Serum Adiponectin and Renal Dysfunction in Men With Type 2 Diabetes

JULIE LIN, MD, MPH[1,2]
FRANK B. HU, MD, PHD[1,3,4]
GARY CURHAN, MD, SCD[1,2,4]

OBJECTIVE — Inflammation is associated with both chronic kidney dysfunction and type 2 diabetes. Adiponectin, a novel circulating anti-inflammatory protein made by adipocytes, has been reported to be lower in diabetic than nondiabetic subjects. In contrast, serum levels of adiponectin are elevated in end-stage renal disease. We sought to investigate the relation between adiponectin and mild to moderate renal dysfunction in men with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Multivariate logistic regression was used to evaluate the relation between serum adiponectin concentrations and the presence of renal dysfunction (estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2 by the four-variable Modification of Diet in Renal Disease equation) in participants with type 2 diabetes in the Health Professionals' Follow-Up Study. A total of 733 men were included in this cross-sectional analysis.

RESULTS — Adiponectin was positively correlated with age (Spearman coefficient, $r = 0.19$, $P < 0.001$) and negatively correlated with weight (Spearman coefficient, $r = -0.18$, $P < 0.001$). Those with adiponectin in the second quartile or higher (>10 μg/ml) compared with those in the first quartile had a reduced odds for renal dysfunction (multivariate odds ratio 0.48 [95% CI 0.28–0.81]). These results were unchanged when serum lipids were included in the multivariate model.

CONCLUSIONS — We conclude that a higher serum adiponectin concentration is associated with reduced odds of moderate renal dysfunction in men with type 2 diabetes.

Diabetes Care 30:239–244, 2007

Systemic inflammation has been implicated in the progression of chronic kidney disease in animal models (1,2) and in humans (3,4). As the leading cause of kidney failure in the world, type 2 diabetes has been postulated to be a generalized inflammatory condition resulting from obesity-induced dysregulation of adipocytes, which produce an excess of inflammatory cytokines (5). Scientists have speculated that this persistent inflammatory state further contributes to the development of the extensive vascular disease characteristic of diabetes.

Adiponectin, a recently discovered circulating 30-kDa protein exclusively secreted by adipocytes, is present at concentrations of 5–30 μg/ml in healthy humans (6) and is considered to be an important modulator of insulin sensitivity (7) and dyslipidemia (8). Anti-inflammatory properties also have been attributed to adiponectin, a theory supported by observations that serum concentrations of adiponectin are inversely associated with inflammatory markers such as fibrinogen, intracellular adhesion molecule-1, E-selectin, and C-reactive protein (9,10). The observation that adiponectin may be protective against vascular disease via the above mechanisms is supported by cross-sectional analyses of individuals with coronary heart disease, who have lower concentrations of adiponectin when compared with control subjects (11,12), and prospective studies revealing that higher adiponectin is associated with a decreased risk for subsequent cardiovascular disease events in nondiabetic subjects (13), type 1 diabetic subjects (14), type 2 diabetic men (15), and in end-stage renal disease patients (16). The role of adiponectin in cardiovascular disease is not definitive, however, because some studies have found no relation between adiponectin and cardiovascular disease risk (17,18).

Adiponectin appears to play an important role in the pathogenesis of type 2 diabetes. Cross-sectional studies (19–22) have demonstrated that serum concentrations of adiponectin are decreased in type 2 diabetic subjects compared with nondiabetic control subjects. Moreover, higher adiponectin levels are associated with better lipid and glycemic control in type 2 diabetic subjects (8,9). One prospective study (23) has reported that lower baseline serum adiponectin appears to be a harbinger for the development of type 2 diabetes.

In kidney disease, higher adiponectin levels are present in dialysis patients (16) but not in nondiabetic patients with predialysis chronic kidney disease (7) when compared with healthy control subjects. The association of adiponectin with kidney function in individuals with type 2 diabetes, however, is not well described. The existing literature has focused mainly on those with glucose intolerance or end-stage renal disease. Previous work (24) by our group has revealed that in male diabetic subjects, estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 is inversely correlated with several circulating lipid and inflammatory markers and that adiponectin is inversely correlated with dyslipidemia and inflammation (8). We therefore hypothesized that higher adiponectin might be associated with decreased odds for mild to moderate renal insufficiency in type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The Health Professionals' Follow-Up Study (HPFS) was estab-

From the [1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the [2]Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the [3]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; and the [4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

Address correspondence and reprint requests to Julie Lin, MD, MPH, Renal Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. E-mail: jlin11@partners.org.

Received for publication 21 June 2006 and accepted in revised form 4 November 2006.

Abbreviations: eGFR, estimated glomerular filtration rate; HPFS, Health Professionals' Follow-Up Study.

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

DOI: 10.2337/dc06-1296

lished in 1986 when 51,529 U.S. male health professionals, aged 40–75 years at study initiation, returned a mailed questionnaire providing information about diet, lifestyle factors, and medical history (25). Participants were mailed follow-up questionnaires every 2 years to update information. In 1993–1994, blood samples were collected and frozen (−130°C) from a subset of these participants (n = 18,159) as previously described (8). Demographic and clinical characteristics at baseline were similar between men who provided blood samples and those who did not.

Diabetes was first identified by self-report on a biennial questionnaire and confirmed by a Diabetes Supplemental Questionnaire in 2000; the validity of the Diabetes Supplemental Questionnaire in confirming diabetes has been demonstrated in the HPFS cohort (26). The HPFS diabetes blood cohort consists of 1,000 men with confirmed diabetes diagnosed before study entry or newly diagnosed up through June 1998 who provided a blood sample in 1993–1994. Exclusion criteria for the current analyses were *1*) age of onset of diabetes ≤25 years of age (to attempt to restrict the study to type 2 diabetes) (n = 31), *2*) reported date of diabetes diagnosis after the date of blood draw (n = 224), *3*) participants who reported on the Diabetes Supplemental Questionnaire that they were on dialysis (n = 9) or had a kidney transplant (n = 1), *4*) serum creatinine >5.0 mg/dl (n = 1), and *5*) serum creatinine ≤0.5 mg/dl (felt to be physiologically implausible) (n = 1). After these exclusions, 733 men were available for analysis. This study was approved by the institutional review boards at the Harvard School of Public Health and the Brigham and Women's Hospital.

Biochemical analysis

Adiponectin was measured by competitive radioimmunoassay using a commercial reagent set from Linco Research (St. Louis, MO). A previous study (27) demonstrated that adiponectin measurements are highly stable and reproducible under transport conditions and in frozen whole-blood samples. The coefficient of variation was 3.4%. A1C was measured by turbidimetric immunoinhibition using hemolyzed whole blood or packed red cells with a coefficient of variation of 7.5%. Plasma creatinine was measured by a modified kinetic Jaffe reaction with a coefficient of variation of 22%.

Assessment of covariates

Race and height were initially reported on the 1986 questionnaire. Other clinical and lifestyle variables (hypertension, weight, physical activity, cigarette smoking, and medication use) were derived from data from the 1994 questionnaire, which included data closest to the time of blood draw. BMI was calculated by weight in kilograms divided by the square of height in meters. A weekly metabolic equivalent (MET) score was calculated from physical activity questions. Cardiovascular disease (myocardial infarction, coronary artery bypass grafting, or angina) was confirmed by medical record review (28).

Asssessment of renal function

Renal dysfunction was defined as an eGFR <60 ml/min per 1.73 m^2 as calculated by the four-variable MDRD (Modification of Diet in Renal Disease) equation (eGFR [ml/min per 1.73 m^2] = $186 \times [\text{PCr } \{\text{mg/dl}\}]^{-1.154} \times [\text{age}]^{-0.203} \times$ [1.21 if subject is black]) (29). We also examined estimated creatinine clearance by the Cockcroft-Gault equation as the measure of kidney function (30). Of note, because the Cockcroft-Gault results were noticeably influenced by weight, as expected, we chose to present data only with eGFR by the MDRD equation.

Statistical analysis

The Wilcoxon signed-rank test was used for comparisons of continuous variables. Spearman correlation coefficients were calculated for pairs of continuous variables. Logistic regression was used to calculate odds ratios for adiponectin levels with eGFR <60 ml/min per 1.73 m^2 as the outcome. Multivariate models were adjusted for age (continuous, years), hypertension (yes/no), BMI (continuous), cigarette smoking status (never, past, or current), physical activity (quartiles, METs/week), duration of type 2 diabetes (quartiles, years), measured A1C (quartiles), and cardiovascular disease (yes/no). ACE and statin use did not change point estimates when included in the model and were removed. All analyses were performed with SAS software version 8.2 (SAS Institute, Cary, NC).

RESULTS

— Characteristics of the HPFS diabetes cohort are presented in Table 1. Participants had a median age of 67 years, were mostly Caucasian, and had been carrying the diagnosis of diabetes for 9 years at the time of blood draw. The majority were overweight (BMI ≥25 kg/m^2), almost half were hypertensive, one-quarter had cardiovascular disease, the median serum creatinine was 1.0 mg/dl, and median eGFR was 78 ml/min per 1.73 m^2.

By Spearman correlation, adiponectin was positively correlated with age (r = 0.19, $P < 0.001$) and inversely correlated with weight ($r = -0.18$, $P < 0.001$) and BMI ($r = -0.24$, $P < 0.001$) but not with eGFR (r = 0.01, P = 0.76). There was no association between adiponectin and serum creatinine ($r = -0.04$, P = 0.25) or adiponectin and eGFR when considering only those with eGFR <60 ml/min per 1.73 m^2 ($r = -0.083$, P = 0.44). Adiponectin was also significantly associated with serum LDL (r = 0.10, P = 0.008), triglycerides ($r = -0.33$, $P < 0.001$), HDL (r = 0.41, $P < 0.001$), and with A1C (r = 0.09, P = 0.007).

Using multivariate logistic regression, men in each of the upper three quartiles of adiponectin had a reduced odds for having eGFR <60 ml/min per 1.73 m^2 when compared with the lowest quartile (Table 2). Because the results suggested a threshold rather than a graded association, we combined the upper three quartiles of serum adiponectin and found that the odds ratio for kidney dysfunction in these individuals was 0.48 (95% CI 0.28–0.81). These results were unchanged after we adjusted for individual lipid markers by quartiles (odds ratio for those with adiponectin in the upper three quartiles remained significant and changed by <15% in all lipid analyses) (data not shown).

CONCLUSIONS

— We found that serum adiponectin was inversely associated with presence of renal dysfunction in men with type 2 diabetes, the majority of whom had well-preserved eGFR (87% had eGFR >60 ml/min per 1.73 m^2). There appeared to be a threshold in that those with an adiponectin level higher than the first quartile all had similar decreased odds ratios for renal dysfunction. Because of the reported associations between dyslipidemia and adiponectin, we also adjusted for these factors in our multivariate models and found that the relation between adiponectin and renal dysfunction remained independent and unchanged.

We adjusted for several potential confounders in the relation between adi-

Table 1—*Demographic and clinical characteristics of type 2 diabetic subjects in the HPFS in 1994*

	Entire cohort	eGFR ≥60 ml/min per 1.73 m^2	eGFR <60 ml/min per 1.73 m^2
n	733	643	90
Age (years)	67 (47–80)	66 (47–80)	69.5 (48–80)*
Race			
Caucasian	675 (92.2)	594 (92.4)	81 (90.0)
African American	11 (1.5)	8 (1.2)	3 (3.3)
Hypertension	399 (45.6)	334 (51.9)	65 (72.2)*
Weight (kg)	85.5 (56.8–210.9)	85.0 (56.8–210.9)	86.4 (65.9–161.8)
BMI (kg/m^2)	27.1 (18.3–56.5)	27.1 (18.3–56.5)	28.2 (20.8–45.7)
BMI categories (kg/m^2)			
<22.0	33 (4.5)	31 (4.8)	2 (2.2)
22–24.9	160 (21.8)	143 (22.2)	17 (18.9)
25–27.9	229 (31.2)	204 (31.7)	25 (27.8)
28–29.9	131 (17.9)	108 (16.8)	23 (25.6)
≥30	180 (24.6)	157 (24.4)	23 (25.6)
Activity (METs/week)	20 (0–228.8)	20.4 (0–228.8)	13.0 (0–160.3)†
Cigarette smoking			
Current	43 (5.8)	38 (5.9)	5 (4.5)
Past	392 (53.5)	351 (54.6)	41 (45.6)
Never	261 (35.7)	225 (35.0)	36 (40.0)
Missing	37 (5.1)	29 (4.5)	8 (8.9)
Age at diabetes diagnosis (years)	55 (26–78)	55 (26–76)	55.5 (32–78)
Duration of diabetes (years)	9 (0.1–41.1)	8.6 (0.1–41)	10.8 (0.1–39.8)‡
Measured A1C (%)	7.2 (4.8–15.6)	7.2 (5.0–15.6)	6.8 (4.8–10.9)†
Baseline cardiovascular disease (myocardial infarction, coronary artery bypass graft, or angina)	194 (26.5)	156 (24.3)	38 (42.2)*
ACE inhibitor medication use	60 (8.2)	49 (7.6)	11 (12.2)
Statin medication	48 (6.6)	42 (6.5)	6 (6.7)
Median adiponectin (μg/ml)	14.3 (1.4–54.8)	14.4 (1.4–54.8)	14.0 (4.4–42.0)
Serum creatinine (mg/dl)	1.0 (0.6–2.9)	1.0 (0.6–1.4)	1.4 (1.3–2.9)
eGFR (ml/min per 1.73 m^2)	78 (23–142)	81 (60–142)	53 (23–59)

Data are median (range) or *n* (%) unless otherwise indicated. *$P < 0.001$; †$P < 0.01$; ‡$P = 0.17$ compared with eGFR >60 ml/min per 1.73 m^2.

ponectin and eGFR, including age, obesity, and hypertension. Consistent with our findings that adiponectin and age were positively correlated, previous investigations have reported that plasma adiponectin is higher in elderly men and women aged >70 years when compared with younger individuals (31). The relation between adiponectin and age appears stronger in diabetic subjects (Spearman $r = 0.44$) than in nondiabetic subjects (Spearman $r = 0.15$) (32). Serum adiponectin is decreased in obesity (10,32,33), in the presence and absence of diabetes, and in hypertension (34). By adjusting for these covariates, we found that the inverse association between serum adiponectin quartiles and presence of renal dysfunction was modestly strengthened.

There is a growing literature on adiponectin and renal disease. Adiponectin is 2.5 times higher in hemodialysis patients (15.0 vs. 6.3 μg/ml, $P < 0.0001$) (16) and three times higher in pediatric

Table 2—*Age-adjusted and multivariate odds ratios for adiponectin quartiles and presence of moderate renal dysfunction (eGFR <60 ml/min per 1.73 m^2)*

	HPFS (*n* = 733)		
	n/*N* (%)	Age-adjusted odds ratio (95% CI)	Multivariate odds ratio (95% CI)*
eGFR <60 ml/min per 1.73 m^2	90/733 (12)		
Adiponectin Q1	29/173 (17)	Referent	Referent
Adiponectin Q2	19/184 (10)	0.54 (0.29–1.02)	0.48 (0.25–0.92)
Adiponectin Q3	18/188 (10)	0.48 (0.26–0.92)	0.38 (0.19–0.75)
Adiponectin Q4	24/188 (13)	0.61 (0.34–1.09)	0.62 (0.33–1.19)
Adiponectin >Q1	61/561 (11)	0.54 (0.33–0.88)	0.48 (0.28–0.81)

*Multivariate models are adjusted for age (continuous, years), hypertension (yes/no), BMI (continuous), cigarette smoking status (never, past, or current), physical activity (quartiles, METs/week), duration of type 2 diabetes (quartiles, years), measured A1C (quartiles), and cardiovascular disease (yes/no).

peritoneal dialysis patients (35) when compared with healthy control subjects. In predialysis individuals, two cross-sectional studies (32,36) of adiponectin and renal function in type 2 diabetic subjects have reported a positive association between adiponectin and renal function, in contrast to our study. Although both studies appropriately adjusted for potential confounding by age and BMI, the study populations were very different from ours, making direct comparisons of the results difficult. The report by Looker et al. (32) included 1,069 Pima Indians in contrast to the mostly Caucasian men in our cohort. The study by Guebre-Egziabher et al. (36) consisted of only 48 patients with a mean inulin GFR of 53.5 ml/min per 1.73 m^2, which is much lower than the eGFR of our study cohort. We did not observe an association, however, between adiponectin and eGFR even when we restricted our analyses to those with eGFR <60 ml/min per 1.73 m^2. Another study analyzed 543 type 1 diabetic subjects and found an adjusted inverse association between adiponectin and creatinine clearance estimated by the Cockcroft-Gault equation of −0.33 ml/min difference in creatinine clearance for every 1 SD increase in adiponectin levels (37). Our study included only type 2 diabetic subjects, however, and associations between renal clearance and adiponectin may not be the same in insulin-resistant states compared with insulin-deficient ones such as type 1 diabetes. Similarly, although a study of 227 nondiabetic renal patients reported a significant inverse association between adiponectin and directly measured GFR ($r = -0.25$, $P < 0.01$) (7), the association between adiponectin and renal clearance could be different in type 2 diabetic subjects because adiponectin levels have been consistently reported to be inversely associated with insulin resistance and are therefore significantly lower in type 2 diabetes.

An alternative explanation for our contrasting findings is that this may be a chance finding, especially in light of the fact that we saw no statistically significant association between adiponectin and eGFR by Spearman correlation. It should be noted, however, that we did not find this result through multiple testing but instead entered into this project with an a priori hypothesis that adiponectin and renal clearance would be directly associated because of the existing literature on inverse association between adiponectin and vascular disease.

One potential explanation for the inverse association observed is that adiponectin reduces vascular disease. Supporting evidence for the role of adiponectin in decreasing vascular endothelial dysfunction is accruing. We previously have reported that adiponectin was positively correlated with HDL cholesterol (Spearman $r = 0.42$, $P < 0.01$) and negatively correlated with triglycerides ($r = -0.38$, $P < 0.01$), apoprotein B ($r = -0.19$, $P < 0.01$), C-reactive protein ($r = -0.18$, $P < 0.01$), and fibrinogen ($r = -0.18$, $P < 0.01$), which was independent of A1C and HDL in adjusted analyses in these diabetic men (8), suggesting that dyslipidemia and inflammation might be attenuated when serum adiponectin is higher. Similar inverse associations between adiponectin and lipids and inflammatory markers have been reported for diabetic female participants in the Nurses' Health Study (9). Adjusting for quartiles of lipid biomarkers in our analyses, however, did not influence the results.

The potential benefits of increasing serum adiponectin levels on decreasing future risk for renal function decline remains to be determined. As a circulating anti-inflammatory molecule, higher serum adiponectin has been reported to be associated with a decreased risk for cardiovascular events in diverse populations including people with nondiabetic chronic kidney disease (7), diabetic subjects (15), and end-stage renal disease patients (16), and therefore, its potential role in vascular disease is intriguing. In particular, diminishing the inflammatory state of diabetes may be central in modifying risk for progressive endothelial dysfunction and renal disease. For example, adiponectin levels are increased by thiazolidinediones (38,39), medications that improve insulin sensitivity at the cellular level (22), so raising low adiponectin states is achievable if proven to be beneficial. Rosiglitazone therapy has been confirmed to increase adiponectin levels in African Americans with impaired glucose tolerance or diabetes (40), although direct evidence for the benefit of thiazolidinediones in human diabetic nephropathy is currently lacking.

Adiponectin levels can be increased through nonmedication factors as well. Low dietary glycemic load and high-fiber diets may contribute to higher adiponectin levels in diabetic subjects (15). Moderate alcohol intake also appears to increase adiponectin levels by 0.8 mg/ml ($P = 0.01$) for each additional drink per day in this cohort (41). Cigarette smoking is another modifiable risk factor reported to be associated with lower adiponectin (42). The effects of these lifestyle modifications and higher adiponectin levels on kidney function decline over time remain to be determined.

Limitations to our study include its cross-sectional design, which limits conclusions about mechanism or temporal relation. No information is available on albuminuria because urine has not been collected and stored in this cohort. Lastly, renal function was estimated from creatinine-based prediction equations. The relatively high coefficient of variation of plasma creatinine would presumably result in random misclassification and bias the results toward the null.

Our observation of the inverse association of adiponectin with moderate renal dysfunction in men with type 2 diabetes needs to be replicated in non-Caucasians and in women. How serum adiponectin is related to eGFR decline over time also warrants further study. Based on these initial data, we hypothesize that sustained higher serum adiponectin levels, independent of glucose and lipid control, would be associated with slower rates of eGFR loss in type 2 diabetes.

Acknowledgments— This work was supported by National Institutes of Health Grants K08 DK066246 (to J.L.), R01HL065582 (to F.B.H.), and P01CA055075 and a Norman S. Coplon Extramural Research Grant through Satellite Healthcare (to J.L.).

A portion of this work was included in a poster presentation at Renal Week 2005, 8–13 November 2005, Philadelphia, Pennsylvania.

References

1. Fattori E, Della Rocca C, Costa P, Giorgio M, Dente B, Pozzi L, Ciliberto G: Development of progressive kidney damage and myeloma kidney in interleukin-6 transgenic mice. *Blood* 83:2570–2579, 1994
2. Karkar AM, Smith J, Pusey CD: Prevention and treatment of experimental crescentic glomerulonephritis by blocking tumour necrosis factor-alpha. *Nephrol Dial Transplant* 16:518–524, 2001
3. Erlinger TP, Tarver-Carr ME, Powe NR, Appel LJ, Coresh J, Eberhardt MS, Brancati FL: Leukocytosis, hypoalbuminemia, and the risk for chronic kidney disease in US adults. *Am J Kidney Dis* 42:256–263, 2003
4. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G: Biomarkers of inflammation

and progression of chronic kidney disease. *Kidney Int* 68:237–245, 2005
5. Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG: Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. *J Clin Endocrinol Metab* 84:272–278, 1999
6. Nedvidkova J, Smitka K, Kopsky V, Hainer V: Adiponectin, an adipocyte-derived protein. *Physiol Res* 54:133–140, 2005
7. Becker B, Kronenberg F, Kielstein JT, Haller H, Morath C, Ritz E, Fliser D: Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: the mild and moderate kidney disease study. *J Am Soc Nephrol* 16: 1091–1098, 2005
8. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB: Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. *Diabetes Care* 27:1680–1687, 2004
9. Mantzoros CS, Li T, Manson JE, Meigs JB, Hu FB: Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. *J Clin Endocrinol Metab* 90:4542–4548, 2005
10. Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A: Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. *Diabetes Care* 27:2450–2457, 2004
11. Rothenbacher D, Brenner H, Marz W, Koenig W: Adiponectin, risk of coronary heart disease and correlations with cardiovascular risk markers. *Eur Heart J* 26: 1640–1646, 2005
12. Dunajska K, Milewicz A, Jedrzejuk D, Szymczak J, Kuliczkowski W, Salomon P, Bialy D, Poczatek K, Nowicki P: Plasma adiponectin concentration in relation to severity of coronary atherosclerosis and cardiovascular risk factors in middle-aged men. *Endocrine* 25:215–221, 2004
13. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 291:1730–1737, 2004
14. Costacou T, Zgibor JC, Evans RW, Otvos J, Lopes-Virella MF, Tracy RP, Orchard TJ: The prospective association between adiponectin and coronary artery disease among individuals with type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia* 48:41–48, 2005
15. Qi L, Rimm E, Liu S, Rifai N, Hu FB: Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. *Diabetes Care* 28:1022–1028, 2005
16. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y: Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 13:134–141, 2002
17. Lindsay RS, Resnick HE, Zhu J, Tun ML, Howard BV, Zhang Y, Yeh J, Best LG: Adiponectin and coronary heart disease: the Strong Heart Study. *Arterioscler Thromb Vasc Biol* 25:e15–e16, 2005
18. Lawlor DA, Davey Smith G, Ebrahim S, Thompson C, Sattar N: Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. *J Clin Endocrinol Metab* 90:5677–5683, 2005
19. Statnick MA, Beavers LS, Conner LJ, Corominola H, Johnson D, Hammond CD, Rafaeloff-Phail R, Seng T, Suter TM, Sluka JP, Ravussin E, Gadski RA, Caro JF: Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. *Int J Exp Diabetes Res* 1:81–88, 2000
20. 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
21. Yenicesu M, Yilmaz MI, Caglar K, Sonmez A, Eyileten T, Kir T, Acikel C, Bingol N, Oguz Y, Ikizler TA, Vural A: Adiponectin level is reduced and inversely correlated with the degree of proteinuria in type 2 diabetic patients. *Clin Nephrol* 64:12–19, 2005
22. 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
23. 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
24. Lin J, Hu FB, Rimm EB, Rifai N, Curhan GC: The association of serum lipids and inflammatory biomarkers with renal function in men with type II diabetes mellitus. *Kidney Int* 69:336–342, 2006
25. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ: Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 338:464–468, 1991
26. 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
27. Pischon T, Hotamisligil GS, Rimm EB: Adiponectin: stability in plasma over 36 hours and within-person variation over 1 year. *Clin Chem* 49:650–652, 2003
28. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB: Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 107:2435–2439, 2003
29. Stevens LA, Coresh J, Greene T, Levey AS: Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med* 354:2473–2483, 2006
30. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
31. Adamczak M, Rzepka E, Chudek J, Wiecek A: Ageing and plasma adiponectin concentration in apparently healthy males and females. *Clin Endocrinol (Oxf)* 62:114–118, 2005
32. Looker HC, Krakoff J, Funahashi T, Matsuzawa Y, Tanaka S, Nelson RG, Knowler WC, Lindsay RS, Hanson RL: Adiponectin concentrations are influenced by renal function and diabetes duration in Pima Indians with type 2 diabetes. *J Clin Endocrinol Metab* 89:4010–4017, 2004
33. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 257: 79–83, 1999
34. D'Anna R, Baviera G, Corrado F, Giordano D, Di Benedetto A, Jasonni VM: Plasma adiponectin concentration in early pregnancy and subsequent risk of hypertensive disorders. *Obstet Gynecol* 106: 340–344, 2005
35. Bakkaloglu SA, Buyan N, Funahashi T, Pasaoglu H, Elhan AH, Hasanoglu E, Soylemezoglu O: Adiponectin levels and atherosclerotic risk factors in pediatric chronic peritoneal dialysis patients. *Perit Dial Int* 25:357–361, 2005
36. Guebre-Egziabher F, Bernhard J, Funahashi T, Hadj-Aissa A, Fouque D: Adiponectin in chronic kidney disease is related more to metabolic disturbances than to decline in renal function. *Nephrol Dial Transplant* 20:129–134, 2005
37. Schalkwijk CG, Chaturvedi N, Schram MT, Fuller JH, Stehouwer CD: Adiponectin is inversely associated with renal function in type 1 diabetic patients. *J Clin Endocrinol Metab* 91:129–135, 2006
38. 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

39. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM: Synthetic peroxisome proliferator–activated receptor-γ agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. *Diabetes Care* 25:376–380, 2002
40. Osei K, Gaillard T, Kaplow J, Bullock M, Schuster D: Effects of rosglitazone on plasma adiponectin, insulin sensitivity, and insulin secretion in high-risk African Americans with impaired glucose tolerance test and type 2 diabetes. *Metabolism* 53:1552–1557, 2004
41. Shai I, Rimm EB, Schulze MB, Rifai N, Stampfer MJ, Hu FB: Moderate alcohol intake and markers of inflammation and endothelial dysfunction among diabetic men. *Diabetologia* 47:1760–1767, 2004
42. Iwashima Y, Horio T, Suzuki Y, Kihara S, Rakugi H, Kangawa K, Funahashi T, Ogihara T, Kawano Y: Adiponectin and inflammatory markers in peripheral arterial occlusive disease. *Atherosclerosis* 188:384–390, 2006