregation (41) and thus has anti-inflammatory and antithrombotic properties. However, adjustment for HDL cholesterol and HbA_{1c} in our study only slightly attenuated the association between adiponectin and CRP and fibrinogen. In vitro studies suggest several other mechanisms, which might explain the observed associations. Adiponectin was found to affect monocyte adhesion to the endothelium (42) and to suppress macrophage-to-foam cell transformation (43). Furthermore, adiponectin inhibits

Table 3—*Parameter estimates and P values for a 10-μg/ml increase in adiponectin in relation to HbA_{1c}, blood lipids, and inflammatory markers in 741 diabetic men*

	Age adjusted		Multivariate adjusted*	
Biomarker	Estimate	*P*	Estimate	*P*
HbA_{1c} (%)	−0.16	0.009	−0.21	0.001
Total cholesterol (mmol/l)	0.05	0.291	0.08	0.090
Triglycerides (mmol/l)†	−0.45	<0.001	−0.39	<0.001
HDL cholesterol (mmol/l)	0.16	<0.001	0.13	<0.001
LDL cholesterol (mmol/l)	0.08	0.054	0.10	0.020
Non-HDL cholesterol (mmol/l)	−0.11	0.009	−0.05	0.260
$apoB_{100}$ (g/l)	−0.06	<0.001	−0.04	<0.001
CRP (mg/l)	−0.97	<0.001	−0.51	0.003
Fibrinogen (μmol/l)	−0.87	<0.001	−0.53	<0.001
sTNFR2 (pg/ml)	52.82	0.262	89.77	0.071
sICAM-1 (ng/ml)	−7.81	0.032	−7.56	0.049
sVCAM-1 (ng/ml)	5.79	0.752	19.12	0.304

*Adjusted for age, BMI, activity (quartiles), smoking (never, past, and current), aspirin use, history of cardiovascular disease, history of high blood pressure, history of high blood cholesterol, history of cancer, fasting status, alcohol intake (0.0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day), and insulin use; †fasting samples only (n = 399).

the production and action of TNF-α (42,44,45), which may influence interleukin-6 and CRP production. Therefore, adiponectin may affect CRP levels in plasma and adipose tissue through modulating the inflammatory cascades (35). Interestingly, adiponectin was not associated with sTNFR2 levels in our study. Similarly, in a previous study (36), adiponectin was associated with CRP and interleukin-6, but no association with TNF-α was observed. It has also been suggested (37) that the association between adiponectin and TNF-α may not be dose dependent, but may rather involve a threshold effect; however, our data do not support this hypothesis. The lack of association between adiponectin and sICAM and sVCAM in our study suggests that adiponectin may play a less important role in monocyte adhesion, although it is critical in subsequent stages of atherosclerosis, e.g., macrophage cytokine production and macrophage-to-foam cell transformation (4).

A major limitation of our study is its cross-sectional nature, which does not allow for inferring causality from our results. In particular, although our results are suggestive of a role of adiponectin in carbohydrate and lipid metabolism and inflammatory processes, we were not able to determine whether decreased adiponectin levels are a cause or an effect of the metabolic state of high glycemia, dyslipidemia, and inflammation. However, these relationships are consistent with a large body of experimental evidence (16,38,39) on the role of adiponectin in glucose metabolism and inflammation.

Although associations between adiponectin and metabolic markers may be modified by the presence and type of cholesterol-lowering and diabetes medications, we did not collect detailed medication data at the time of blood draw in our cohort and were therefore unable to evaluate this. The cross-sectional study design would, however, complicate the interpretation of such an analysis with respect to causality.

In conclusion, our study supports the hypothesis that increased adiponectin levels may be associated with lower hyperglycemia and dyslipidemia, as well as with a lower inflammatory state in diabetic subjects. Lifestyle and pharmaceutical approaches that increase adiponectin levels might be valuable in decreasing the atherosclerotic risk present in type 2 diabetes.

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References

1. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB: The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Coll Cardiol* 40:954–960, 2002
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
3. Dandona P, Aljada A, Chaudhuri A, Bandyopadhyay A: The potential influence of inflammation and insulin resistance on the pathogenesis and treatment of atherosclerosis-related complications in type 2 diabetes. *J Clin Endocrinol Metab* 88:2422–2429, 2003
4. Chandran M, Phillips SA, Ciaraldi T, Henry RR: Adiponectin: more than just another fat cell hormone? *Diabetes Care* 26:2442–2450, 2003
5. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
6. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF: Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228, 2003
7. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57–58, 2002
8. Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H, Ohnuma H, Igarashi M, Tominaga M, Kato T: Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population: the Funagata study. *Diabetes Care* 26:2015–2020, 2003
9. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20:1595–1599, 2000
10. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report

of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
12. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 161:1542–1548, 2001
13. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1:466–473, 1990
14. Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, Ascherio A, Willett WC: Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 7:81–86, 1996
15. White H: A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica* 48:817–838, 1980
16. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T: The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 7:941–946, 2001
17. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE: The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7:947–953, 2001
18. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T: Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 8:1288–1295, 2002
19. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM: The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes* 51:2968–2974, 2002
20. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y: PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094–2099, 2001
21. Hirose H, Kawai T, Yamamoto Y, Taniyama M, Tomita M, Matsubara K, Okazaki Y, Ishii T, Oguma Y, Takei I, Saruta T: Effects of pioglitazone on metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients with type 2 diabetes. *Metabolism* 51:314–317, 2002
22. Satoh N, Ogawa Y, Usui T, Tagami T, Kono S, Uesugi H, Sugiyama H, Sugawara A, Yamada K, Shimatsu A, Kuzuya H, Nakao K: Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. *Diabetes Care* 26:2493–2499, 2003
23. Tsunekawa T, Hayashi T, Suzuki Y, Matsui-Hirai H, Kano H, Fukatsu A, Nomura N, Miyazaki A, Iguchi A: Plasma adiponectin plays an important role in improving insulin resistance with glimepiride in elderly type 2 diabetic subjects. *Diabetes Care* 26:285–289, 2003
24. Matsubara M, Maruoka S, Katayose S: Decreased plasma adiponectin concentrations in women with dyslipidemia. *J Clin Endocrinol Metab* 87:2764–2769, 2002
25. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE: Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 46:459–469, 2003
26. Addy CL, Gavrila A, Tsiodras S, Brodovicz K, Karchmer AW, Mantzoros CS: Hypoadiponectinemia is associated with insulin resistance, hypertriglyceridemia, and fat redistribution in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy. *J Clin Endocrinol Metab* 88:627–636, 2003
27. Furuhashi M, Ura N, Higashiura K, Murakami H, Tanaka M, Moniwa N, Yoshida D, Shimamoto K: Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension* 42:76–81, 2003
28. Matsubara M, Namioka K, Katayose S: Decreased plasma adiponectin concentrations in women with low-grade C-reactive protein elevation. *Eur J Endocrinol* 148: 657–662, 2003
29. Shand BI, Scott RS, Elder PA, George PM: Plasma adiponectin in overweight, nondiabetic individuals with or without insulin resistance. *Diabetes Obes Metab* 5:349–353, 2003
30. Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, Staiger H, Maerker E, Haring H, Stumvoll M: Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 52:239–243, 2003
31. Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, Okazaki Y, Ishii T, Nishikai K, Saruta T: Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin Sci (Lond)* 103:137–142, 2002
32. Zietz B, Herfarth H, Paul G, Ehling A, Muller-Ladner U, Scholmerich J, Schaffler A: Adiponectin represents an independent cardiovascular risk factor predicting serum HDL-cholesterol levels in type 2 diabetes. *FEBS Lett* 545:103–104, 2003
33. Valsamakis G, Chetty R, McTernan PG, Al-Daghri NM, Barnett AH, Kumar S: Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. *Diabetes Obes Metab* 5:131–135, 2003
34. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, Kobes S, Tataranni PA, Hanson RL, Knowler WC, Lindsay RS: Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. *Diabetes Care* 26:1745–1751, 2003
35. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H, Matsuzawa Y: Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* 107:671–674, 2003
36. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Mohlig M, Pfeiffer AF, Luft FC, Sharma AM: Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 52:942–947, 2003
37. Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R, Ricart W: Novel interactions of adiponectin with the endocrine system and inflammatory parameters. *J Clin Endocrinol Metab* 88:2714–2718, 2003
38. Morohoshi M, Fujisawa K, Uchimura I, Numano F: Glucose-dependent interleukin 6 and tumor necrosis factor production by human peripheral blood monocytes in vitro. *Diabetes* 45:954–959, 1996
39. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D: Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 106:2067–2072, 2002
40. Garner B, Witting PK, Waldeck AR, Christison JK, Raftery M, Stocker R: Oxidation of high density lipoproteins. I. Formation of methionine sulfoxide in apolipoproteins AI and AII is an early event that accompanies lipid peroxidation and can be enhanced by alpha-tocopherol. *J Biol Chem* 273:6080–6087, 1998

41. Nofer JR, Walter M, Kehrel B, Wierwille S, Tepel M, Seedorf U, Assmann G: HDL3-mediated inhibition of thrombin-induced platelet aggregation and fibrinogen binding occurs via decreased production of phosphoinositide-derived second messengers 1,2-diacylglycerol and inositol 1,4,5-tris-phosphate. *Arterioscler Thromb Vasc Biol* 18:861–869, 1998
42. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y: Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 100:2473–2476, 1999
43. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T, Matsuzawa Y: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 103:1057–1063, 2001
44. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y: Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 96: 1723–1732, 2000
45. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y: Role of adiponectin in preventing vascular stenosis: the missing link of adipo-vascular axis. *J Biol Chem* 277:37487–37491, 2002