Low Plasma Adiponectin Levels Are Associated With Increased Hepatic Lipase Activity In Vivo

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OBJECTIVE — Hepatic lipase plays a key role in hydrolyzing triglycerides and phospholipids present in circulating plasma lipoproteins. Plasma hepatic lipase activity is known to be regulated by several hormonal and metabolic factors, but hepatic lipase responsiveness to insulin is still controversial. Hypoadiponectinemia is known to be associated with insulin resistance, diabetes, and obesity. These conditions are often characterized by high plasma triglyceride and low HDL cholesterol levels, and they have been shown to be associated with high plasma hepatic lipase activity. We therefore raised the question whether adiponectin may be associated with plasma hepatic lipase activity in vivo.

RESEARCH DESIGN AND METHODS — We measured plasma adiponectin and postheparin hepatic lipase activity in 206 nondiabetic men and in a second group of 110 patients with type 2 diabetes. The correlation of these parameters with markers of insulin resistance and systemic inflammation was investigated.

RESULTS — In nondiabetic patients, adiponectin levels were significantly inversely correlated with plasma hepatic lipase activity ($r = -0.4$, $P < 0.01$). These results were confirmed in the group of patients with type 2 diabetes ($r = -0.32$, $P = 0.004$). Multivariate analysis revealed that adiponectin was the strongest factor influencing hepatic lipase activity. The association was independent of age, sex, BMI, plasma triglycerides, insulin, HDL cholesterol, and high-sensitivity C-reactive protein and accounted for ~10 and 12% of the variation in hepatic lipase activity in the two different patient cohorts, respectively.

CONCLUSIONS — These results demonstrate for the first time a significant inverse association between adiponectin and postheparin plasma hepatic lipase activity that is independent of other factors such as markers of insulin resistance or inflammation. Therefore, adiponectin, rather than insulin, may represent an important factor contributing to the regulation of hepatic lipase activity in both nondiabetic individuals and patients with type 2 diabetes. The effect of adiponectin on hepatic lipase activity may also help to explain the HDL cholesterol–elevating action of adiponectin.

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Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; hs-CRP, high-sensitivity CRP; HOMA, homeostasis model assessment; PPAR, peroxisome proliferator–activated receptor; SREBP, sterol regulatory element–binding protein.

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

Hepatic lipase functions as a lipolytic enzyme that hydrolyzes triglycerides and phospholipids in lipoproteins of intermediate and high density. It is thereby involved in the formation of small, dense LDL and represents a major determinant of the plasma HDL cholesterol concentration (1,2). Hepatic lipase activity is regulated by several hormonal and metabolic factors (3). In insulin resistance, most studies show increased hepatic lipase activity, although the exact regulation of hepatic lipase in insulin resistance is still controversial (4). Adiponectin is a member of a class of bioactive substances known as adipocytokines (5). It is related to tumor necrosis factor-α expression (6) and has the ability to suppress tumor necrosis factor-α–induced activation of nuclear transcription factor κB (7), thereby demonstrating anti-inflammatory potential. Recent studies suggest associations between low levels of adiponectin and a lipid profile of low HDL cholesterol and increased plasma triglyceride levels (8). Furthermore, adiponectin plasma levels are inversely correlated with BMI (9), insulin resistance, and type 2 diabetes (10). Low HDL cholesterol levels, hypertriglyceridemia, insulin resistance, type 2 diabetes, and abdominal obesity have also been consistently shown to be associated with postheparin hepatic lipase activity (11–13). In addition, the liver, as the main expression site for hepatic lipase, is also a major target of adiponectin action (14). These data suggest a direct or indirect relationship between hepatic lipase activity and adiponectin by an as yet unknown mechanism. We therefore investigated in two different groups of patients whether adiponectin is associated with plasma hepatic lipase activity and whether this relationship is affected by systemic inflammatory activity, insulin resistance, or overt diabetes.

RESEARCH DESIGN AND METHODS

— Two different cohorts of patients were studied. *1*) A total of 206 nondiabetic men were recruited from the

University Hospital Heidelberg, Department of Medicine. All individuals in this group had diagnosed or suspected coronary artery disease (CAD) (nondiabetic CAD subjects) and underwent elective coronary angiography. The overt diagnosis of diabetes, according to American Diabetes Association criteria (fasting plasma glucose >126 mg/dl) (15), was an exclusion criterion. 2) A total of 110 patients (82 male and 28 female subjects) with known type 2 diabetes were recruited from the Diabetes Outpatient Clinic of the University Hospital Heidelberg. The diabetic patients enrolled in the study were treated by either dietary intervention or oral antidiabetic drugs (sulfonylurea drugs, metformin, acarbose, glinides, or combinations); 29 patients (4 female and 25 male subjects) were treated with insulin and were omitted from the homeostasis model assessment [HOMA] calculation).

Treatment with subcutaneous or intravenous heparin in the previous 72 h, severe kidney or liver disease, treatment with drugs known to affect adiponectin plasma levels (such as peroxisome proliferator–activated receptor [PPAR]-γ agonists), and a fasting triglyceride level >11.4 mmol/l (1,000 mg/dl), suggesting secondary lipid disorders, were exclusion criteria in both nondiabetic subjects with CAD and type 2 diabetic subjects. The study was approved by the Internal Ethics Committee of Heidelberg University, and each patient gave informed consent. The patients were advised not to consume alcohol during the study period to avoid abnormal changes in plasma triglyceride levels caused by excessive consumption of alcohol. Patients were also advised to maintain a standard diet composed of ~25% protein, 15% fat, and 60% carbohydrate during the study period. The patients were requested to not eat or drink from 10 P.M. on the day before the study visit. In the diabetic patients, antidiabetic medication was maintained at a constant dose throughout the study period, and patients were instructed not to take their morning dose of antidiabetic medication on study days. Concomitant medications were also maintained at a constant dose.

Analysis of lipids/lipoproteins

Total cholesterol, HDL cholesterol, and triglyceride concentrations were enzymatically determined with a Synchron LX-20 (Beckman Coulter, Munich, Germany). LDL and VLDL were separated by ultracentrifugation in a Beckman LM-8 ultracentrifuge in 100-μl volumes with a VT-51.2 rotor (Beckman Coulter). The atherogenic index was calculated by the formula: (TC – HDL cholesterol)/HDL cholesterol.

Hepatic lipase

After an overnight fast, venous blood samples were drawn into EDTA tubes before and 10 min after intravenous injection of 60 IU heparin (Braun Melsungen, Melsungen, Germany) per kg body wt. The samples were immediately chilled to 4°C, centrifuged, and stored at −80°C until assayed. Postheparin hepatic lipase activity was determined with a triolein–phosphatidylcholine emulsion as described previously (16). Selective measurement of hepatic lipase was based on the inactivation of LPL by 1.0 mol/l NaCl. The samples were quantitated in duplicate, and postheparin plasma from pooled normal control subjects was used to correct for interassay variation. The intra-assay coefficient was 7.8%, and the interassay coefficient was 11.4%.

Blood variables

In the morning after an overnight fast, venous blood was sampled for the measurement of plasma concentrations of adiponectin, glucose, insulin, and C-reactive protein (CRP). Adiponectin samples were quantitated in duplicate by enzyme-linked immunosorbent assay (ELISA) (B-Bridge International, San Jose, CA), and plasma from four normal control subjects was used for interassay variation. Both the intra- and interassay coefficients of variation were <5.0%. Plasma glucose was measured by a glucose oxidase method. Serum insulin immunoreactivity was determined from frozen serum by ELISA (CIS Bio International, Gif-Sur-Yvette, France). Plasma concentrations of CRP in a highly sensitive assay (high-sensitivity CRP [hs-CRP]) were determined by ELISA (Dade Behring, Cupertino, CA).

Statistical analyses

Statistical analyses were performed with SPSS for Windows (version 12.0; SPSS, Chicago, IL). Spearman correlation coefficients were used to describe the association between adiponectin and other continuous variables of interest. Linear regression was used to control for potentially confounding variables. The model, fitted for hepatic lipase activity as a dependent variable, included age, sex, BMI, plasma triglyceride concentration, HDL cholesterol concentration, hs-CRP, and plasma adiponectin concentration as independent variables to demonstrate the relative contribution of each of these variables to the outcome variable. Variables that were not normally distributed, such as plasma adiponectin, triglyceride, and hs-CRP concentrations, were log transformed before they were entered into the statistical evaluation to better approximate normal distributions. Results are expressed as means ± SE. A P value <0.05 was considered statistically significant.

RESULTS — The clinical characteristics of the subjects studied are reported in Table 1. Hepatic lipase activity was significantly higher in male versus female dia-

Table 1—*Anthropometric and biochemical variables of the study subjects*

	Nondiabetic subjects	Diabetic subjects
n	206	110
Age (years)	60.9 ± 10.4	55.9 ± 9.6
BMI (kg/m²)	27.3 ± 3.2	28.6 ± 4.1
Total cholesterol (mmol/l)	5.3 ± 1.1	5.7 ± 1.4
LDL cholesterol (mmol/l)	3.6 ± 1.0	3.8 ± 1.1
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.0 ± 0.4
VLDL cholesterol (mmol/l)*	0.6 ± 0.4	1.0 ± 1.4
Triglycerides (mmol/l)*	1.5 ± 0.8	2.3 ± 2.2
Glucose (mg/dl)	96.6 ± 13.0	159.4 ± 51.0
Insulin (μU/ml)†	21.2 ± 8.0	36.9 ± 26.0
HOMA-IR†	4.9 ± 1.6	13.1 ± 7.9
Adiponectin (μg/ml)*	5.9 ± 4.4	5.7 ± 4.4

Data are means or *medians ± SE. Diabetes was defined by history or by a fasting plasma glucose >126 mg/dl. †Subjects not being treated with insulin. HOMA-IR, HOMA of insulin resistance.

Table 2—*Spearman correlation coefficients with plasma adiponectin and hepatic lipase activity*

	Nondiabetic subjects		Diabetic subjects	
	r	*P* value	*R*	*P* value
Plasma adiponectin				
Age	−0.1	0.2	−0.2	0.2
BMI	−2.976	0.004	−2.3	0.025
Total cholesterol	0.08	0.22	0.07	0.4
LDL cholesterol	0.072	0.3	0.13	0.18
HDL cholesterol	0.364	0.001	0.4	0.001
Triglycerides	−0.194	0.003	−0.285	0.003
VLDL cholesterol	−0.196	0.005	−0.297	0.002
Insulin	−0.322	0.001	−0.343	0.001
HOMA	−0.316	0.001	−0.13	0.9
hs-CRP	−0.219	0.001	−0.1	0.5
Atherogenic index	−0.222	0.001	−0.307	0.001
Hepatic lipase				
Age	−0.07	0.2	−0.21	0.1
BMI	0.072	0.27	−0.06	0.5
Total cholesterol	0.02	0.7	0.07	0.5
LDL cholesterol	0.04	0.5	0.08	0.3
HDL cholesterol	−0.2	0.02	−0.2	0.04
Triglycerides	0.08	0.2	0.134	0.1
VLDL cholesterol	0.07	0.3	0.224	0.02
Insulin	0.125	0.1	0.116	0.2
HOMA	0.1	0.2	0.11	0.4
hs-CRP	0.05	0.40	−0.07	0.5
Atherogenic index	0.14	0.03	0.22	0.02

betic patients (283.5 ± 112 vs. 220.1 ± 74 nmol · ml^{-1} · min^{-1}, $P < 0.05$), as expected. In the nondiabetic CAD group, the hepatic lipase activity was 272.7 ± 110 nmol · ml^{-1} · min^{-1} on average and higher in patients with more severe CAD (severe score >1) (286.02 ± 108 nmol · ml^{-1} · min^{-1}).

Plasma adiponectin levels were significantly higher in female compared with male diabetic patients (8.26 ± 5.3 vs. 4.23 ± 3.3 μg/ml, $P < 0.001$). In the nondiabetic subjects with CAD, the median plasma adiponectin level was 5.9 ± 4.4 μg/ml. In the presence of CAD (severe score >1), adiponectin levels were significantly lower (4.67 ± 3.5 μg/ml [$n = 166$] vs. 6.39 ± 4.9 μg/ml [$n = 40$], $P = 0.003$).

Table 2 shows the association between adiponectin and selected variables for both nondiabetic subjects with CAD and diabetic subjects. As expected, we found significant inverse associations between adiponectin and BMI, plasma triglycerides, and VLDL cholesterol and a positive correlation with HDL cholesterol in both cohorts. The correlation coefficients obtained for hepatic lipase activity are also displayed in Table 2. Hepatic lipase activity was found to be significantly inversely associated with HDL cholesterol in both groups. In both nondiabetic subjects with CAD and type 2 diabetic subjects, adiponectin levels were strongly correlated with postheparin plasma hepatic lipase activity (Fig. 1). In multivariate analyses, including markers of systemic inflammation (hs-CRP), BMI, age, insulin, and HDL cholesterol as factors known to influence hepatic lipase activity, adiponectin was the only independent predictor for hepatic lipase activity in the nondiabetic patients with CAD (Table 3). Regression analyses revealed that plasma adiponectin levels accounted for 12% of the variation in hepatic lipase activity in nondiabetic subjects with CAD.

In the male and female patients of the diabetic study cohort analyzed separately, adiponectin levels were significantly inversely correlated with plasma hepatic lipase activity ($r = −0.25$, $P = 0.027$ and $r = −0.37$, $P < 0.05$, respectively), corresponding to the correlation for all diabetic patients as presented in Fig. 1*B*. When sex was entered in the linear model as an independent variable, it predicted hepatic lipase activity significantly ($T = −2.831$, $P = 0.005$). When both adiponectin and sex were included in the analysis, adiponectin remained a significant predictor (~10%) of hepatic lipase activity (Table 3).

The inverse correlation between hepatic lipase activity and HDL cholesterol and the positive correlation between adiponectin and HDL cholesterol were tested in a multivariate regression analysis with HDL cholesterol as the dependent variable and BMI, age, total cholesterol, adiponectin, insulin, HOMA, and hepatic lipase activity as independent variables. This analysis revealed that adiponectin and BMI were the strongest predictors of HDL cholesterol in the nondiabetic subjects with CAD (adiponectin $T = 5.33$, $P < 0.001$; BMI $T = −2.978$, $P = 0.003$, respectively). Adiponectin alone was the strongest predictor of HDL cholesterol in the diabetic patients ($T = 3.352$, $P = 0.002$). When sex was included in the analysis of the diabetic patients, both adiponectin and sex were the strongest predictors of HDL cholesterol ($T = 2.505$, $P < 0.05$ and $T = 2.105$, $P < 0.05$, respectively), with hepatic lipase activity being collinear to adiponectin in both cohorts ($r = 0.34$ and 0.23), and to female sex in diabetes ($r = −0.26$). Finally, adiponectin was inversely and hepatic lipase activity positively correlated with the atherogenic index.

CONCLUSIONS — This is the first study showing an independent inverse correlation between adiponectin and hepatic lipase activity in two different patient cohorts. Our findings may help to explain observations made in several previous studies. These previous studies have demonstrated correlations either between elevated plasma hepatic lipase activity (11–13,17) or hypoadiponectinemia (8–10,18) with parameters of the insulin resistance (metabolic) syndrome, such as obesity, type 2 diabetes, hypertriglyceridemia, and low HDL cholesterol. Hepatic lipase is regulated predominantly by cell cholesterol content, steroids, and thyroid hormones (3). The hepatic lipase regulatory interactions with insulin are, however, not clear-cut, and hepatic lipase responsiveness to insulin is controversial. Most studies in patients with chronic hy-

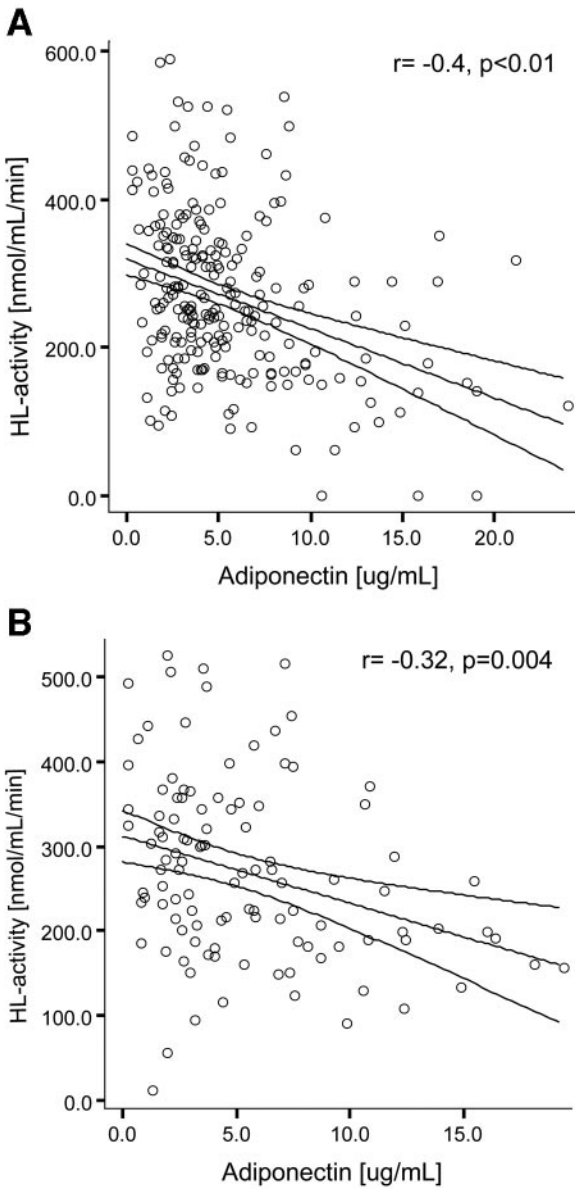

Figure 1—A*: Linear regression line of hepatic lipase activity as a dependent variable curve with 95% prediction interval in nondiabetic patients.* B*: Linear regression line of hepatic lipase activity as a dependent variable curve with 95% prediction interval in the diabetic patients.*

perinsulinemia show higher hepatic lipase activities than in control subjects (11,13,17,19), whereas others report either reduced hepatic lipase activity in type 1 diabetic patients (20) or upregulated hepatic lipase activity by insulin treatment in general (21,22). Therefore, hepatic lipase activity appears to be not clearly upregulated by insulin, and the precise mechanism that links hepatic lipase activity to insulin resistance remains unclear. It was suggested that, instead of insulin per se, a secondary factor might contribute to the regulation of hepatic lipase in obesity and insulin resistance. Recently, it has been speculated that adiponectin, an adipokine known to be related to obesity, insulin resistance, and even CAD (18,23–25), may be such a factor and that reduced adiponectin concentrations may mediate plasma hepatic lipase activity. Support for this hypothesis can be derived from the fact that both hypoadiponectinemia and high hepatic lipase activity occur in the setting of increased abdominal fat mass (18) and that the liver, as the main source of hepatic lipase and primary organ maintaining normal homeostasis in energy metabolism (26), is also a major target organ for the action of adiponectin (14). Our data of a significant association of plasma adiponectin and postheparin hepatic lipase activity in two independent cohorts are the first evidence to support such a role of adiponectin. Although we did not obtain a direct measurement of fat mass, the observation of an inverse relationship between adiponectin and hepatic lipase activity does complement the findings by Cnop et al. (18). These authors suggested that adiponectin concentrations are determined by visceral fat mass and that hypoadiponectinemia in the setting of central adiposity may lead to increased hepatic lipase activity, which could in turn contribute to low HDL cholesterol levels.

The exact mechanism for the inverse correlation between adiponectin and hepatic lipase activity in vivo, however, remains to be studied. Potential explanations include decreased hepatic lipase promoter activity mediated by cholesterol depletion of the cell. This hypothesis suggests a role for a sterol regulatory element–binding protein (SREBP) in controlling hepatic lipase expression with a modulating role of adiponectin. The fact that an inverse relation between the cell cholesterol content and the levels of hepatic lipase mRNA and activity has been described (3) supports this theory. In addition, incubation with mevinolin, a blocker of cholesterol synthesis, induced a stimulation of both hepatic lipase transcripts and activity in vitro, an effect reversed by mevalonate (27). Accordingly, Botma et al. (28) very recently reported SREBP-mediated inhibition of an upstream stimulatory factor–stimulated hepatic lipase gene expression. Adiponectin, on the other hand, has been shown to modulate hepatic lipogenesis by the reduction of SREBP-1c expression (29), which in turn could reduce transcription of the hepatic lipase gene by the above-described mechanism. Alternatively, the association between adiponectin and hepatic lipase activity could be mediated through the PPARγ. The recent finding of a partial normalization of increased hepatic lipase activity in insulin-resistant hamsters by a PPARγ agonist (4) supports this hypothesis. Adiponectin has been demonstrated to upregulate PPARγ mRNA in adipocytes in vitro (30), and circulating adiponectin was associated with increased expression of PPARγ tran-

Table 3—*Multiple regression analysis result of variables with significant effect on hepatic lipase activity*

	Nondiabetic subjects		Diabetic subjects	
Independent variable*	*T*	β	*T*	β
Adiponectin	−3.5*	−0.344*	−3.5†	−0.307†
BMI	−0.314	−0.27	−1.49	−0.134
HDL	0.726	0.221	−0.646	−0.066
Age	−1.168	−0.096	−2.58‡	−0.227‡
Insulin	1.1	0.104	0.03	0.003
Index	1.707	0.089	−0.273	0.03
Sex	NA	NA	−1.85	−0.323

The dependent variable is hepatic lipase (nanomoles per milliliter per minute). $r = 0.347$; $r^2 = 0.121$. β is the standardized coefficient, and *T* represents the estimated coefficient, divided by its own standard error. *T* values below −2 or above 2 are considered as useful predictors in the model. *$P < 0.01$; †$P = 0.001$; ‡$P < 0.05$.

scripts in another study (31). Even reduced expression of inflammatory cytokines by the anti-inflammatory action of adiponectin could play a role, because both adiponectin and hepatic lipase are regulated by interleukin-1 on a mRNA level (32), (33). Finally, a direct effect of adiponectin on hepatic lipase transcription is possible, mediated by the direct action of adiponectin on its receptor in liver (14) by a so far unknown mechanism. These speculations about the exact mechanism linking adiponectin with hepatic lipase merit further investigations. The importance of HDL cholesterol in its meaning as a prognostic factor for the individual atherosclerotic risk is indisputable (34). Although we did not compare our two study groups, the data obtained from our study correspond to previous reports suggesting that adiponectin levels are lower in diabetic male versus female subjects and lower in the presence of CAD (10,25). Low plasma adiponectin has also been shown to be associated with low HDL cholesterol levels (8,35), but the mechanism by which adiponectin influences plasma lipoproteins has not been elucidated. Hepatic lipase is a major determinant of HDL cholesterol concentration, converting HDL subclasses by hydrolyzing phospholipids and triglycerides (36,37) and/or mediating the uptake of HDL cholesterol directly or indirectly by lipoprotein receptors or scavenger receptors (38,39). Because of these functions, hepatic lipase activity is inversely correlated with HDL cholesterol in plasma. Our findings demonstrate that hypoadiponectinemia is associated with increased hepatic lipase activity, which in turn could contribute to a low HDL cholesterol level in vivo, a critical feature of the dyslipidemia in the metabolic syndrome.

In summary, we demonstrate for the first time that low plasma levels of adiponectin are significantly correlated with elevated hepatic lipase activity in two independent cohorts, nondiabetic subjects with CAD and patients with type 2 diabetes. This relationship is independent of systemic inflammatory or metabolic markers and may help to explain the HDL-elevating action of adiponectin.

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