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Adiponectin levels are associated with coronary artery disease across Caucasian and African-American ethnicity

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The hypothesis was tested that plasma levels of adiponectin would be associated with coronary artery disease (CAD) across African-American and Caucasian ethnicity and gender. Adiponectin levels, cardiovascular risk factors, and extent of CAD were measured in 453 subjects (173 African-American and 280 Caucasian men and women). The distribution of adiponectin levels differed significantly between African-Americans and Caucasians ($P < 0.0001$). Among African-Americans, the adiponectin distribution was skewed toward lower levels. For women, adiponectin levels were higher among Caucasians compared with African-Americans ($P < 0.001$), whereas no interethnic difference was observed for men. Irrespective of ethnic group, subjects with CAD had lower levels of adiponectin than did subjects without CAD. Adiponectin was negatively and significantly associated with waist-hip ratio, body mass index, diastolic blood pressure, insulin level, and homeostasis model assessment—insulin resistance in both ethnic groups. Among lipid parameters, total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels were negatively correlated with adiponectin, whereas the high-density lipoprotein cholesterol level correlated positively for both African-Americans and Caucasians. In a multiple regression model, controlling for gender, ethnicity, and other CAD risk factors, adiponectin levels were negatively associated with CAD ($P < 0.05$). The results indicate that, across gender and ethnicity, low adiponectin levels may be an independent risk factor for CAD. (Translational Research 2007;149:317–323)

Abbreviations: CAD = coronary artery disease; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment—insulin resistance; LDL = low-density lipoprotein; OR = odds ratio; SD = standard deviation

Adiponectin, an adipokine initially described about 10 years ago, has prominent effects on both lipid and carbohydrate metabolism, including increased lipid oxidation, decreased hepatic glucose production, enhanced insulin action, and glucose lowering.[1–3] These actions may be mediated through activation of adenosine monophosphate-dependent protein kinase, resulting in improved fat oxidation

in liver and skeletal muscle, leading to a reduced potential for ectopic fat accumulation.[4] Plasma levels of adiponectin are affected by age and lifestyle factors, and in addition, there is a sexual dimorphism, where women have higher levels than men.[5,6] Decreased adiponectin levels are associated with the metabolic syndrome and conditions of insulin resistance.[7,8] Furthermore, it has been suggested that adiponectin may interact with genetic and environmental factors in the development of insulin resistance, the metabolic syndrome, and type 2 diabetes mellitus.[9–12] In addition to its putative role in energy metabolism, adiponectin has been suggested to affect the atherosclerotic process as it accumulates in injured vessel walls and influences many components of the vessel wall.[13–15]

Results from clinical studies support the contention that adiponectin may have antiatherogenic properties, and that low adiponectin levels constitute a cardiovascular risk factor. Hypoadiponectinemia has been observed in patients with coronary artery disease (CAD) as well as in patients at increased risk for cardiovascular disease with obesity and diabetes mellitus.[12,16–18] However, an increase in adiponectin levels was associated with overall mortality in Caucasian patients undergoing coronary angiography in a recent study.[19] Adiponectin levels are regulated dynamically, as either substantial weight reduction or administration of insulin sensitizers to patients with diabetes mellitus increase circulating adiponectin levels.[20,21] As several factors potentially influencing adiponectin levels, such as high-density lipoprotein (HDL) cholesterol, triglycerides, obesity, and hypertension differ markedly between African-Americans and Caucasians,[22,23] the hypothesis was tested that adiponectin levels would be associated with CAD as determined by coronary angiography in Caucasian and African-American men and women. In addition, the role of adiponectin was explored in relation to other cardiovascular risk factors across gender and ethnicity.

RESEARCH DESIGN AND METHODS

Subjects. Subjects were recruited from a patient population scheduled for diagnostic coronary arteriography at either Harlem Hospital Center in New York City or the Mary Imogene Bassett Hospital in Cooperstown, NY.[24,25] All consecutive patients scheduled for elective coronary arteriography at the 2 sites between June 1993 and April 1997 were approached. A total of 648 patients, 401 men and 247 women, ethnically self-identified as Caucasians (n = 344), African-Americans (n = 232), or other (n = 72) were enrolled. The recruitment procedure, including inclusion and exclusion criteria, have been described earlier.[26,27] In this study, plasma samples were available from 453 of the 576 Caucasians

and African-Americans enrolled in the study (177 Caucasian men, 103 Caucasian women, 100 African-American men, and 73 African-American women). The study was approved by the Institutional Review Boards at Harlem Hospital, Bassett Healthcare, Columbia University College of Physicians and Surgeons, and University of California—Davis, and informed consent was obtained from all participants.

Clinical and biochemical assessment. Fasting blood samples were drawn approximately 2 to 4 h before the catheterization procedure, and plasma samples were stored at −80°C before analysis. Plasma adiponectin levels were measured using a radioimmunoassay (Linco Research Inc., St. Louis, Mo) with intra-assay and interassay coefficients of variation of 5.5% and 9.3%, respectively. Plasma total cholesterol, triglyceride, and HDL cholesterol were determined by standard enzymatic procedures.[28] The low-density lipoprotein (LDL) cholesterol levels were calculated in subjects with triglyceride levels <400 mg/dL with the formula of Friedewald et al.[29] Plasma insulin was measured using a commercial radioimmunoassay procedure (Diagnostic Products, Los Angeles, Calif). Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated using the updated model available from the Oxford Centre for Endocrinology and Diabetes (Oxford, UK).[30,31] BMI was calculated as weight divided by the square of height.

Coronary angiography The coronary angiograms were read by 2 experienced readers blinded to patient identity, the clinical diagnosis, and the lipoprotein results. The readers recorded the location and extent of luminal narrowing for 15 segments of the major coronary arteries.[32] In the current study, patients were classified as having CAD if a stenosis of >50% was found in at least 1 segment. Patients without CAD were defined as having <50% stenosis in all segments.

Statistical analysis. Data are described as mean ± standard deviation (SD) or as the median and interquartile range as appropriate. As the plasma adiponectin frequency distribution was skewed in both Caucasians and African-Americans, we explored transformation of adiponectin levels using either logarithm or square root. Square root transformation resulted in the most normal distribution and was therefore used in subsequent analysis. Levels of triglycerides, insulin, and HOMA-IR were log transformed to achieve normal distributions before statistical analysis. Group means were compared using the Student *t*-test. Differences in the distribution of adiponectin levels between CAD and non-CAD subjects for each ethnic group were analyzed using the nonparametric Kolmogorov–Smirnov test. Univariate relationships between adiponectin levels and anthropometric variables were described by the Pearson corre-

Table I. Clinical characteristics of subjects with and without CAD

	CAD (n = 235)	Non-CAD (n = 218)	P value
Men/women	166/69	111/107	
African-American/ Caucasian	76/159	97/121	
Age (years)	59.3 ± 8.5	51.4 ± 10.4	<0.001
BMI (kg/m²)	29.2 ± 5.5	29.3 ± 6.3	NS
Waist–hip ratio	0.96 ± 0.07	0.94 ± 0.07	0.003
Glucose (mmol/L)	7.4 ± 3.7	6.7 ± 3.5	0.030
Insulin (μU/mL)	15.7 (9.5–28.2)	13.7 (8.9–22.2)	0.035
HOMA-IR	4.3 (2.6–10.7)	3.4 (2.1–6.5)	0.010
Cholesterol (mg/dL)	203 ± 43	189 ± 39	<0.001
Triglyceride (mg/dL)	144 (106–216)	115 (86–162)	<0.001
LDL cholesterol (mg/dL)	129 ± 37	117 ± 33	<0.001
HDL cholesterol (mg/dL)	41 ± 14	46 ± 14	<0.001

Notes: Results expressed as means ± SD, or for non-normally distributed variables as median (interquartile range). SI units given with brackets where appropriate.
Abbreviation: NS, not significant.

lation coefficients. Multiple logistic regression analysis was used to assess the association with case-control status of the various known and potential risk factors. Although initially several potential variables were explored in this analysis, including established cardiovascular risk factors significantly associated with CAD in previous studies, the final model included only variables that were significantly associated with CAD in the current dataset.

RESULTS

Characteristics of the subjects are shown in Table I. The CAD group was older and had lower HDL cholesterol and higher triglyceride, total cholesterol, LDL cholesterol, insulin, and glucose levels as compared with the non-CAD group. In addition, the waist–hip ratio and insulin resistance as estimated by HOMA-IR were higher in the CAD group.

The distribution of adiponectin levels differed between Caucasians and African-Americans (Fig 1). Among African-Americans, the adiponectin distribution was skewed toward lower levels. The maximum difference in the cumulative adiponectin frequency between the 2 ethnic groups was 0.22 at an adiponectin level of 4.04, with a Kolmogorov–Smirnov statistic of 2.291, $P < 0.0001$, confirming a significant difference in the interethnic adiponectin frequency distribution. As observed in Fig 2, of the 4 gender/ethnicity groups, Caucasian women had significantly higher median adiponectin levels compared with the 3 other groups ($P < 0.001$).

Adiponectin levels were associated with cardiovascular risk parameters across ethnicity. Adiponectin was negatively associated with waist–hip ratio ($P = 0.016$), BMI ($P < 0.0001$), diastolic blood pressure ($P = 0.037$), insulin level ($P < 0.001$), and HOMA-IR ($P <0.001$). Among lipid parameters, total cholesterol ($P = 0.026$), triglyceride ($P < 0.001$), and LDL cholesterol levels ($P = 0.007$) were negatively correlated with adiponectin, whereas the HDL cholesterol level ($P < 0.001$) correlated positively. No significant correlations were observed between adiponectin and age, systolic blood pressure, or glucose.

Next the cumulative distribution of adiponectin levels was analyzed in subjects with and without CAD in the 2 ethnic groups. As observed in Fig 3, subjects with CAD had lower levels than subjects without CAD, irrespective of ethnicity. For both ethnic groups, differences between CAD and non-CAD subjects were observed over the entire span of adiponectin level. Furthermore, differences between the CAD and the non-CAD subjects were similar for African-Americans and Caucasians. Thus, the maximum difference of the cumulative adiponectin distribution between CAD and non-CAD subjects in African-Americans and Caucasians were 0.22 and 0.20, respectively.

To assess the independent association of adiponectin levels with CAD, a multiple logistic regression was initially performed controlling for gender and ethnicity, where adiponectin levels remained independently and inversely associated with CAD [odds ratio (OR) = 0.68, $P = 0.001$]. Then a more comprehensive analysis was performed adjusting for age, hypertension, smoking, LDL cholesterol, ethnicity, BMI, diabetes mellitus, and HOMA-IR. As observed in Table II, adiponectin levels remained significantly and independently inversely associated with CAD (OR = 0.58, $P = 0.003$) in the latter model. Other positive predictors for CAD were age (OR = 1.10, $P < 0.001$), gender (OR = 2.10, $P = 0.017$), hypertension (OR = 2.06, $P = 0.029$), LDL cholesterol (OR = 1.01, $P = 0.011$), ethnicity (OR = 2.85, $P = 0.001$), and diabetes mellitus (OR = 3.07, $P = 0.001$).

DISCUSSION

The relationship of adiponectin and CAD was examined in a biracial Caucasian and African-American group, where many predictors of adiponectin levels differ across ethnicity. The adiponectin level distribution differed significantly between Caucasians and African-Americans. Caucasian women had significantly higher adiponectin levels than the other 3 gender/ethnicity groups. Furthermore, adjusting for gender, ethnicity, and other CAD risk factors, lower circulating
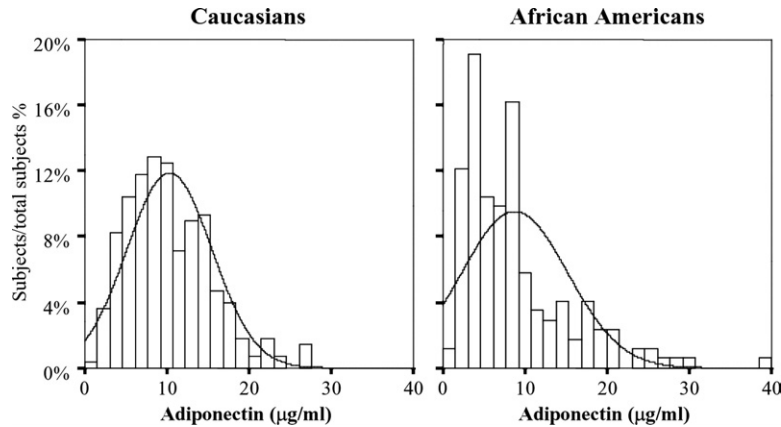
Fig 1. Frequency distribution of adiponectin levels in Caucasians and African-Americans. Untransformed adiponectin levels were reported.
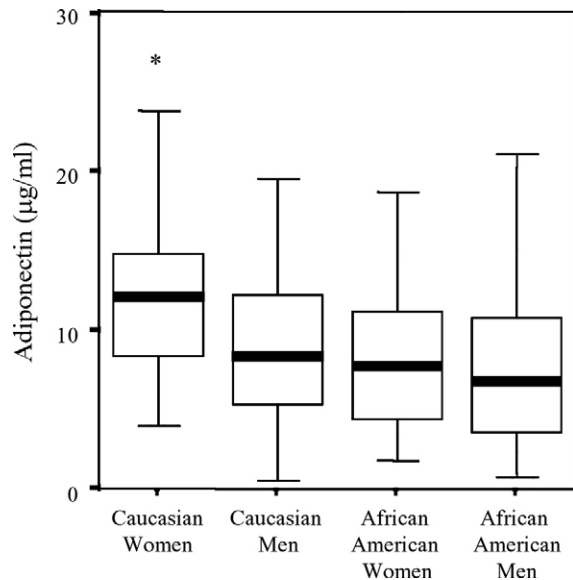

Fig 2. Adiponectin levels in 4 gender/ethnicity groups (African-American men and women and Caucasian men and women). Levels are reported as medians and interquartile range. *$P < 0.001$; Caucasian women had different adiponectin levels compared with the other 3 groups.

levels of adiponectin were independently associated with CAD.

Compared with Caucasians, African-Americans had a skewed adiponectin distribution toward lower levels, and the largest difference in the cumulative frequency was at adiponectin levels of about 4 μg/mL. Among the 4 gender/ethnicity groups (African-American men and women, and Caucasian men and women), adiponectin levels were higher among Caucasian women in keeping with previous reports of higher plasma adiponectin levels in female subjects.[33] However, African-American women had levels similar to men. Previous studies

have demonstrated an effect of both obesity and ethnicity on adiponectin levels in women, as levels were significantly higher in Caucasian non-obese women compared with either non-obese African-American women or obese Caucasian or African-American women.[34] These findings of lower adiponectin levels among African-American women compared with Caucasian women are in agreement with these results. Furthermore, a lack of difference is reported here across gender among African-Americans. However, it is possible that a difference in body fat distribution across ethnicity might be contributory. Arguing against this possibility, there was no significant difference in BMI levels or waist–hip ratio between the 2 ethnicity/gender groups, although differences in central/visceral obesity cannot totally be ruled out. Furthermore, other studies have also reported differences in adiponectin levels among various ethnic groups. Thus, pregnant women of South Asian descent exhibited significantly reduced plasma adiponectin concentrations compared with pregnant Caucasian women.[35] Furthermore, plasma adiponectin levels were lower in Pima Indians as compared with Caucasians.[36]

The association between adiponectin and CAD was independent of gender, BMI, and ethnicity, and of established cardiovascular risk factors such as smoking, hypertension, and LDL cholesterol. The demonstration that the association of adiponectin with CAD was independent of established risk factors suggests the possibility of differences in mechanisms underlying the impact of adiponectin compared with those other risk factors. In support of this, recent studies reported that adiponectin has anti-atherogenic properties, as adiponectin modulates the inflammatory response of endothelial cells,[13] suppresses foam cell formation,[37] and suppresses the proliferation and migration of smooth muscle cells.[38] Adiponectin has also been reported to
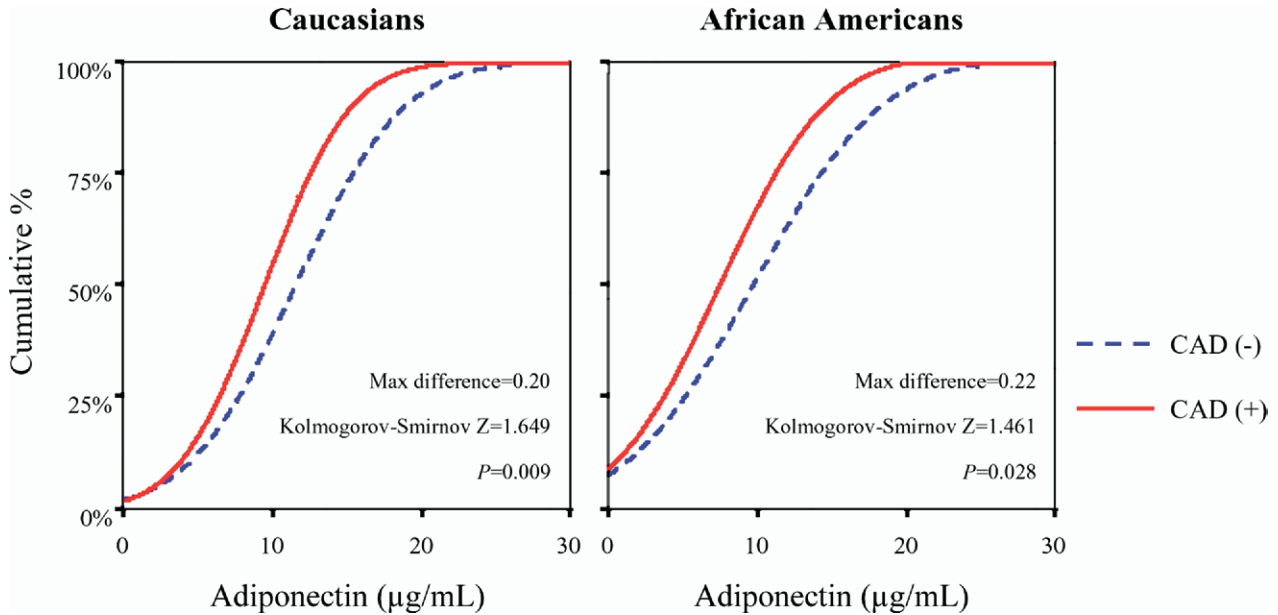
Fig 3. Cumulative distribution of adiponectin levels in Caucasians and African-Americans with and without coronary artery disease.

Table II. Multiple logistic regression analysis with CAD

Variables	OR	95% CI	P value
Adiponectin (μg/mL)	0.58	0.41–0.84	0.003
Age	1.10	1.06–1.14	<0.001
Gender	2.10	1.08–3.94	0.017
Hypertension	2.06	1.00–3.53	0.029
Smoking	1.87	0.94–1.04	NS
LDL-C (per 40 mg/dL)	1.01	1.58–5.96	0.011
Race/ethnicity	2.85	1.14–3.85	0.001
BMI	0.99	1.00–1.02	NS
Diabetes mellitus	3.07	1.52–5.34	0.001
HOMA-IR	0.99	0.98–1.01	NS

Note: Results are reported for beta coefficient.
Abbreviation: NS, not significant.

be associated with insulin resistance, and high adiponectin levels protect against the impairment of glucose metabolism in obese subjects and reduces the risk of developing type 2 diabetes mellitus.[8,39]

In this study, associations between adiponectin and established cardiovascular risk factor and degree of coronary artery disease in 2 ethnic groups with pronounced differences in risk factor spectrum were explored. Notably, the relative distribution pattern of adiponectin in CAD and non-CAD subjects was similar for African-Americans and Caucasians. Thus, the differences in the cumulative adiponectin distribution between CAD and non-CAD subjects were 0.22 for African-Americans and 0.20 for Caucasians. This might

suggest that the impact of adiponectin in relation to CAD might be similar in the 2 groups.

Despite a negative association found between adiponectin levels and CAD reported in this as well as several other studies, an association between increased adiponectin levels and mortality among subjects undergoing coronary angiography was recently reported.[19] It is noteworthy also that, in the latter study, adiponectin levels were negatively associated with signs of cardiovascular disease, ie, luminal narrowing,[19] which is in agreement with the current findings. This raises the possibility that adiponectin, despite its association with anti-atherogenicity, may be a marker of additional cardiovascular risk factors. These intriguing results indicate the need for a more comprehensive understanding of the role of adiponectin as a disease modulator.

Potential limitations of the current study need to be discussed. Subjects in this study were recruited from patients scheduled for elective coronary angiography, and therefore, they may not be representative of the population at large. However, none of the patients had acute coronary symptoms, and clinical and laboratory parameters were in agreement with differences generally observed between African-American and Caucasian populations from other studies. Thus, in previous studies, differences found in population-based studies have been verified between Caucasians and African-Americans in lipid and lipoprotein levels as well as in genotype frequencies.[24,40–42] Furthermore, this study was limited to measurement of plasma adiponectin

levels, and it did not assess whether high molecular forms of this protein would be associated with cardiovascular disease.

In conclusion, these results indicate that plasma adiponectin levels differed among Caucasians and African-Americans, and that levels were higher in Caucasian women compared with the other 3 gender/ethnicity groups. The finding of an inverse association between adiponectin and CAD in both ethnic groups studied suggests that low adiponectin levels may be a risk factor for cardiovascular disease in both Caucasians and African-Americans. In view of the apparent contradictory findings regarding a potential role of adiponectin as a risk factor for cardiovascular disease or overall mortality, more prospective studies across ethnic groups are needed.

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