Adiponectin and Future Coronary Heart Disease Events Among Men with Type 2 Diabetes

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Matthias B. Schulze,[1] Iris Shai,[1,2,3] Eric B. Rimm,[1,2,4] Tricia Li,[1] Nader Rifai,[5] and Frank B. Hu[1,2,4]

Adiponectin, predominantly synthesized in the adipose tissue, seems to have substantial anti-inflammatory properties and to be a major modulator of insulin resistance and dyslipidemia, mechanisms that are associated with an increased atherosclerotic risk in diabetic patients. However, it is unknown whether higher levels of adiponectin are associated with a reduced risk for coronary heart disease (CHD) among diabetic individuals. We investigated the association between plasma adiponectin levels and incidence of CHD among 745 men with confirmed type 2 diabetes in the Health Professionals Follow-up Study. Participants were aged 46–81 years and were free of diagnosed cardiovascular disease at the time of blood draw in 1993/1994. During an average of 5 years of follow-up (3,980 person-years), we identified 89 incident cases of CHD (19 myocardial infarction and 70 coronary artery bypass surgery), confirmed by medical records. Levels of adiponectin were inversely associated with BMI and directly associated with age, alcohol intake, and duration of diabetes ($P < 0.05$). After adjustment for age, BMI, smoking, alcohol consumption, duration of diabetes, and other lifestyle factors, adiponectin was associated with a decreased risk for CHD events. The multivariate relative risk for CHD for a doubling of adiponectin was 0.71 (95% CI 0.53–0.95). Further adjustment for HDL cholesterol attenuated this association (0.78 [0.57–1.06]). The inverse association between adiponectin and CHD was consistent across strata of aspirin use, family history of myocardial infarction, alcohol consumption, insulin use, duration of diabetes, and levels of HbA_{1c}, triglycerides, C-reactive protein, and HDL cholesterol. Our study suggests that increased adiponectin levels are associated with a moderately decreased CHD risk in diabetic men. This association seems to be mediated in part by effects of adiponectin on HDL cholesterol levels. *Diabetes* 54: 534–539, 2005

From the [1]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the [2]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [3]S. Daniel Abraham International Center for Health and Nutrition, Department of Epidemiology, Ben-Gurion University, Beer-Sheva, Israel; the [4]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the [5]Department of Laboratory Medicine, Children's Hospital and Harvard Medical School, Boston, Massachusetts.

Address correspondence to Matthias B. Schulze, DrPH, German Institute of Human Nutrition, Department of Epidemiology, Arthur-Scheunert-Allee 114–116, 14558 Nuthetal, Germany. E-mail: mschulze@mail.dife.de.

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CHD, coronary heart disease; CRP, C-reactive protein; sTNFR2, soluble fractions of tumor necrosis factor-α receptor 2.

Adiponectin, predominantly synthesized in the adipose tissue, seems to play an important role in carbohydrate and lipid metabolism and vascular biology (1). It has been found to be a major modulator of insulin action and resistance (2) and to predict the development of type 2 diabetes (3–8). Furthermore, it seems to have substantial anti-inflammatory properties (1). Adiponectin is also related to lipid metabolism, particularly higher levels of HDL cholesterol and lower levels of triglycerides (9). These data suggest that high adiponectin levels may be related to lower risk for coronary heart disease (CHD), and we demonstrated recently that adiponectin levels are associated with a lower risk for myocardial infarction among healthy men in the Health Professionals Follow-up Study (10). Lifestyle and pharmaceutical approaches that increase adiponectin levels therefore might be valuable in decreasing atherosclerotic risk, particularly in individuals with type 2 diabetes, who are at high risk. However, it remains unclear whether adiponectin levels predict CHD risk among individuals with type 2 diabetes, in whom a complex array of metabolic abnormalities most likely contributes to the elevated risk. Glycemia, blood lipids, and inflammatory markers seem to be independently associated with adiponectin levels (11), but it also remains unresolved which pathways may mediate the potential association between adiponectin and CHD risk among diabetic individuals. We therefore evaluated whether adiponectin levels predict CHD events among diabetic men and whether inflammatory markers, cholesterol levels, or HbA_{1c} mediates this association.

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) who were aged 40–75 years at study initiation in 1986. This cohort is followed through biennial mailed questionnaires that focus on various lifestyle factors and health outcomes. In addition, between 1993 and 1994, 18,159 study participants provided blood samples by overnight courier. Among participants who returned blood samples, 1,000 had a confirmed diagnosis of type 2 diabetes (as reported on a supplementary questionnaire sent to all men who reported a diagnosis of diabetes) at baseline or during follow-up through 1998. The present study included 745 men who did not report a diagnosis of angina pectoris, myocardial infarction, coronary bypass surgery or coronary angioplasty, or stroke on any of the biennial questionnaires before blood collection.

Diabetes and cardiovascular end point definitions. The supplementary diabetes questionnaire ascertained the type of diabetes diagnosed (type 1 or type 2), results of diagnostic blood sugars, and information about symptoms at time of diagnosis and use of hypoglycemic medication. In accordance with the criteria of the National Diabetes Data Group (12), confirmation of type 2 diabetes required at least one of the following self-reports on the supplementary questionnaire: *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 participants had their diabetes diagnosed before the release of the American Diabetes Association criteria in 1997 (13). 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 records, whereas the diagnosis of type 2 diabetes was confirmed in 57 (97%) of the remaining 59 (14).

Cardiovascular end points consisted of fatal CHD, nonfatal myocardial infarction, and coronary bypass surgery/coronary angioplasty. The end point did not include angina pectoris. Nonfatal myocardial infarction was confirmed by reviewing medical records using the criteria of the World Health Organization of symptoms plus either typical electrocardiographic changes or elevated cardiac enzyme levels (15). Cardiovascular deaths were confirmed by review of medical records or autopsy reports with the permission of the next of kin. The cause listed on the death certificate was not sufficient alone to confirm a coronary death. Sudden deaths (i.e., death within 1 h of symptom onset in a man without known disease that could explain death) were considered cardiovascular deaths. Physicians who reviewed the records had no knowledge of the self-reported risk factor status. Deaths were reported by next of kin, the postal system, and through records of the National Death Index. Using all sources combined, it is estimated that follow-up for deaths was >98% complete (16).

Blood collection and processing. Each interested participant was sent a blood collection kit that contained instructions and needed supplies (blood tubes, tourniquet, gauze, band-aid, 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; >95% of the samples arrived within 24 h. After receipt, the chilled blood was centrifuged; aliquotted into plasma, erythrocytes, and buffy coat; and stored in continuously monitored nitrogen freezers at a temperature no higher than −130°C. We requested information on the date and the time of the blood sample drawing and the time elapsed since the preceding meal to identify nonfasting (>8 h) participants.

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; coefficients of variation for these measurements were <1.8%. LDL cholesterol was measured by a homogeneous direct method from Genzyme (Cambridge, MA). The day-to-day variability at LDL cholesterol concentrations of 2.32, 2.74, and 3.34 mmol/l was <3.1%. Measurement of apolipoprotein B-100 ($apoB_{100}$) was based on the immunonephelometric assay using reagents and calibrators from Wako Chemicals USA (Richmond, VA) with a day-to-day variability of <5%. We calculated non-HDL cholesterol as the difference between total and HDL cholesterol. C-reactive protein (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 was 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 μg/l was 0.9, 1.1, and 1.5%, respectively. Plasma-soluble fractions of tumor necrosis factor-α receptor 2 (sTNFR2) were measured by ELISA from R & D Systems (Minneapolis, MN). 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. Creatinine was measured by a rate-blanked method that is based on the Jaffe reaction using Roche Diagnostics reagents with a day-to-day variability of 5.0 and 2.2% at concentrations of 106.1 and 565.8 μmol/l.

Assessment of lifestyle exposures. Participants provided information biennially on their age, weight, smoking status, aspirin use, cholesterol-lowering medication, and physical activity. When 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 squared height (in meters). Self-reports of body weight have been shown to be highly correlated with technician-measured weights ($r = 0.97$) in this cohort (17). 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 (18). History of high blood pressure, high blood cholesterol, and cancer was determined from self-reports preceding the blood collection. Family history of CHD was reported in 1986. Alcohol intake was estimated with a dietary questionnaire in 1994. Detailed information on medication among diabetic participants, including the use of insulin, metformin, or other antidiabetic drugs and statins, was acquired with a supplementary questionnaire in 2000.

Statistical analysis. Person-months of follow-up accumulated starting with the reported date of blood draw. Participants who had a diagnosis of cardiovascular disease or died during follow-up were censored at the date of diagnosis or death. All other participants were followed through January 2000 or the return date of the last questionnaire if no questionnaire was returned in 2000. We used Cox proportional hazards analysis stratified on 5-year age categories and over each 2-year follow-up interval to estimate the multivariable-adjusted relative risk associated with a doubling in adiponectin levels. Adiponectin was log transformed, and the relative risk was estimated for an increase by 2 units on the log scale, which corresponds to a doubling on the original scale. We also estimated the relative risks for an increase by 1 SD on the log scale and for each quartile of adiponectin compared with the lowest category and tested for linear trend across categories using log-transformed adiponectin levels. Multivariate models included the following covariates: physical activity (quartiles, missing), family history of myocardial infarction, history of high blood pressure, history of high blood cholesterol, current aspirin use, smoking (never, past, current, or missing), fasting status, and duration of diabetes (no diabetes at baseline, <5 years, 5–9 years, 10–14 years, and 15+ years). We additionally controlled for alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and 15.0+ g/day) and BMI (missing, <23, 23–24, 25–27, 28–30, and 31+) in separate models. Additional analysis included adjustments for HbA_{1c}, fibrinogen, CRP, sTNFR2, triglycerides, HDL cholesterol, $apoB_{100}$, and non-HDL cholesterol to estimate whether adiponectin predicts CHD risk independent of these risk markers. We furthermore evaluated potential effect modifications by aspirin use; family history of myocardial infarction; alcohol consumption; diabetes duration; and HbA_{1c}, triglyceride, sTNFR2, CRP, and HDL cholesterol levels by performing Cox proportional hazards analyses stratified by these variables and by evaluating interaction terms. All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

RESULTS

During an average of 5 years of follow-up (3,980 person-years), we identified 89 incident cases of CHD (19 myocardial infarction and 70 coronary artery bypass surgery), confirmed by medical records. Among the study population of 745 men, increasing adiponectin levels were inversely associated with BMI and family history of myocardial infarction and directly associated with age, alcohol intake, insulin use, and duration of diabetes ($P < 0.05$; Table 1). Levels of HDL cholesterol significantly increased with increasing adiponectin, whereas the opposite was observed for fasting triglycerides, $apoB_{100}$, CRP, fibrinogen, and sTNFR2. Creatinine levels were not significantly associated with adiponectin levels.

After adjustment for age, smoking, duration of diabetes, and other lifestyle factors, adiponectin was associated with a decreased risk for CHD events (Table 2). The multivariate relative risk for CHD for a doubling of adiponectin was 0.69 (95% CI 0.52–0.92). Further adjustment for BMI and alcohol consumption slightly attenuated this association, but adiponectin remained significantly associated with a reduced CHD risk (relative risk 0.71; 95% CI 0.53–0.95). We additionally controlled for HbA_{1c}, blood lipids, and inflammatory markers, but only adjustment for HDL cholesterol appreciably attenuated the association (relative risk 0.78; 95% CI 0.57–1.06). The relative risk associated with a doubling of adiponectin after simultaneous adjustment for HDL cholesterol, $apoB_{100}$, triglycerides, non-HDL cholesterol, CRP, fibrinogen, sTNFR2, and HbA_{1c} was 0.77 (95% CI 0.56–1.06).

TABLE 1
Baseline characteristics by quartiles of adiponectin in 745 diabetic men

Variable	Quartiles of adiponectin 1	2	3	4	*P* for trend*
Adiponectin (μg/ml) [mean (range)]	6.94 (1.41–10.25)	11.82 (10.28–13.92)	16.68 (13.93–19.80)	25.89 (19.81–54.78)	
Age (years; mean)	60.7	62.6	63.7	65.4	<0.001
BMI (kg/m^2; mean)†	29.1	28.5	27.5	26.2	<0.001
Physical activity (MET/week; mean)‡	27.2	30.7	29.0	32.0	0.188
Alcohol intake (g/day; mean)§	7.8	9.0	9.1	11.4	0.011
Currently smoking (%)	4.3	11.0	3.1	6.6	0.615
Aspirin use (%)	38.3	37.4	35.6	43.1	0.604
Insulin use (%)	11.7	14.3	19.1	32.0	<0.001
Family history of myocardial infarction (%)	17.6	12.1	11.9	8.8	<0.001
History of hypertension (%)	46.8	53.3	44.9	43.1	0.078
History of high blood cholesterol (%)	46.3	45.6	41.2	40.3	0.214
Fasting (%)	56.4	52.8	53.6	55.8	0.985
Duration of diabetes (years; mean)	4.4	5.7	7.5	12.3	<0.001
HbA_{1c} (%; mean)*	7.0	7.3	7.2	7.2	0.348
Fasting triglycerides (mmol/l; mean)*‖	2.17	2.02	1.75	1.33	<0.001
HDL cholesterol (mmol/l; mean)	0.89	0.98	1.05	1.19	<0.001
Apolipoprotein B-100 (g/l; mean)*	1.04	1.07	1.03	0.95	<0.001
Non-HDL (mmol/l; mean)*	4.22	4.42	4.37	4.08	0.356
CRP (mg/l; mean)*	2.04	1.91	1.71	1.12	<0.001
Fibrinogen (μmol/l; mean)*	14.1	13.4	13.0	12.7	<0.001
sTNFR2 (pg/ml; mean)*	2,732	2,835	2,765	2,952	0.040
Creatinine (μmol/l; mean)*	92.5	90.6	87.9	92.0	0.820

*Biomarkers were log transformed. †A total of 715 participants as a result of missing values. ‡A total of 696 participants as a result of missing values. §A total of 698 participants as a result of missing values. ‖A total of 407 participants as a result of nonfasting values.

Similarly, the multivariate relative risk for an increase in adiponectin levels by 1 SD on a log scale was 0.77 (95% CI 0.62–0.96). Adjustment for HDL cholesterol attenuated this association (relative risk 0.83; 95% CI 0.66–1.04), but further adjustment for $apoB_{100}$, triglycerides, non-HDL cholesterol, CRP, fibrinogen, sTNFR2, and HbA_{1c} did not appreciably attenuate the association any further (relative risk 0.82; 95% CI 0.65–1.04).

Table 3 shows the estimated relative risks across quartiles of adiponectin. After multivariate adjustment, participants with higher adiponectin levels had a lower risk for CHD (relative risk for extreme quartiles 0.52; 95% CI 0.27–1.01; $P = 0.010$ for trend). Further adjustment for BMI and alcohol consumption attenuated this association (relative risk 0.56; $P = 0.020$ for trend). The relative risk for extreme quartiles of adiponectin after additional adjustment for HDL cholesterol was 0.68 (95% CI 0.34–1.37) with a nonsignificant test for trend ($P = 0.110$). Further adjustment for $apoB_{100}$, triglycerides, non-HDL cholesterol, CRP, fibrinogen, sTNFR2, and HbA_{1c} did not appreciably attenuate the association any further (relative risk for extreme quartiles 0.68; 95% CI 0.33–1.42; $P = 0.110$ for trend).

TABLE 2
Relative risk of CHD associated with a doubling of adiponectin

	RR	95% CI
Age adjusted	0.72	0.55–0.94
MV adjusted*	0.69	0.52–0.92
MV + alcohol and BMI	0.71	0.53–0.95
MV + alcohol, BMI, and HDL cholesterol	0.78	0.57–1.06
MV + alcohol, BMI, HDL cholesterol, $apoB_{100}$, triglycerides, CRP, sTNFR2, and fibrinogen	0.77	0.56–1.06

*Multivariate relative risks adjusted for age, physical activity (quartiles, missing), family history of myocardial infarction, history of high blood pressure, history of high blood cholesterol, current aspirin use, smoking (never, past, current, or missing), fasting status, and duration of diabetes (no diabetes at baseline, <5 years, 5–9 years, 10–14 years, and 15+ years). MV, multivariate.

We used stratified analysis to assess whether aspirin use; family history of myocardial infarction; alcohol consumption; diabetes duration; and HbA_{1c}, triglyceride, sTNFR2, CRP, and HDL cholesterol levels modified this association (Table 4). Associations across most strata were relatively uniform, and tests for interaction were not significant. However, levels of sTNFR2 seemed to modify the association between adiponectin and CHD, with the association being only significant among men with relatively high sTNFR2 levels ($P = 0.012$ for interaction). Also, the association seemed to be stronger among participants with a family history of myocardial infarction and a relatively short duration of diabetes (<5 years); however, the tests for interaction were not statistically significant. The use of insulin, metformin, or statins in or before the year 2000 did not significantly modify this association, although the association seemed to be strong among men who did not report metformin use, whereas no association was observed among metformin users (relative risk 0.96; 95% CI 0.61–1.52). In addition, the use of cholesterol-lowering medication at baseline did not appreciably mod-

TABLE 3
Relative risk of CHD by quartiles of adiponectin

	Quartiles of adiponectin				*P* for trend*
	1	2	3	4	
No. of cases	25	20	28	16	
Age adjusted	1.00	0.75 (0.42–1.36)	1.02 (0.59–1.75)	0.55 (0.29–1.04)	0.017
MV adjusted†	1.00	0.75 (0.41–1.36)	0.97 (0.56–1.69)	0.52 (0.27–1.01)	0.010
MV + alcohol and BMI	1.00	0.80 (0.43–1.46)	1.04 (0.59–1.83)	0.56 (0.28–1.10)	0.020
MV + alcohol, BMI, and HDL cholesterol	1.00	0.82 (0.45–1.52)	1.19 (0.67–2.12)	0.68 (0.34–1.37)	0.110
MV + Alcohol, BMI, HDL cholesterol, apoB_{100}, triglycerides, CRP, sTNFR2, and fibrinogen	1.00	0.76 (0.41–1.43)	1.06 (0.58–1.94)	0.68 (0.33–1.42)	0.110

Data are relative risk (95% CI). *Based on log-transformed adiponectin levels. †Relative risks adjusted for age, physical activity (quartiles, missing), family history of myocardial infarction, history of high blood pressure, history of high blood cholesterol, current aspirin use, smoking (never, past, current, missing), fasting status, and duration of diabetes (no diabetes at baseline, <5 years, 5–9 years, 10–14 years, and 15+ years). MV, multivariate.

ify the association between adiponectin and CHD risk ($P = 0.87$ for interaction).

DISCUSSION

We found that among men with type 2 diabetes, high plasma levels of adiponectin were associated with a reduced risk for incident CHD events. This association was independent of age, BMI, alcohol consumption, and other lifestyle risk factors. HDL cholesterol partly accounted for the observed association between adiponectin and risk for CHD but not other blood lipids, HbA_{1c}, or inflammatory markers. Even after adjustment for HDL cholesterol, adiponectin seemed to be associated with a reduced CHD risk, but this association was no longer statistically significant.

Our results are supported by previous prospective studies among nondiabetic individuals (10,19). In a study among 227 patients with end-stage renal disease, plasma adiponectin levels were an inverse predictor of cardiovascular events (19). Over a period of 31 months, there was a 3% risk reduction for each 1-μg/ml increase in plasma adiponectin levels. Among healthy men in the Health Professionals Follow-up Study, a doubling of adiponectin levels was associated with a 30% decreased risk for myocardial infarction after adjustment for traditional cardiovascular risk factors (10). This association was independent of HbA_{1c}, triglycerides, and CRP but was partly attenuated after adjustment for LDL and HDL cholesterol (relative risk 0.77). Evidence from cross-sectional studies further supports our findings. Plasma levels of adiponectin in diabetic individuals with coronary artery disease were found to be lower than those in diabetic patients without coronary artery disease (9). Similarly, plasma concentrations of adiponectin in 123 patients with coronary artery disease were significantly lower than among 17 control subjects (20). Lower adiponectin levels were found to be associated with an approximately doubled risk for coronary artery disease in a study among 225 consecutive male patients who underwent coronary angiography and 225 voluntary blood donors (21). Adiponectin levels were found to be significantly lower among 35 patients with acute myocardial infarction compared with 35 individuals who had atypical chest pain but had no significant coronary artery stenosis and who were selected from patients who underwent elective cardiac catheterization (22). Adiponectin concentration was also lower among 99 hypertensive male patients with coronary artery disease compared to 62 BMI-matched healthy male blood donors (23).

Our data suggest that HDL cholesterol might partly mediate the association between adiponectin and CHD risk. Adiponectin was associated with substantially higher HDL cholesterol (11), and HDL cholesterol was associated with a borderline significant reduced risk for CHD in this cohort (relative risk for extreme quartiles 0.57; 95% CI 0.32–1.04; $P = 0.05$ for trend) (24). Similar to our cohort, higher adiponectin levels were found to be positively associated with HDL cholesterol among nondiabetic (25–32) and diabetic individuals (33,34), and adjustment for HDL and LDL cholesterol attenuated the association between adiponectin and risk for myocardial infarction among healthy men (10). The mechanisms by which adiponectin may affect HDL cholesterol levels are largely unknown. Effects of adiponectin on hepatic lipase activity, which is increased in central obesity and insulin resistance, are suspected (26). However, associations between adiponectin and HDL cholesterol seem to be generally independent of body fat (11,25–27,30–34) and insulin resistance (11,30–34). This suggests that mechanisms other than effects on insulin resistance and hepatic lipase activity most likely mediate the association between adiponectin and HDL cholesterol and that this association is only in part a mediation of metabolic effects of body fat. Adiponectin induces AMP-activated protein kinase (35,36), resulting in the stimulation of glucose uptake in muscle; fatty acid oxidation in muscle and liver; and the inhibition of hepatic glucose production, cholesterol and triglyceride synthesis, and lipogenesis. Adiponectin therefore may decrease tissue fatty acid content and serum lipids. As a secondary effect of low adiponectin levels, the increase in HDL core triglyceride content that occurs as a result of increased neutral lipid exchange between triglyceride-rich lipoproteins and HDL in hypertriglyceridemic, insulin-resistant states may lead to a decline in HDL particle numbers and cholesterol content, potentially by predisposing HDL particles to enhanced catabolism (37).

Besides its association with blood lipid levels, adiponectin has insulin-sensitizing and anti-inflammatory properties that may lower the risk for CHD. Adiponectin treatment reversed insulin resistance in lipoatrophic mice (38), increased hepatic glucose uptake (39), and stimulated muscular fatty acid oxidation (35). Strong correlations between adiponectin and measures of insulin sensitivity

TABLE 4
Relative risk of CHD associated with a doubling of adiponectin levels, stratified by baseline aspirin use; family history of myocardial infarction; alcohol consumption; reported insulin, metformin, or statin use; and levels of HbA_{1c}, triglycerides, sTNFR2, CRP, and HDL cholesterol

	No. of cases	Relative Risk	95% CI	*P* for interaction*
Aspirin use				0.281
No	45	0.86	0.57–1.29	
Yes	42	0.58	0.39–0.87	
Family history of myocardial infarction				0.520
No	74	0.80	0.57–1.10	
Yes	13	0.36	0.14–0.93	
Alcohol consumption				0.265
0 g/day	35	0.85	0.54–1.32	
>0 g/day	52	0.65	0.44–0.94	
Insulin use				0.779
No	73	0.75	0.55–1.03	
Yes	14	0.72	0.33–1.58	
Metformin use				0.220
No	51	0.66	0.46–0.96	
Yes	36	0.96	0.61–1.52	
Statin use				0.447
No	42	0.66	0.44–0.99	
Yes	45	0.84	0.55–1.29	
Duration of diabetes				0.255
<5 years	39	0.66	0.42–1.02	
≥5 years	48	0.92	0.62–1.37	
HbA_{1c}*				0.188
<6.9%	42	0.84	0.56–1.26	
≥6.9%	45	0.53	0.35–0.81	
Triglycerides*				0.761
<1.93 mmol/l	37	0.72	0.46–1.14	
≥1.93 mmol/l	50	0.76	0.52–1.12	
sTNFR2*				0.012
<2779 pg/ml	33	1.02	0.63–1.67	
≥2779 pg/ml	54	0.57	0.41–0.80	
CRP*				0.783
<1.63 mg/l	30	0.78	0.48–1.26	
≥1.63 mg/l	57	0.63	0.43–0.93	
HDL cholesterol*				0.843
<1.01 mmol/l	54	0.78	0.54–1.14	
≥1.01 mmol/l	33	0.69	0.43–1.10	

Relative risks were adjusted for age, physical activity (quartiles), family history of myocardial infarction, history of high blood pressure, history of high blood cholesterol, aspirin use (currently, not currently), smoking (never, past or current, missing), fasting status, BMI (continuous), alcohol intake (0, 0.1–4.9, 5.0–9.9, and 10.0+ g/day), and duration of diabetes (no diabetes at baseline, <5 years, 5–9 years, and 10+ years), depending on model. *Strata based on population median.

have been well established in humans (1), and low adiponectin levels predict the development of type 2 diabetes (3–8). Potential anti-inflammatory effects of adiponectin include reduced monocyte adhesion (40), suppression of macrophage–to–foam cell transformation (41), and modulation of the inflammatory cascades (11,40,42–44). However, although markers of glycemia and inflammation as well as other blood lipids were also associated with adiponectin levels in our cohort, they seemed to not be relevant effect mediators. Similar to our observation, adjustment for HbA_{1c} or CRP levels had little impact on the association between adiponectin and risk for myocardial infarction among healthy men (10). Noteworthy, blood lipids and other metabolic CHD risk factors may be causal mediators rather than confounders, and adjustment for these variables would tend to underestimate the true association between adiponectin and CHD risk. However, adiponectin might not be a useful screening tool among diabetic patients beyond these established risk factors.

Adiponectin levels were positively associated with diabetes duration in our study. Although adiponectin secretion may be enhanced to mitigate microvascular damage in diabetic nephropathy (45), creatinine levels were not associated with adiponectin levels in our study. Also, exclusion of participants with elevated creatinine levels ($n = 42$) did not alter the observed association between adiponectin and diabetes duration.

A limitation of our study is the relatively small sample size, which may have led to unstable estimates and a lack of power to detect significant associations, particularly when adiponectin was modeled as categorical variable and in stratified analyses. In addition, similar to a cohort among healthy subjects (10), the association between adiponectin and CHD risk seemed not to be linear across categories of adiponectin levels in our study. However, the use of quartiles makes it unlikely that our results are driven by outliers.

In conclusion, our findings support the hypothesis that high adiponectin levels reduce the risk for CHD events among men with type 2 diabetes, independent of currently established lifestyle risk factors. This association seems to be mediated mainly by HDL cholesterol levels but not by potential effects of adiponectin on glycemia and inflammation.

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