Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1011 – 1016
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Plasma adiponectin concentrations and correlates in African Americans in the Hypertension Genetic Epidemiology Network (HyperGEN) study

James M. Shikany[a,*], Cora E. Lewis[a], Barry I. Freedman[b], Donna K. Arnett[c], Catherine Leiendecker-Foster[d], Tamekia L. Jones[e], David T. Redden[e], Albert Oberman[a]

[a]Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, USA
[b]Department of Internal Medicine, School of Medicine, Wake Forest University, Winston-Salem, NC 27157, USA
[c]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL 35294, USA
[d]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA
[e]Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL 35294, USA

Received 25 September 2006; accepted 22 February 2007

Abstract

Adiponectin has demonstrated insulin-sensitizing, antiatherogenic, and anti-inflammatory properties, and may be an important risk factor for coronary heart disease and diabetes. Relatively few previous studies of plasma adiponectin have included sizable numbers of African Americans. The objective of the study was to investigate plasma concentrations of adiponectin and correlates of these concentrations in African Americans. This was a cross-sectional analysis that took place within the Hypertension Genetic Epidemiology Network. This study included 211 normotensive offspring (aged 22-37 years) of hypertensive siblings recruited by the Hypertension Genetic Epidemiology Network Birmingham, AL, field center. In addition to measuring plasma adiponectin, demographic and lifestyle data were collected, and anthropometric, clinical, and laboratory measurements were obtained. Mean plasma adiponectin concentration was 5.5 ± 3.8 μg/mL. Adiponectin was 55% higher in women than in men: 6.5 ± 4.4 vs 4.2 ± 2.5 μg/mL, respectively ($P < .0001$). In a multivariable analysis, high-density lipoprotein cholesterol concentration was positively associated and male sex and insulin concentration were negatively associated with plasma adiponectin concentration. Plasma adiponectin concentrations in these African Americans were lower than those reported in other racial/ethnic groups, including Japanese, whites, and Pima Indians. The directions of the associations of plasma adiponectin with other factors were in agreement with results in other racial/ethnic groups.

1. Introduction

Adiponectin is an adipocyte-derived peptide that exhibits insulin-sensitizing, antiatherogenic, and anti-inflammatory properties [1-3]. Adiponectin is present in relatively high concentrations in human plasma, accounting for approximately 0.01% of total plasma protein [4]. Plasma concentrations of adiponectin have been positively associated with age and have generally been shown to be higher in women compared to men [5]. It has been hypothesized that adiponectin may be the link between markers of inflammation, endothelial dysfunction, and obesity and risk of type 2 diabetes mellitus [6].

Plasma adiponectin has been inversely correlated with body mass index (BMI) and visceral adiposity [5] and is increased by weight loss [7,8]. Adiponectin has been negatively associated with insulin concentration in previous studies [7,9]. This inverse association may be mediated by adiponectin's insulin-sensitizing effects in tissues involved in glucose and lipid metabolism [10,11]. Hypoadiponectinemia may result in insulin resistance, increasing the risk of type 2 diabetes mellitus [12].

Hypoadiponectinemia may be a novel and important risk factor for coronary heart disease (CHD) [13]. Lower adiponectin concentrations have been associated with hypertension [14]. Adiponectin concentrations have shown inverse associations with plasma triglycerides [5,7,15] and positive associations with high-density lipoprotein (HDL) cholesterol [5,15]. Adiponectin has also shown inverse relationships with plasma C-reactive protein and other

* Corresponding author. Tel.: +1 205 975 7989; fax: +1 205 934 7959.
E-mail address: jshikany@dopm.uab.edu (J.M. Shikany).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.03.020

markers of inflammation [6,16,17]. Because of the documented associations between adiponectin and multiple components of the metabolic syndrome, it has been speculated that adiponectin may play a key role in the development and prevention of this syndrome [10]. High plasma adiponectin concentrations are also associated with lower risk of myocardial infarction in men, independent of traditional risk factors [18].

Comparative studies of plasma adiponectin concentrations in populations with different propensity for obesity, insulin resistance, type 2 diabetes mellitus, and CHD are warranted [4]. Previous studies of concentrations and correlates of plasma adiponectin have been conducted primarily in Japanese [7,15-17,19,20], Pima Indians [4,6,11], whites [4,21], or in individuals of unreported race/ethnicity [5,14,22]. Less is known about plasma concentrations and correlates in African Americans, a population at particular risk of obesity, hypertension, and diabetes, although 3 cohort studies have reported adiponectin concentrations in African American adults [23-25]. The pool of subjects in the Hypertension Genetic Epidemiology Network (HyperGEN) Birmingham, AL, field center consists almost exclusively of African Americans. Unlike previous studies, this highly characterized population provided us with an opportunity to report on plasma concentrations of adiponectin and correlates of these concentrations in African Americans predisposed to hypertension.

2. Methods

2.1. The HyperGEN study

The Hypertension Genetic Epidemiology Network has as its core objective to detect and characterize genes promoting hypertension in humans. Details on methodology and recruitment in HyperGEN have been published elsewhere [26]. Briefly, this collaborative network is composed of the National Heart, Lung, and Blood Institute (NHLBI) and 4 field centers from the population-based NHLBI Family Heart Study—Framingham, Minneapolis, Salt Lake City, and Forsyth County, NC—and a fifth field center in Birmingham, AL, to ensure that African Americans represented more than one half of the sample size. Three categories of subjects were recruited during phase I of HyperGEN between 1996 and 1999: a sample of severe and mild hypertensive sibships (n = 2407); a random sample of age-matched persons from the same base populations, from which normotensive controls could be drawn (n = 918); and unmedicated, normotensive adult offspring of one of the hypertensive siblings (n = 515).

2.2. Subjects

Of the 515 normotensive offspring enrolled in the study, 257 were African American. This included 211 African American subjects enrolled at the Birmingham field center, which was the subsample included in this analysis. In addition to the routine measurements performed in all HyperGEN subjects, plasma adiponectin concentration was measured in subjects in this subsample. The study was conducted in accordance with the guidelines in the Declaration of Helsinki. The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham, and all subjects gave informed consent.

2.3. Clinical examination

Subjects attended a clinical examination at the field center for questionnaire administration, clinical measurements, and collection of blood and urine samples for laboratory measurements.

2.4. Personal history

Personal history data, including basic demographic information (eg, sex, age, race), smoking history, and alcohol use, were collected through an interviewer-administered questionnaire. Current smoking and alcohol use were 0/1 (no/yes) variables that recorded whether a subject currently smoked cigarettes or drank alcohol.

2.5. Clinical measurements

Height was measured on a wall-mounted stadiometer, and weight was measured on a balance-beam scale. Waist circumference was measured with a constant-tension tape measure at the level of the umbilicus. Blood pressure was measured using an automated device (Dinamap model 1846 SX/P; Critikon, Tampa, FL). All measurements were performed by trained and certified personnel according to written protocols.

2.6. Laboratory assays

A 12-hour fasting blood sample and 12-hour overnight timed urine sample were collected from all subjects. Total adiponectin concentration in EDTA plasma was measured with a solid-phase ELISA method (Human Adiponectin/Acrp30 Quantikine ELISA kit, no. DRP300; R&D Systems, Minneapolis, MN). The reliability coefficient for adiponectin measurements based on blind duplicate samples was 0.87. Serum glucose was measured by a thin-film adaptation of a glucose oxidase enzymatic, spectrophotometric procedure using the Vitros 700 Chemistry Analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY). Serum insulin was measured using a chemiluminescent, immunoenzymatic method on an Access analyzer (Beckman Coulter, Brea, CA). Insulin resistance (IR) was estimated with homeostasis model assessment (HOMA) as [fasting serum glucose (mmol/L) × fasting serum insulin (μU/mL)]/22.5 [27]. Creatinine in serum and urine was measured by a thin-film adaptation of the amidohydrolase enzymatic, spectrophotometric method using the Vitros analyzer. Albumin in urine was measured by a thin-film adaptation of a bromcresol green colorimetric procedure using the Vitros analyzer. Serum uric acid was measured by a thin-film adaptation of a uricase enzymatic, spectrophotometric method using the Vitros analyzer. Plasma

total cholesterol was measured using a commercial cholesterol oxidase method on a Roche COBAS FARA centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Plasma HDL cholesterol was measured after precipitation of non–HDL cholesterol with magnesium/dextran [28]. Plasma triglycerides were measured using Triglyceride GB reagent on the Roche COBAS FARA centrifugal analyzer. For samples with triglyceride concentrations of less than 400 mg/dL, plasma low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation [29]. For samples with triglyceride concentrations of 400 mg/dL or higher, LDL cholesterol quantitation was performed by ultracentrifugation [30] using a Beckman TLA 100 table-top ultracentrifuge with a Beckman TLA 100.3 fixed-angle rotor (Beckman).

2.7. Statistical analysis

Statistical analyses included calculation of descriptive statistics (mean, SD, median, and interquartile range). Preliminary analyses indicated that the residuals of the response variable adiponectin were nonnormally distributed. To address this issue, adiponectin was transformed to a logarithmic scale. Subjects were excluded from the analysis if they were taking antidiabetic medication, on insulin treatment, or had not fasted for at least 10 hours before the blood draw. This resulted in 10 subjects being excluded, resulting in a final sample size of 201. One female subject was missing data on systolic blood pressure and 2 male subjects were missing data on urine albumin-creatinine ratio. The sample included offspring from 98 families (1-11 offspring each).

Because of the sibling recruitment in the HyperGEN study, we constructed mixed linear models in Proc Mixed to account for the nonindependence of the observations. First, mixed linear univariate models were constructed regressing log base 10 adiponectin upon potential covariates while accounting for the familial correlation, where family was modeled as a random effect. Because no measures of correlation have been developed for mixed linear models, measures of strength of the univariate associations were not possible to report. However, based on the parameter estimates, the direction and significance of the associations could be stated. Mixed linear models with multiple covariates were then constructed, initially including all predictors achieving a significance level of .15 or less in the univariate analyses. A threshold of 0.15 was chosen to limit the predictors to be examined to a reasonable number, while allowing the examination of the interdependence of predictors. The parsimonious mixed linear model constructed was isolated using backward elimination selection methodology, iteratively removing all nonsignificant terms ($P > .05$) until all remaining terms were significant in the presence of each other. All analyses were performed using SAS statistical software, version 9.0 (SAS Institute, Cary, NC).

3. Results

3.1. Clinical and biological characteristics

On average, women were younger and had higher BMIs than men (Table 1). Women also had lower blood pressure and slightly better lipid profiles than men. Women had higher insulin concentrations and HOMA-IR, and slightly lower glucose concentrations, than their male counterparts. Women had lower concentrations of uric acid and serum creatinine than men, and higher urine albumin-creatinine ratio. Whereas more than a third of men smoked cigarettes (35.6%) and more than half drank alcohol (54.0%), few women either smoked (9.7%) or drank alcohol (14.0%) (data not shown).

Mean (±SD) plasma adiponectin concentration was 5.5 ± 3.8 μg/mL, and the median (interquartile range) concentration was 4.5 (3.0-6.8) μg/mL. Mean adiponectin concentration was 55% higher in women than in men: 6.5 ± 4.4 vs

Table 1
Clinical and biological characteristics of subjects

	Men (n = 87)		Women (n = 114)	
Age (y)	32.1 ± 8.0	31.5 (26-37)	29.1 ± 8.0	28.0 (22-34)
BMI (kg/m^2)	28.9 ± 6.5	27.5 (25.1-33.4)	30.5 ± 7.9	29.3 (24.6-35.1)
Waist circumference (cm)	95 ± 18	92 (83-104)	93 ± 16	93 (81-102)
Systolic blood pressure (mm Hg)	120 ± 12	120 (112-129)	111 ± 13	110 (102-117)
Diastolic blood pressure (mm Hg)	72 ± 10	71 (65-77)	67 ± 10	65 (60-72)
Adiponectin (μg/mL)	4.2 ± 2.5	3.7 (2.3-5.7)	6.5 ± 4.4	5.3 (3.6-7.5)
Total cholesterol (mg/dL)	181.9 ± 39.8	182.6 (158.7-204.6)	171.8 ± 34.0	171.8 (148.6-193.8)
LDL cholesterol (mg/dL)	112.0 ± 39.0	112.7 (83.0-136.7)	103.9 ± 30.9	101.9 (80.7-124.7)
HDL cholesterol (mg/dL)	52.9 ± 15.1	47.9 (42.1-59.1)	54.8 ± 12.0	53.3 (45.9-61.0)
Triglycerides (mg/dL)	87.6 ± 45.1	79.6 (59.3-107.1)	70.8 ± 31.9	66.4 (49.6-84.1)
Glucose (mg/dL)	91.0 ± 9.0	91.0 (85.0-96.9)	87.0 ± 7.9	85.9 (81.1-91.0)
Insulin (μU/mL)	8.4 ± 6.4	6.6 (4.1-10.5)	10.9 ± 7.2	9.4 (6.0-13.5)
HOMA-IR	1.9 ± 1.5	1.5 (0.9-2.5)	2.4 ± 1.8	2.1 (1.2-2.8)
Uric acid (mg/dL)	6.3 ± 1.3	6.3 (5.4-6.9)	4.5 ± 1.1	4.4 (3.6-5.2)
Serum creatinine (mg/dL)	1.1 ± 0.2	1.1 (1.0-1.2)	0.8 ± 0.1	0.8 (0.8-0.9)
Urine albumin-creatinine ratio (μg/mg)	7.2 ± 15.2	2.6 (2.0-4.7)	13.2 ± 30.0	4.0 (2.6-9.4)

Values are expressed as mean ± SD and median (interquartile range).

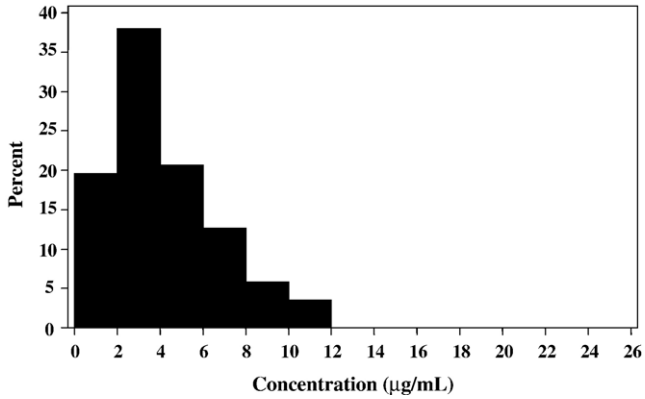

Fig. 1. The frequency distribution of plasma adiponectin concentrations in male subjects.

4.2 ± 2.5 μg/mL, respectively ($P < .0001$). Plasma adiponectin concentrations were positively skewed, especially in female participants (Figs. 1 and 2). Accordingly, the median concentration was 5.3 (3.6-7.5) μg/mL in women and 3.7 (2.3-5.7) μg/mL in men.

3.2. Univariate analysis

In univariate analyses (Table 2), adiponectin was negatively and significantly associated with BMI, current smoking, waist circumference, systolic blood pressure, triglycerides, glucose, insulin, HOMA-IR, uric acid, and serum creatinine. Adiponectin was positively and significantly associated with serum HDL cholesterol concentration. Adiponectin was not significantly associated with age, current alcohol consumption, diastolic blood pressure, total or LDL cholesterol, or urine albumin-creatinine ratio.

3.3. Multivariable analysis

In a multivariable analysis (Table 3), HDL cholesterol concentration was positively associated with plasma adiponectin concentration and statistically significant in the presence of the other variables. Insulin concentration was negatively associated with plasma adiponectin concentration and statistically significant in the presence of the other variables. Males exhibited statistically significant lower plasma adiponectin concentrations when compared to females after adjusting for the effects of the other variables. High-density lipoprotein cholesterol, insulin sensitivity, and sex reduced the observed residual variance of log-transformed adiponectin concentration by 31% while controlling for family structure.

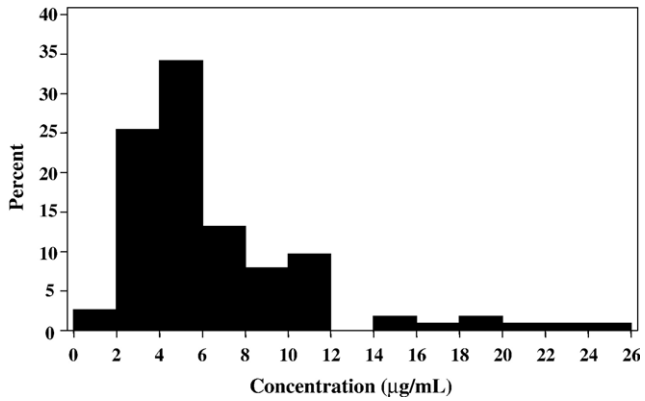

Fig. 2. The frequency distribution of plasma adiponectin concentrations in female subjects.

Table 2
Univariate results from mixed linear models using log base 10 adiponectin as the outcome

	Parameter estimate	SE	*P*
Age (y)	−0.0040	0.0025	.1137
BMI (kg/m^2)	−0.0062	0.0026	.0190
Currently smoke (yes)	−0.1014	0.0451	.0266
Currently drink alcohol (yes)	−0.0296	0.0403	.4649
Waist circumference (cm)	−0.0049	0.0011	<.0001
Systolic blood pressure (mm Hg)	−0.0032	0.0014	.0258
Diastolic blood pressure (mm Hg)	−0.0016	0.0019	.4139
Total cholesterol (mg/dL)	0.0001	0.0005	.8224
LDL cholesterol (mg/dL)	−0.0006	0.0006	.2685
HDL cholesterol (mg/dL)	0.0085	0.0013	<.0001
Triglycerides (mg/dL)	−0.0021	0.0005	<.0001
Glucose (mg/dL)	−0.0099	0.0021	<.0001
Insulin (μU/mL)	−0.0121	0.0027	<.0001
HOMA-IR	−0.0509	0.0109	<.0001
Uric acid (mg/dL)	−0.0610	0.0121	<.0001
Serum creatinine (mg/d/L)	−0.4074	0.0983	<.0001
Urine albumin-creatinine ratio (μg/mL)	0.0006	0.0008	.4366

4. Discussion

In this study, we determined plasma concentrations of adiponectin and the correlates of these concentrations exclusively in African Americans, a group at high risk of obesity, hypertension, and diabetes, which has been included in relatively few previous studies of adiponectin. In particular, this group of African Americans was at particular risk of hypertension because of their relatedness to HyperGEN participants with documented hypertension. The present study revealed several important findings. First, the median adiponectin concentrations for men and women in this study (3.7 and 5.3 μg/mL, respectively; 4.5 μg/mL combined) were less than median concentrations

Table 3
Final mixed linear model of the relationship between adiponectin and other variables after backward removal of nonsignificant variables

	Parameter estimate	SE	*P*
Intercept	0.5207	0.0807	<.0001
Sex (male)	−0.1898	0.0031	<.0001
HDL cholesterol (mg/dL)	0.0064	0.0012	<.0001
Insulin (μU/mL)	−0.0119	0.0024	<.0001

reported in African American men and women in the Coronary Artery Risk Development in Young Adults study (6.0 and 9.0 μg/mL, respectively) [24] and the Health, Aging, and Body Composition study (8.0 μg/mL for men and women combined) [25]. The overall mean concentration of plasma adiponectin in this study (5.5 μg/mL) was less than the adjusted mean adiponectin concentration in African Americans of 7.95 μg/mL reported in the Atherosclerosis Risk in Communities study [23]. The mean concentrations of plasma adiponectin in men and women in this study (4.2 and 6.5 μg/mL, respectively) were somewhat lower than mean concentrations in Japanese individuals in previous studies, which ranged from 7.4 to 7.9 μg/mL and from 9.3 to 11.7 μg/mL in men and women, respectively [7,31]. Mean adiponectin concentrations in these African American individuals were also lower than those reported in previous studies of whites, which ranged from 6.9 to 10.2 μg/mL in men and women combined [4,12], 8.7 to 17.9 μg/mL in men [18,32], and 11.2 μg/mL in women [32]. The median adiponectin concentration for all subjects in this study (4.5 μg/mL) was slightly lower than median adiponectin concentrations in 2 previous studies of Pima Indians (5.3 μg/mL) [6,9]. It should be noted that the lower adiponectin concentrations seen in the present study compared to others could be due to the lower mean BMIs seen in many of the studies compared to ours [7,12,18,23]. However, 2 of these studies had mean BMIs similar to those in the present study [4,32], and 2 others had substantially higher mean BMIs [6,9]. It is also possible that racial/ethnic differences in body fat distribution could partially explain differences in adiponectin levels. Motoshima and colleagues [33] have previously reported that the secretion of adiponectin from visceral fat, but not subcutaneous fat, was negatively correlated with the BMI of the subjects. Finally, it is also possible that differences in analytical methods could account for some of the differences in adiponectin concentrations noted among studies.

Second, the study extended previous findings in other racial/ethnic groups to African Americans, demonstrating higher adiponectin concentrations in women compared to men. This finding has been previously demonstrated in Japanese subjects [7,20], whites [21,32], and in those of unknown race/ethnicity [5,12], although there was no difference in adiponectin concentration in male and female Pima Indians in one study [4].

Third, this study confirmed in African Americans the association between plasma adiponectin and many of the various physical and metabolic parameters that were previously shown in other racial/ethnic groups. Specifically, the positive association between adiponectin and HDL cholesterol seen in African Americans in this study has been widely observed in Japanese subjects [7,15], whites [18,21], and in subjects of unknown race/ethnicity [5,14,34]. The mechanism underlying the close association between plasma adiponectin and HDL cholesterol is presently unknown but may be mediated through adiponectin's effects on insulin sensitivity and resulting insulin concentration [4]. In fact, we demonstrated an independent inverse association between adiponectin and serum insulin concentration in these African American subjects, an association also reported in Japanese subjects [7,17], whites [21], Pima Indians [4,6,9], and in subjects of unknown race/ethnicity [14]. Consistent with our results, plasma adiponectin was inversely correlated with BMI in a multitude of studies in all of the racial/ethnic groups discussed previously [4-9,17,18,22,34]. Finally, the inverse association between adiponectin and waist circumference in this study was also in agreement with previous studies in other racial/ethnic groups, including Pima Indians [4,6] and in subjects of unknown race/ethnicity [5,34].

Strengths of this study were the focus on an understudied racial/ethnic group (African Americans), rigorous data collection protocols of the parent study (HyperGEN), and the statistical methods used in adjusting for the familial correlation. Limitations included the cross-sectional nature of the study, the relatively young and healthy sample population, and the lack of sophisticated measures of insulin sensitivity. We also did not have measures of adiponectin multimers, which may have more clinical relevance than total adiponectin concentrations alone [35]. It also may not be possible to generalize the results of this study (conducted in normotensive offspring of African American participants in the HyperGEN study in the Birmingham, AL, metropolitan area) to other African American populations.

In conclusion, we found that plasma concentrations of adiponectin in these African American participants in the HyperGEN study were somewhat lower than those reported in previous studies of African Americans, as well as in other racial/ethnic groups, including Japanese, whites, and Pima Indians. In agreement with studies in other racial/ethnic groups, plasma adiponectin was higher in women than in men, positively associated with HDL cholesterol, and negatively associated with serum insulin.

Acknowledgment

HyperGEN is funded by cooperative agreements (U10) with the National Heart, Lung, and Blood Institute: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, and HL54515.

References

[1] Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab 2004;89:2563-8.
[2] Holst D, Grimaldi PA. New factors in the regulation of adipose differentiation and metabolism. Curr Opin Lipidol 2002;13:241-5.
[3] Gil-Campos M, Canete RR, Gil A. Adiponectin, the missing link in insulin resistance and obesity. Clin Nutr 2004;23:963-74.
[4] Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.

[5] Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459-69.
[6] Krakoff J, Funahashi T, Stehouwer CD, et al. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. Diabetes Care 2003;26:1745-51.
[7] Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
[8] Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived, anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001;86:3815-9.
[9] Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002;360:57-8.
[10] Matsuzawa Y, Funahashi T, Kihara S, et al. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29-33.
[11] Stefan N, Vozarova B, Funahashi T, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 2002;51:1884-8.
[12] Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8 [erratum in: Lancet 361 (2002) 1060].
[13] Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
[14] Mallamaci F, Zoccali C, Cuzzola F, et al. Adiponectin in essential hypertension. J Nephrol 2002;15:507-11.
[15] Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. J Clin Endocrinol Metab 2002;87:2764-9.
[16] Ouchi N, Kihara S, Funahashi T, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671-4.
[17] Matsubara M, Namioka K, Katayose S. Decreased plasma adiponectin concentrations in women with low-grade C-reactive protein elevation. Eur J Endocrinol 2003;148:657-62.
[18] Pischon T, Girman CJ, Hotamisligil GS, et al. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291: 1730-7.
[19] Kazumi T, Kawaguchi A, Sakai K, et al. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. Diabetes Care 2002;25:971-6.
[20] Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
[21] Zoccali C, Mallamaci F, Tripepi G, et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 2002;13:134-41.
[22] Kern PA, Di Gregorio GB, Lu T, et al. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-α expression. Diabetes 2003;52:1779-85.
[23] Duncan BB, Schmidt MI, Pankow JS, et al. Adiponectin and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study. Diabetes 2004;53:2473-8.
[24] Steffes MW, Gross MD, Schreiner PJ, et al. Serum adiponectin in young adults—interactions with central adiposity, circulating levels of glucose, and insulin resistance: the CARDIA study. Ann Epidemiol 2004;14:492-8.
[25] Kanaya AM, Fyr CW, Vittinghoff E, et al. Serum adiponectin and coronary heart disease risk in older black and white Americans. J Clin Endocrinol Metab 2006;91:5044-50.
[26] Williams RR, Rao DC, Ellison C, et al. NHLBI Family Blood Pressure Program: methodology and recruitment in the HyperGEN Network. Ann Epidemiol 2000;10:389-400.
[27] Phillips DI, Clark PM, Hales CN, et al. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. Diabet Med 1994;11: 286-92.
[28] Warnick GR, Benderson J, Albers JJ. Dextrab sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem 1982;28:1379-88.
[29] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
[30] David JA, Naito NK. Separation of lipoprotein (Lp) fraction by the Beckman TL-100 table-top ultracentrifuge (UC). [abstract]Clin Chem 1986;32:1094.
[31] Ouchi N, Kihara S, Arita Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
[32] Fernandez-Real JM, Castro A, Bazquez G, et al. Adiponectin is associated with vascular function independent of insulin sensitivity. Diabetes Care 2004;27:739-45.
[33] Motoshima H, Wu X, Sinha MK, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clin Endocrinol Metab 2002;87:5662-7.
[34] Tan KC, Xu A, Chow WS, et al. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. J Clin Endocrinol Metab 2004;89:765-9.
[35] Pajvani UB, Hawkins M, Combs TP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem 2004;279: 12152-62.