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Associations of BMI and insulin resistance with leptin, adiponectin, and the leptin to adiponectin ratio across ethnic groups: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Purpose—Associations of adiponectin and leptin and their ratio with BMI and HOMA-IR have been investigated in different ethnic groups but variability in both assays and statistical methods have made cross-study comparisons difficult. We examined associations among these variables across four ethnic groups in a single study.

Methods—Adiponectin and leptin were measured in a subset of MESA participants. We calculated associations (using both partial correlations and adjusted linear regression) in each ethnic group and then compared the magnitude of these associations across groups.

Results—After excluding individuals with type 2 diabetes there were 714 White, 219 Chinese, 332 African American, and 405 Hispanic individuals, in the study sample. Associations of BMI with adiponectin and leptin differed significantly ($P < 0.05$) across the ethnic groups in regression analyses, while associations of HOMA-IR with adiponectin and leptin did not differ across ethnic groups. The leptin to adiponectin ratio was not associated with a greater amount of adiposity or HOMA-IR variance than leptin or adiponectin in any ethnic group.

Conclusions—Given the consistency of HOMA-IR and adipokine associations, the differing means of adiponectin and leptin across ethnic groups may help to explain ethnic differences in mean insulin resistance.

Adiponectin and Leptin are cytokines produced by adipose tissue. It has been demonstrated that adiposity, as measured through body mass index (BMI), is associated cross-sectionally with circulating levels of these cytokines; leptin has a positive association with adiposity while the relationship between adiponectin and adiposity is negative (1). It is also known

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that higher leptin and lower adiponectin levels are cross-sectionally associated with higher insulin resistance (2, 3). However, the mechanisms behind these associations are incompletely understood, particularly the mechanism of association for the two cytokines with insulin resistance. It has been hypothesized, based on results from animal studies(4, 5), that increased fat mass leads to altered levels of adipokines, which contributes to insulin resistance(6).

Adiponectin and leptin levels vary by ethnicity; African-Americans or Asians are often reported to have having lower mean levels of adiponectin than Whites (7–10) and African Americans are reported to have higher mean levels of leptin (10, 11). Many studies have examined associations of adiponectin and leptin with BMI and insulin resistance in different ethnic groups. However, it is difficult to compare measures of association across studies, given the variability in the adiponectin and leptin assays and statistical analysis methods across studies. Cross-ethnic comparisons of these associations may help explain if adipokines contribute to the observed differences in mean insulin resistance between ethnic groups (12). A better understanding of these inter-ethnic differences should help inform future research into the pathophysiology of insulin resistance in all ethnic groups.

In addition to interest in leptin and adiponectin, there has been recent interest in the leptin to adiponectin ratio (LAR) as a novel predictor of cardiometabolic and other chronic disease outcomes. The ratio was associated with carotid intima media thickness (13), “at risk phenotype” in young severely obese patients (14), metabolic syndrome (15), and endometrial cancer (16), among others. Notably, several studies have examined the association of the ratio with insulin resistance (17, 18), but none across multiple ethnic groups.

The Multi-Ethnic Study of Atherosclerosis (MESA) includes cross-sectional measurements of adiponectin, leptin, and insulin resistance, as well as adiposity, on a subset of the cohort which included African, Chinese, Hispanic Americans and non-Hispanic Whites. These uniform measurements across four ethnic populations in a single study provide the unique opportunity to rigorously compare the strengths of association of BMI and homeostasis model assessment of insulin resistance (HOMA-IR) with adiponectin and leptin, as well as with the LAR across ethnic groups. We hypothesize that the strength of associations between BMI and leptin and adiponectin will differ significantly across ethnic groups. We also hypothesize that associations with LAR will not differ significantly from associations with Leptin within ethnic groups.

MATERIALS AND METHODS

Subjects

MESA is a longitudinal cohort study which includes four ethnic groups: African, Chinese and Hispanic Americans, as well as non-Hispanic Whites. Details about the study design for the MESA have been published previously (19). In brief, between 2000 and 2002, 6,814 men and women who were 45 to 84 years old and were free of clinically apparent cardiovascular disease (CVD) were recruited from six United States communities. Enrolled participants returned for follow-up clinic visits approximately 2, 4 and 6 years after the baseline clinic visit. The MESA study was approved by the Institutional Review Boards of all participating field sites and reading centers, and participants gave informed consent for participation.

At clinic visits 2 and 3, a random subsample of 1,970 participants (approximately ½ of these participants were at visit 2 and the remaining ½ at visit 3 with no participant enrolled at both visits) enrolled in an ancillary study examining aortic calcium, body composition, and

inflammation through blood draws and CT scans.(20) Measurements from this sub-study (adiponectin, leptin, and insulin) and additional measurements obtained in the regular MESA visits were used in this analysis. All data in this analysis is cross-sectional; individuals who participated in the sub-study at MESA visit 2 had additional visit 2 MESA variables used for analysis, individuals who participated in the sub-study at MESA visit 3 had additional visit 3 MESA variables used for analysis. Participants of this sub-study were excluded from this analysis if they had missing or outlying values for adiponectin, leptin, or HOMA-IR (n= 15), prevalent diabetes (n= 283, as HOMA-IR may not be an accurate representation of insulin resistance in this group), or if they reported fasting less than 8 hours (n = 2). After these exclusions there were 1670 participants available for analysis (714 White, 219 Chinese, 332 African American, and 405 Hispanic).

Data collection

At all MESA clinic visits, standardized questionnaires were used to obtain socio-demographic, ethnicity and health history information. Cigarette smoking was defined as current, former, or never and participants were asked “do you presently drink alcoholic beverages?” with those answering yes coded as current drinkers. Maximum education level was self-reported Physical activity was measured with a 28 item survey. Height and weight were measured with participants wearing light clothing and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Umbilicus-level waist circumference was measured using a standard tape measure with 4 oz tension. Blood was collected and stored at each clinic visit.

Laboratory

At all clinic visits, glucose levels were measured from blood samples obtained after a suggested 12-hour fast. Prevalent diabetes was defined as fasting glucose ≥ 7.0 mmol/L (126 mg/dl) and/or use of anti-diabetes medications, a definition based on the 2003 American Diabetes Association criteria (21).

Adiponectin, leptin, and insulin were measured using stored fasting blood samples from visits 2 and 3. Insulin was determined by radioimmunoassay using the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO). The analytical coefficient of variation (CV) was 4.9%. HOMA-IR was calculated using the formula fasting insulin (mU/L) * fasting glucose (mmol)/22.5. Adiponectin and leptin were measured using Bio-Rad Lumines flow cytometry (Millepore, Billerica, MA). Analytical CVs across several control samples for these analytes ranged from 6.5–13.0%. LAR was calculated by dividing leptin (in ng/ml) level by adiponectin level (in μ g/ml).

Statistical analysis

All statistical analyses were performed in SAS v. 9.2 (Cary, NC). For all analyses, leptin, adiponectin, and HOMA-IR were ln-transformed. LAR was ln-transformed after the ratio was calculated from untransformed variables. Adjusted means by ethnic group were calculated and compared using the lsmeans statement in Proc GLM and a P of < 0.05 was considered significant. Correlations and regression analyses were carried out stratified by self-identified ethnicity. Adjusted correlations were calculated using the “partial” statement in Proc Corr. As these correlations are not independent, the strength of “correlated correlations” within ethnic groups was compared using the Meng test (22). The strength of correlations across ethnic groups was compared using the Fisher r to z transformation. The size of adjusted regression coefficients across ethnic groups was compared by including all four ethnic groups in a single regression model with an ethnicity*variable interaction term. In addition to the global p -value for this term, the significance of the interaction term for each of the ethnicities (alternating the ethnicity chosen as the referent) was used to determine if the

strength of association differed across ethnic groups. Terms with a $P < 0.05$ were considered significant.

RESULTS

Table 1 shows the characteristics of the study population, by self-identified ethnicity. Unadjusted means or percentages of all variables in the table (except sex) differed across the four ethnic groups. Supplemental Table 1 lists geometric means of adiponectin, leptin, and LAR by ethnic group after adjustment for age, sex, education, alcohol intake, smoking status, physical activity and study site. Adjusted geometric means of adiponectin differed significantly ($p < .05$) between every possible pair of ethnic groups except between Chinese and African American. Adjusted geometric means of leptin differed significantly between every possible pair of ethnic groups. The adjusted mean levels of adiponectin, leptin, and LAR were all lowest in the Chinese while adiponectin was highest in Whites and leptin and LAR were highest in African Americans. Supplemental Table 2 lists geometric mean levels of adiponectin, leptin, and LAR by ethnic group after additional adjustment for BMI. This additional adjustment for BMI increased the mean levels of leptin and LAR in Chinese while lowering mean levels in African Americans and Hispanics, but did not eliminate significant differences in the means among ethnic groups.

Table 2 shows the association of BMI with adiponectin, leptin, and LAR by ethnicity using regression coefficients. The global p-values for ethnicity *BMI regression coefficients were less than 0.05 for adiponectin, leptin, and LAR, indicating that, in regression analyses, the strength of associations between these variables and BMI differed significantly across ethnic groups. For leptin, adiponectin, and LAR, the regression coefficient per unit of BMI was significantly larger in Chinese than in the other ethnic groups. For leptin and LAR, the regression coefficient per unit of BMI was also significantly larger in Whites compared to African Americans or Hispanics. Supplementary Table 3 shows the association of BMI with adiponectin, leptin, and LAR by ethnicity using correlation coefficients. In correlation analyses, the association between adiponectin and BMI was significantly larger in Chinese than in Hispanics or African Americans, while correlations of leptin and LAR with BMI were similar across ethnic groups. Within all four ethnic groups, adjusted correlations of leptin and LAR with BMI were similar, while correlations of adiponectin with BMI were significantly smaller (by the Meng test). When analyses were repeated using waist instead of BMI, the results were similar (data not shown). Also, when BMI was modeled in quartiles to test the linearity of the association, results were similar and supported a linear association (data not shown).

Table 3 shows the association of HOMA-IR with adiponectin, leptin, and LAR across ethnic groups using regression coefficients. Regression coefficients (difference in HOMA-IR per one unit difference in adiponectin, leptin, and LAR) did not differ significantly across ethnic groups. Supplementary Table 4 shows the association of HOMA-IR with adiponectin, leptin, and LAR across ethnic groups using correlations. In these analyses, associations of adiponectin, leptin, and LAR with HOMA-IR were also similar. In each ethnic group, adjusted correlations of leptin and LAR with HOMA-IR were similar while correlations of adiponectin with HOMA-IR were significantly smaller (by the Meng test). When leptin, adiponectin, and LAR were modeled in quartiles to test the linearity of the associations, results were similar and supported a linear association (data not shown).

Supplementary Table 5 lists the means of HOMA-IR by ethnic group before and after adjustment for various covariates. After all adjustments, Chinese and Hispanics had the highest mean HOMA-IR. Before adjustment for BMI, leptin, and adiponectin, the means of HOMA-IR were significantly different for all pairwise comparisons of ethnic groups except

White and Chinese. After adjustment for BMI, leptin, and adiponectin, the means of HOMA-IR were similar in all ethnic groups except African Americans who had lower levels.

DISCUSSION

In this paper we sought to better understand the relationships of leptin, adiponectin, and LAR with BMI and insulin resistance by comparing these associations across ethnicities in a single cohort with large samples of four ethnic groups. The analysis demonstrated that A) the association of BMI with adiponectin and leptin differed between ethnic groups, and adjustment for BMI and other known covariates did not eliminate differences in mean leptin or adiponectin levels between ethnic groups and B) the association of HOMA-IR with leptin and adiponectin did not vary significantly between ethnic groups and means of insulin resistance are similar in Whites, Chinese, and Hispanics after adjustment for BMI, leptin and adiponectin. Therefore, these results suggest the differing means of adiponectin and leptin among ethnic groups may explain, in part, ethnic differences in insulin resistance. We also noted that LAR was not associated with a greater amount of adiposity or HOMA-IR variance than leptin or adiponectin. Instead, the association of LAR with BMI and HOMA-IR closely resembled the observed association with leptin (the component of the ratio with the stronger observed associations in the MESA cohort).

Several other papers have demonstrated that the means of adiponectin and leptin differ across two or more ethnic groups, although the reports have adjusted means of the adipokines for different combinations of known covariates (7, 9, 23, 24). In contrast, few papers have formally compared the strength of the *associations* between adiposity and adipokines in a single study and none have done it in a study including Whites, Chinese, African Americans and Hispanics. In a Singaporean multiethnic population study, the unit decrease in adiponectin per unit increase in BMI was significantly greater in Chinese than in Malay or Asian-Indians (25). In another study the association of visceral fat and adiponectin was significantly stronger in African Americans as compared to Hispanics (26). In our data, the association between adiponectin and BMI differed across ethnic groups in both regression and correlation analyses. One proposed hypothesis for the notably stronger association between adiponectin and BMI observed in the Chinese subgroup is related to the higher correlation of lean muscle mass to BMI seen in Chinese compared to other ethnic groups (M. Allison, personal communication).

Of note, the unit change in leptin per unit change in BMI (as measured through linear regression) differed significantly across ethnic groups, while the correlations of leptin and BMI were similar across groups. This result demonstrates the importance of using consistent analytic techniques when attempting to compare significant effect modification of associations by ethnic groups across studies. We chose to report both correlation coefficients in addition to regression analyses to highlight these potential differences.

Few papers have also formally compared the strength of associations between adipokines and insulin resistance in a single study and none have done it comparing these four specific ethnic groups. In contrast to our results, a study including European, Chinese, South Asian, and Aboriginal individuals in Canada found a significant difference in the strength of association between adiponectin (but not leptin) and insulin resistance between ethnic groups (27). The difference in these results may be attributable to the different ethnic groups examined.

Recently, several papers have been published suggesting that LAR is an important and novel predictor of insulin resistance and type 2 diabetes. However, many of these papers did not

formally compare associations between a given trait and LAR to associations with leptin and adiponectin, presenting only associations with LAR (17, 28), or only comparing associations to one of the component measures (i.e. adiponectin) and not employing a formal test to compare correlated associations (18). Similar to our findings, studies that have more formally compared the association of LAR to leptin and adiponectin using receiver operating characteristic curves or formal comparisons of the percent variance explained have also concluded that LAR is not statistically significantly more strongly associated with insulin resistance or related traits like metabolic syndrome than its component parts (15, 29). Associations with LAR will usually be similar to whichever component of the ratio (adiponectin or leptin) explains a greater percentage of variance for a trait. We do not mean to suggest that there is no value in including both adiponectin and leptin as variables in models, but rather, it is preferable to include the traits individually, rather than creating a ratio that does not add value. Indeed, an analysis in the MONICA/KORA study comparing the area under the curve (AUC) for different combinations of leptin, adiponectin, and LAR in predicting incident type 2 diabetes, found the largest AUC for the model which included leptin, adiponectin, and a term for interaction between them simultaneously in a regression model (30).

Given the consistent association between adiponectin or leptin and insulin resistance across the ethnic groups in this study, we speculated that some of the ethnic differences in insulin resistance may be due to differing means of leptin and adiponectin across these ethnic groups. This speculation is supported by the fact that means of HOMA-IR are similar in Whites, Chinese, and Hispanics after adjustment for BMI, leptin, and adiponectin, although no conclusions can be drawn due to the cross-sectional nature of our analysis. Clearly variables other than adiponectin and leptin are also important in the ethnic differences in HOMA-IR, given that the mean of HOMA-IR in African Americans still differed significantly from the three other ethnic groups after adjustment for adiponectin and leptin. The relatively consistent association of adiponectin and HOMA-IR across the ethnic groups also offers hope that pharmacologic agents aimed at increasing adiponectin may offer promise in treating insulin resistance—perhaps particularly in the Chinese population where mean adiponectin is particularly low and the mean insulin resistance high, after adjustment for BMI.

The strengths of this study include the large multi-ethnic sample. The large sample size in each ethnic group and the uniform measurement of adipokines across the ethnic groups allowed for the well-powered formal comparison of the strength of associations across ethnic groups. An additional strength was the use of formal statistical tests to compare the strengths of both regression and correlation analyses across ethnic groups. Weaknesses include the cross-sectional study design and our use of HOMA-IR to measure insulin sensitivity and BMI and waist to measure adiposity rather than gold-standard measures of these traits. We also tested multiple comparisons across ethnic groups using a p-value of .05 and thus some associations deemed significantly different across groups may have occurred by chance. Finally, we were limited by single measurements of leptin, adiponectin, and insulin so we cannot account for intra-individual variation. However, assay variability would be expected to bias findings towards the null so the observed associations are potentially underestimations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of the Study Population

	White (n=714)	Chinese (n=219)	African American (n=332)	Hispanic (n=405)
Age (years)	65.2 (9.8)	64.5 (9.9)	64.4(9.8)	63.2 (9.7)
BMI (mg/kg/m ²)	27.5(4.7)	24.0 (3.2)	29.3(5.3)	29.1(4.7)
Waist (cm)	98.0 (13.5)	86.8 (9.1)	99.1 (14.6)	100.3 (12.5)
Adiponectin * (μg/ml)	24.3 (14.4–30.7)	14.0 (9.8–22.0)	15.2 (10.5–22.8)	17.0 (12.4–24.2)
Leptin * (ng/ml)	17.2 (5.2–22.6)	7.2 (2.8–14.3)	22.0 (8.9–43.8)	16.2 (6.4–28.4)
LAR *	0.51 (0.21–1.23)	0.47 (0.18–1.15)	1.42 (0.54–2.90)	0.89 (0.39–1.79)
HOMA-IR *	1.17 (0.77–1.66)	1.07- (0.78–1.57)	1.26 (0.82–1.87)	1.42 (1.00–2.27)
Weekly moderate and vigorous physical activity (Met-min/wk)	5080 (4308)	3633 (4176)	5389 (5424)	5585 (5220)
% male	51.8	51.1	43.4	48.4
% indicating Current Alcohol consumption	70.3	33.8	47.7	43.7
<i>Cigarette smoking</i>				
% never	40.3	72.6	40.6	48.0
% former	47.5	23.7	43.9	40.8
% current	12.2	3.7	15.5	11.2
<i>Education</i>				
% high school diploma or less	19.8	37.6	26.2	61.2
% some college or college diploma	52.8	43.2	55.1	32.1
% graduate School	27.4	19.2	18.7	6.7
<i>Recruitment site</i>				
% Winston-Salem, NC	29.8	0.0	42.5	0.0
% New York NY	9.9	0.9	28.6	42.2
%Minneapolis, MN	28.4	0.0	0.0	34.1
% Chicago, IL	24.9	49.8	22.0	0.0
% Los Angeles, CA	7.0	49.3	6.9	23.7

Mean (sd)

* Median (IQR)

Table 2

Associations of adiposity measures with adiponectin, leptin, LAR, by ethnicity in MESA

	White	Chinese	African American	Hispanic
β for ln(adiponectin) per unit of BMI	-0.035 ^b (-0.042, -0.027)	-0.063 ^a (-0.084, -0.041)	-0.026 ^b (-0.038, 0-.014)	-0.026 ^b (-0.035, -0.016)
β for ln(Leptin) per unit of BMI	0.134 ^a (0.122, 0.145)	0.175 ^a (0.146, 0.205)	0.102 ^c (0.087, 0.118)	0.122 ^c (0.107, 0.136)
β for ln(LAR) per unit of BMI	0.168 ^a (0.154, 0.183)	0.238 ^a (0.200, 0.275)	0.129 ^c (0.109, 0.149)	0.147 ^c (0.129, 0.166)

Regression coefficient (95% C.I.)

Regression coefficients adjusted for age, sex, education, current alcohol intake, current smoking status, Weekly moderate and vigorous physical activity, and MESA study site

^aStrength of association differs significantly (P < .05) between all ethnic groups^bStrength of association differs significantly (P < .05) from Chinese^cStrength of association differs significantly (P < .05) from Chinese and Whites

Table 3

Associations (regressions) of adiponectin, leptin and LAR with HOMA-IR, by ethnicity in MESA

	White	Chinese	African American	Hispanic
β for HOMA-IR per unit $\ln(\text{adiponectin})$	-0.39 (-0.47, -0.30)	-0.29 (-0.42, -0.15)	-0.42 (-0.54, -0.31)	-0.44 (-0.56, -0.32)
β for HOMA-IR per unit $\ln(\text{Leptin})$	0.34 (0.30, 0.38)	0.35 (0.28, 0.42)	0.35 (0.29, 0.42)	0.35 (0.30, 0.41)
β for HOMA-IR per unit $\ln(\text{LAR})$	0.28 (0.25, 0.31)	.27 (0.21, 0.32)	0.31 (0.26, 0.35)	0.31 (0.26, 0.35)

Regression coefficient (95% C.I.)

Regression coefficients adjusted for age, sex, education, current alcohol intake, current smoking status, Weekly moderate and vigorous physical activity, and MESA study site

All regression coefficients DO NOT differ significantly ($P < 0.05$) across ethnic groups