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Journal

Journal of the American Heart Association, 13(18)

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Publication Date

2024-09-17

DOI

10.1161/JAHA.123.030548

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

Associations of Adipokine Levels With Levels of Remnant Cholesterol: The Multi-Ethnic Study of Atherosclerosis

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BACKGROUND: The metabolic syndrome phenotype of individuals with obesity is characterized by elevated levels of triglyceride-rich lipoproteins and remnant particles, which have been shown to be significantly atherogenic. Understanding the association between adipokines, endogenous hormones produced by adipose tissue, and remnant cholesterol (RC) would give insight into the link between obesity and atherosclerotic cardiovascular disease.

METHODS AND RESULTS: We studied 1791 MESA (Multi-Ethnic Study of Atherosclerosis) participants who took part in an ancillary study on body composition with adipokine levels measured (leptin, adiponectin, and resistin) at either visit 2 or visit 3. RC was calculated as non–high-density lipoprotein cholesterol minus low-density lipoprotein cholesterol, measured at the same visit as the adipokines, as well as subsequent visits 4 through 6. Multivariable-adjusted linear mixed-effects models were used to assess the cross-sectional and longitudinal associations between adipokines and log-transformed levels of RC. Mean±SD age was 64.5±9.6 years; mean±SD body mass index was 29.9±5.0 kg/m^2; and 52.0% were women. In fully adjusted cross-sectional models that included body mass index, diabetes, low-density lipoprotein cholesterol, and lipid-lowering therapy, for each 1-unit increment in adiponectin, there was 14.6% (95% CI, 12.2–16.9) lower RC. With each 1-unit increment in leptin and resistin, there was 4.8% (95% CI, 2.7–7.0) and 4.0% (95% CI, 0.2–8.1) higher RC, respectively. Lower adiponectin and higher leptin were also associated with longitudinal increases in RC levels over median follow-up of 5 (interquartile range, 4–8) years.

CONCLUSIONS: Lower adiponectin and higher leptin levels were independently associated with higher levels of RC at baseline and longitudinal RC increase, even after accounting for body mass index and low-density lipoprotein cholesterol.

Key Words: adipokines ■ obesity ■ remnant cholesterol

Obesity is one of the most important risk factors for the development of atherosclerotic cardiovascular disease (ASCVD),[1–3] and it is projected that 1 in 2 adults in the United States will be classified as having obesity (defined by a body mass index [BMI] ≥30 kg/m^2) by 2030.[4] The pathophysiological link between obesity and ASCVD is not fully understood.[5] In this regard, the metabolic syndrome lipid phenotype of individuals with obesity is often characterized by elevation of triglyceride levels and low levels of high-density lipoprotein cholesterol (HDL-C).[6]

Mounting evidence from the past decade has shown the role of triglyceride-rich lipoproteins (TGRLs) in the development of ASCVD.[7] Remnant lipoprotein particles are partially lipolyzed lipoproteins derived from TGRL of both liver (very low-density lipoprotein) and intestinal (chylomicron) origins,[8] which have been shown to contribute to atherosclerosis independent of,

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This article was sent to Mahasin S. Mujahid, PhD, MS, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Preprint posted on MedRxiv, April 26, 2023. doi: https://doi.org/10.1101/2023.04.24.23289072.

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We examined the association of adipokines with remnant cholesterol (RC) among individuals without a history of cardiovascular disease.
- Adiponectin was inversely associated with cross-sectional levels of RC, whereas leptin and resistin were directly associated with RC, even after accounting for body mass index and low-density lipoprotein cholesterol.
- Adiponectin also had an inverse association with progression of RC levels over time.

What Are the Clinical Implications?

- Adiponectin levels were not associated with low-density lipoprotein cholesterol levels but with levels of triglyceride-rich lipoproteins, particularly RC.
- Incrementing adiponectin via lifestyle modification or pharmacologic therapies (ie, Glucagon-Like Peptide-1 [GLP-1] receptor agonists) could possibly be a mechanism to reduce RC levels and ultimately cardiovascular risk but warrants further study.

Nonstandard Abbreviations and Acronyms

MESA	Multi-Ethnic Study of Atherosclerosis
RC	remnant cholesterol
TGRL	triglyceride-rich lipoprotein

and in addition to, low-density lipoprotein cholesterol (LDL-C).[9,10] These remnant particles contain a large amount of cholesterol and contribute to endothelial dysfunction, inflammation, and ultimately atherogenesis.[7,11] Elevated levels of remnant cholesterol (RC) are strongly associated with higher ratios of triglyceride/HDL-C,[12] which are often encountered among individuals with obesity and metabolic syndrome. The association between RC and ASCVD has been established by genetic[13,14] as well as observational studies.[15]

Adipokines, such as leptin, adiponectin, and resistin, are endogenous hormones that are released from adipose tissue or adjacent inflammatory cells and have been shown to influence several metabolic processes, such as insulin sensitivity, endothelial function, and appetite regulation.[16–20] However, the association of adipokines with levels of RC has not been fully elucidated, as well as the role of different adipokines in the prediction of change in RC levels. In the analysis described below, we evaluated the associations between endogenous adipokines and (1) cross-sectional levels of RC; and (2) progression of RC levels over time.

METHODS

Study Population

The MESA (Multi-Ethnic Study of Atherosclerosis) cohort enrolled 6814 men and women, aged 45 to 84 years, who were free of clinical cardiovascular disease at baseline (2000–2002) to study subclinical atherosclerosis and other risk factors for the development of clinical events. The original MESA aims and design have been previously published.[21] In an ancillary study in MESA, a randomly selected subset of 1970 participants underwent a noncontrast abdominal computed tomography (CT) scan at either visit 2 (2002–2004) or visit 3 (2004–2005) (randomly assigned) to study abdominal aortic calcification.[22] In a subsequent ancillary study evaluating body composition, the abdominal CT scans were overread to assess for visceral and subcutaneous adipose tissue, and adipokine levels were measured from frozen samples that were obtained at the same study visit as the abdominal CT.[23–25] We included all MESA participants who had adipokines (leptin, adiponectin, and resistin) and a standard lipid panel obtained at either visit 2 or visit 3 (n=1791); thus, visit 2 or 3 (the time of the adipokine assessment) is the baseline visit for the current analyses. No missing data were seen for the exposure variables, the outcome variables, or the covariates in this study sample.

The MESA protocols have been approved by the institutional review boards at all study sites, and all participants gave written informed consent.

Independent Variable Assessment

The primary independent variables were levels of the endogenous adipokines (leptin, adiponectin, and resistin). Samples of fasting serum were obtained at either visit 2 (2002–2004) or visit 3 (2004–2005), at the visit of the abdominal CT scan,[23–25] and immediately frozen at –70 °C. In 2009, the adipokines (adiponectin, leptin, and resistin) were measured from these stored serum samples using a Bio-Rad Luminex flow cytometry (Millipore, Billerica, MA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT), as previously reported.[26,27] The coefficients of variation for these assays ranged from 6% to 13%.

Dependent Variable Assessment

From a standard lipid panel, RC levels were estimated as non–HDL-C minus LDL-C. LDL-C was estimated using the Martin/Hopkins equation. This method estimates LDL-C using 1 of 174 different factors for the triglyceride/

very low-density lipoprotein cholesterol ratio according to non–HDL-C and triglyceride levels when triglyceride levels are <400 mg/dL.[28] We additionally performed similar estimation when triglyceride levels were 400 to 799 mg/dL using an expanded version of the Martin/Hopkins method that uses several more factors with increased accuracy.[29] Our group has previously shown that this estimation method for RC levels is more accurate than using the Friedewald equation.[30]

Covariates

The covariates included in this study include the following demographic, behavioral, and ASCVD risk factors measured at the visit of the adipokine assessment: age, self-reported sex, race and ethnicity, study site, education (less than high school; high school or vocational school; college; or graduate or professional school), cigarette smoking status (current, former, or never), physical activity (metabolic equivalent task minutes/week of moderate or vigorous activity), BMI (in kg/m^2), total cholesterol (mg/dL), HDL-C (mg/dL), use of lipid-lowering medications (yes/no), diabetes (defined as fasting blood sugar ≥126, nonfasting glucose ≥200 mg/dL, or medication use), and measures of abdominal body composition (visceral and subcutaneous adipose tissue in cm^2) by CT. In exploratory models, we replaced BMI with visceral and subcutaneous adipose tissue measures from abdominal CTs from visits 2/3. We also explored new use of lipid-lowering medications during follow-up at visits 4, 5, and 6.

Statistical Analysis

We described the baseline demographics and clinical characteristics of the study participants at the time of their adipokine level measurement, stratified by tertiles of each adipokine (adiponectin, leptin, and resistin, separately). Continuous variables were expressed as mean and SD, and categorical variables were expressed as frequency and percentage. For our regression models, both RC and adipokine levels and their ratios underwent natural log transformation given their nonnormal distribution. The regression results were then exponentiated and shown as percentage differences using the following formula: $(\varepsilon^{\beta}-1)\times 100$.

Our primary outcome was RC levels (estimated as described above) assessed cross-sectionally at visit 2 or 3. Our secondary outcome was the prospective change in RC levels from the time of measurement of adipokines (either visit 2 or visit 3) to visit 6. We used standard lipid panels from visits 2, 3, 4, 5, and 6 to leverage all available lipid panels in mixed-effects linear regression models.

We assessed the longitudinal change in RC levels associated with each of the adipokine levels separately by using multivariable-adjusted linear mixed-effects models, allowing for random variations in baseline RC levels and longitudinal slope for RC progression across participants. The mixed-effects model for longitudinal data leverages all available lipid panel (RC) information from all participants, including those without follow-up measurements, to jointly model the level of RC at baseline and RC change over time. In this mixed-effect model, cross-sectional associations are represented by coefficients of the adipokines, which estimate the difference in RC at baseline by varying adipokine levels. Longitudinal associations are represented by coefficients of interactions between adipokines and time since baseline, which estimate the rate of change in RC levels associated with adipokines.

The linear regression models were progressively adjusted as follows: model 1: age, sex, race and ethnicity, and study site; model 2: model 1+education, smoking status, and physical activity; model 3: model 2+BMI; model 4: model 3+LDL-C; model 5: model 4+use of lipid-lowering therapy; model 6 (primary model): model 5+diabetes; model 7: model 5+subcutaneous fat area, in cm^2 (instead of BMI); and model 8: model 5+visceral fat area, in cm^2 (instead of BMI).

For sensitivity analyses, we evaluated interactions by sex, diabetes, and obesity status (BMI ≥30 versus <30 kg/m^2).

Transparency and Openness Promotion

The data, methods, and materials used to conduct this study will be made available to other researchers for the purposes of reproducing or expanding on the results on application to and approval by the MESA publications and presentations committee. Requests for the use of MESA data can also be done through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Coordinating Center (https://biolincc.nhlbi.nih.gov/studies/mesa/).

RESULTS

Study Population

The mean (SD) age of the population was 64.5 (9.6) years, and approximately half of them were women (52%). In terms of race and ethnicity, most individuals were of White race (39.8%), followed by Hispanic ethnicity (25.5%), Black race (21.1%), and Chinese American race (13.6%). The mean (SD) BMI of the population was 29.9 (5.0) kg/m^2. The median (interquartile range) triglyceride level was 113 (77–161) mg/dL, and the median (interquartile range) RC level was 21.8 (16.9–27.8) mg/dL. The median (interquartile range)

values for adipokines were as follows: adiponectin, 17.5 (11.9–26.4) ng/mL; leptin, 13.1 (5.6–28.2) ng/mL; and resistin, 14.9 (11.9–18.8) ng/mL.

Baseline Characteristics by Adipokine Levels

The baseline characteristics were estimated per tertiles of each adipokine separately to more evenly distribute the population, and are shown in Table 1 (adiponectin), Table 2 (leptin), and Table 3 (resistin).

Compared with lower tertiles of adiponectin, we observed significantly higher proportions of women, White individuals, and never smokers, but lower proportions of individuals with diabetes ($P<0.05$) in the highest tertile of adiponectin. In the highest tertile of adiponectin, we also observed lower levels of both triglyceride and RC, but higher levels of HDL-C. We did not observe significant differences in levels of BMI, total cholesterol, and LDL-C across adiponectin tertiles (Table 1).

Compared with lower tertiles of leptin, we observed significantly higher proportions of women, Black and Hispanic individuals, and never smokers in the highest tertile of leptin. We also observed higher proportions of diabetes, along with greater use of antihypertensive and lipid-lowering medications with higher leptin. With regard to lipid parameters, we observed higher levels of triglyceride and RC in the highest compared with lower leptin tertiles. We found that those in the highest leptin tertile had significantly higher BMI levels compared with lower tertiles ($P<0.05$). Contrarily, we did not find significant differences in total cholesterol and LDL-C across leptin tertiles (Table 2).

Finally, we found significantly higher BMI levels in the highest compared with lower tertiles of resistin, along with prevalence of diabetes and use of antihypertensive

Table 1. Baseline Characteristics by Tertiles of Adiponectin (n=1791)

Characteristic	Lowest tertile	Second tertile	Highest tertile	*P* value
Age, y	62.2±9.2	64.5±9.5	66.8±9.5	0.591
Female sex	210 (35.2)*	300 (50.3)*	421 (70.5)*	<0.001*
Race or ethnicity				<0.001*
Black	171 (28.6)*	115 (19.3)*	92 (15.4)*	
Chinese American	119 (19.9)*	71 (11.9)*	53 (8.9)*	
Hispanic	149 (25.0)*	186 (31.2)*	122 (20.4)*	
White	158 (26.5)*	225 (37.7)*	330 (55.3)*	
Smoking status				0.023*
Never	265 (44.4)*	272 (45.6)*	302 (50.6)*	
Former	246 (41.2)*	258 (43.2)*	242 (40.5)*	
Current	86 (14.4)*	67 (11.2)*	53 (8.9)*	
BMI, kg/m^2	29.0±5.0	28.2±4.9	26.4±4.8	0.523
Educational level				0.696
Less than high school	105 (17.6)	111 (18.6)	105 (17.6)	
High school or vocational school	287 (48.1)	262 (43.9)	277 (46.4)	
College or graduate or professional school	205 (34.3)	224 (37.5)	215 (36.0)	
Physical activity, MET-min/wk	3277.5 (1732.5–5505)	3195 (1515–5460)	3367.5 (1980–5805)	0.2867
SBP, mm Hg	124.2±20.5	123.6±19.9	123.3±22.1	0.031*
Triglycerides, mg/dL	130 (93–180)*	117 (81–164)*	89 (65–136)*	<0.001*
RC, mg/dL	23.6 (19.1–30.2)*	22.3 (17.3–28.8)*	18.8 (15–24.9)*	<0.001*
Total cholesterol, mg/dL	185.6±36.0	191.0±34.6	193.5±35.4	0.632
LDL-C, mg/dL	115.1±31.1	115.5±30.2	112.5±30.7	0.764
HDL-C, mg/dL	44.8±11.2*	51.3±13.2*	60.0±16.8*	<0.001*
Diabetes	112 (18.8)*	72 (12.1)*	54 (9.1)*	<0.001*
Antihypertensive medications	251 (43.3)	244 (42)	246 (42.3)	0.901
Lipid-lowering medications	147 (25.3)	152 (26.2)	133 (22.9)	0.406
Visceral adipose tissue, cm^2	183 (124.6–247.0)*	160.2 (103.7–232.4)*	103.8 (59.8–71.5)*	<0.001*
Subcutaneous adipose tissue, cm^2	151.6 (103.2–215.3)*	155.8 (112.4–210.9)*	134.4 (94.1–186.2)*	<0.001*

Values are shown using mean±SD for normal and median (25th–75th percentile) for nonnormal continuous variables, and number (percentage) for categorical variables. Comparison was made using χ^2 test (categorical), *t* test (normal), or Kruskal-Wallis test (nonnormal). BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; and SBP, systolic blood pressure.

*Statistically significant ($P<0.05$).

Table 2. Baseline Characteristics by Tertiles of Leptin (n=1791)

Characteristic	First tertile	Second tertile	Third tertile	*P* value
Age, y	64.3±9.9	64.3±9.9	65.0±9.2	0.177
Female sex	125 (20.9)*	295 (49.4)*	511 (85.6)*	<0.001*
Race or ethnicity				<0.001*
Black	76 (12.7)*	110 (18.4)*	192 (32.2)*	
Chinese American	126 (21.1)*	82 (13.7)*	35 (5.9)*	
Hispanic	129 (21.6)*	151 (25.3)*	177 (29.6)*	
White	266 (44.6)*	254 (42.6)*	193 (32.3)*	
Smoking status				<0.001*
Never	231 (38.7)*	298 (49.9)*	310 (51.9)*	
Former	280 (46.9)*	235 (39.4)*	231 (38.7)*	
Current	86 (14.4)*	64 (10.7)*	56 (9.4)*	
BMI, kg/m^2	24.8±3.2*	27.2±3.6*	31.5±5.4*	<0.001*
Educational level				<0.001*
Less than high school	107 (17.9)*	99 (16.6)*	115 (19.3)*	
High school or vocational school	239 (40.0)*	287 (48.1)*	300 (50.2)*	
College or graduate or professional school	251 (42.0)*	211 (35.3)*	182 (30.5)*	
Physical activity, MET-min/wk	3652.5 (1837.5–6390)*	3255 (1920–5392.5)*	2925 (1440–5100)*	<0.001*
SBP, mmHg	120.0±19.7*	123.1±20.0*	127.9±22.0*	0.013*
Triglycerides, mg/dL	100 (69–141)*	118 (83–165)*	121 (83–177)*	<0.001*
RC, mg/dL	20 (15.7–25.4)*	22.4 (17.4–28.3)*	22.8 (17.8–30)*	<0.001*
Total cholesterol, mg/dL	185.5±33.8	190.2±36.0	194.4±36.1	0.204
LDL-C, mg/dL	111.7±29.2	114.4±31.2	117.1±31.4	0.154
HDL-C, mg/dL	51.8±16.2*	51.7±15.7*	52.6±13.8*	<0.001*
Diabetes	64 (10.7)*	80 (13.4)*	94 (15.8)*	0.037*
Antihypertensive medications	186 (31.9)*	246 (42.3)*	309 (53.7)*	<0.001*
Lipid-lowering medications	115 (19.7)*	164 (28.2)*	153 (26.5)*	0.002*
Visceral adipose tissue, cm^2	137.8 (76.0–205.4)*	162.9 (92.8–241.3)*	155.9 (107.9–221.1)*	<0.001*
Subcutaneous adipose tissue, cm^2	99.7 (76.2–131.0)*	149.6 (118.2–189.6)*	220.9 (170.0–294.2)*	<0.001*

Values are shown using mean±SD for normal and median (25th–75th percentile) for nonnormal continuous variables, and number (percentage) for categorical variables. Comparison was made using χ^2 test (categorical), *t* test (normal), or Kruskal-Wallis test (nonnormal). BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; and SBP, systolic blood pressure.

*Statistically significant (*P*<0.05).

medications (*P*<0.05). In the highest resistin tertile, the average triglyceride level was higher and HDL-C was lower, but we did not find any significant differences between lipid parameters, including LDL-C and RC, across tertiles (Table 3).

Cross-Sectional Association Between Adipokines and RC

The associations between adipokines and RC are shown graphically in the figures. Figure 1 shows an inverse association between adiponectin and RC levels, whereas Figure 2 shows a direct association between leptin and RC. Levels of resistin appear to be equally dispersed across levels of RC in Figure 3.

In our cross-sectional linear regression models, we observed that after adjustment for demographic variables (model 1), each 1-unit increment in adiponectin was associated with a 17.2% (95% CI, 14.6–19.6) lower level of RC, whereas similar 1-unit increments in leptin and resistin were associated with 7.7% (95% CI, 5.9–9.6) and 6.0% (95% CI, 1.6–10.5) higher RC levels (Table 4). In fully adjusted models that included BMI, diabetes status, LDL-C, and lipid-lowering therapy (model 6), we observed that for each 1-unit increment in adiponectin, RC levels were 14.6% (95% CI, 12.2–16.9) lower. Conversely, 1-unit increment changes in leptin and resistin were associated with higher RC levels by 4.8% (95% CI, 2.7–7.0) and 4.0% (95% CI, 0.2–8.1), respectively. Similar results were observed in models that included subcutaneous (model 7) and visceral fat area (model 8) instead of BMI (Table 4). We did not find effect modification by sex, diabetes, or obesity (*P* for interaction >0.05).

Table 3. Baseline Characteristics by Tertiles of Resistin (n=1791)

Characteristic	First tertile	Second tertile	Third tertile	*P* value
Age, y	62.8±9.0	64.0±9.5	66.8±9.7	0.139
Female sex	307 (51.4)	292 (48.9)	332 (55.6)	0.065
Race or ethnicity				<0.001*
Black	122 (20.4)*	103 (17.3)*	153 (25.6)*	
Chinese American	105 (17.6)*	64 (10.7)*	74 (12.4)*	
Hispanic	161 (27.0)*	152 (25.5)*	144 (24.1)*	
White	209 (35.0)*	278 (46.6)*	226 (37.9)*	
Smoking status				0.068
Never	298 (49.9)	263 (44.1)	278 (46.6)	
Former	242 (40.5)	249 (41.7)	255 (42.7)	
Current	57 (9.6)	85 (14.2)	64 (10.7)	
BMI, kg/m^2	27.1±4.7*	28.1±4.8*	28.4±5.4*	0.002*
Educational level				0.156
Less than high school	115 (19.3)	101 (16.9)	105 (17.6)	
High school or vocational school	257 (43.1)	272 (45.6)	297 (49.8)	
College or graduate or professional school	225 (37.7)	224 (37.5)	195 (32.7)	
Physical activity, MET-min/wk	3510 (1845–5992.5)*	3255 (1845–5580)*	3000 (1477.5–5250)*	0.0078*
SBP, mmHg	122.3±20.4	122.1±20.5	126.6±21.3	0.550
Triglycerides, mg/dL	109 (76–149)	113 (76–164)	117 (80–171)	0.0371
RC, mg/dL	21.4 (16.6–26.3)	21.9 (16.7–28)	22 (17.3–28.9)	0.1222
Total cholesterol, mg/dL	194.3±35.8	188.4±33.8	187.4±36.6	0.144
LDL-C, mg/dL	117.2±31.1	112.7±30.1	113.2±30.7	0.762
HDL-C, mg/dL	54.1±16.3*	52.0±14.9*	50.1±14.2*	0.003*
Diabetes	63 (10.6)*	75 (12.6)*	100 (16.8)*	0.006*
Antihypertensive medications	210 (36.3)*	238 (40.8)*	293 (50.6)*	<0.001*
Lipid-lowering medications	141 (24.4)	156 (26.7)	135 (23.3)	0.388
Visceral adipose tissue, cm^2	142.9 (84.1–212.5)*	157.6 (93.7–236.5)*	150.7 (98.5–223.9)*	0.0059*
Subcutaneous adipose tissue, cm^2	138.5 (99.9–195.5)*	148.7 (102.1–206.4)*	153.4 (107.9–205.8)*	0.0131*

Values are shown using mean±SD for normal and median (25th–75th percentile) for nonnormal continuous variables, and number (percentage) for categorical variables. Comparison was made using χ^2 test (categorical), *t* test (normal), or Kruskal-Wallis test (nonnormal). BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; and SBP, systolic blood pressure.

*Statistically significant (*P*<0.05).

Longitudinal Association Between Adipokines and RC

Participants were followed up for a median (interquartile range) of 5 (4–8) years. In longitudinal analyses, we observed that for each 1-unit higher baseline adiponectin level, there was a 14.1% (95% CI, 11.9–16.3) lower change in RC levels over time after adjusting for demographic variables (model 1). After further adjusting for other time-varying covariates, such as BMI, diabetes status, LDL-C, and lipid-lowering therapy (model 6), we observed an 11.6% (95% CI, 9.5–13.6) lower change in RC levels over time.

We found a 6.4% (95% CI, 4.8–8.0) greater increase in RC levels over time for each increase in 1-unit higher leptin (model 1), although this increase was only 1.8% higher after further adjusting for BMI, diabetes status, LDL-C, and lipid-lowering therapy (model 6, Table 5). We did not find statistically significant associations between resistin levels and longitudinal changes in RC in our primary model (model 6, Table 5), although resistin levels were directly associated with change in RC levels in models where subcutaneous or visceral fat was adjusted for instead of BMI (models 7 and 8).

DISCUSSION

In this multiethnic cohort of individuals, we observed a significant inverse cross-sectional association between higher levels of adiponectin and lower levels of RC, whereas we found a significant but less potent positive association of higher leptin and resistin with greater levels of RC. In longitudinal analyses, we found that only higher baseline levels of adiponectin continued to have a strong independent inverse association

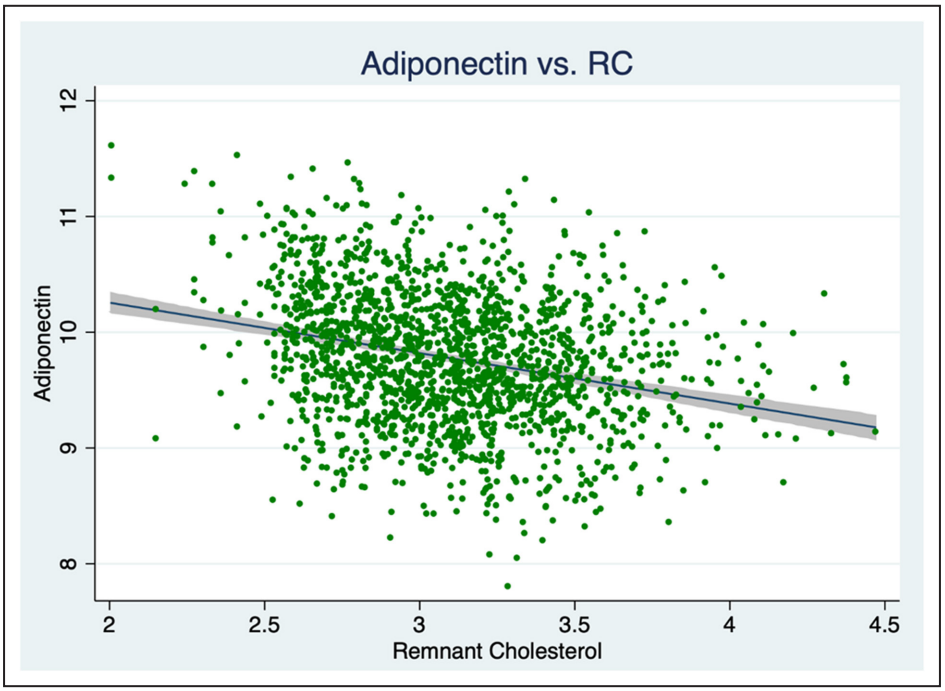

Figure 1. Adiponectin vs RC levels (log transformed).
Regression line with 95% CI is displayed. RC indicates remnant cholesterol.

with RC levels over time, whereas leptin had a more modest association and resistin was not associated with longitudinal change in RC levels in our primary model that accounted for BMI, diabetes, and LDL-C.

The relationship between triglyceride and ASCVD has been complex and historically difficult to define. It has been shown that individuals with hypertriglyceridemia have increased rates of secretion of triglyceride-overloaded very low-density lipoproteins, which then metabolize to small dense low-density lipoprotein particles, which are shown to be highly atherogenic.[31] On the other hand, many epidemiologic studies showed a strong role for low HDL-C as a predictor of cardiovascular risk, suggesting it may even be a better predictor than high triglyceride. The association between triglyceride and ASCVD was shown to be attenuated after adjusting for HDL-C. However, triglyceride and HDL-C have a strong inverse association with each other,[14] and it was unclear which of the 2 was really the culprit for development of ASCVD. Over the past decade, multiple trials of HDL-C raising therapies failed to show a benefit with regard to risk[32–34]; furthermore, genetic studies[35,36] have helped to confirm that HDL-C is not a causal risk factor for ASCVD, but it may rather be a marker of high triglyceride levels.

TGRLs contain both triglycerides and cholesterol. However, the simplest measurements of TGRL are serum triglyceride and RC, both of which can easily be obtained from the standard lipid panel.[37] To cause atherosclerosis, TGRLs need to enter into the arterial intimal space. It has been suggested that serum/plasma levels of triglyceride should be considered as a marker of high levels of cholesterol within TGRLs (ie, RC).[37] RC represents the concentration of all plasma cholesterol not found in low-density lipoprotein and high-density lipoprotein, or in other words, in all TGRLs. RC has been shown to be associated with events by several observational studies. For instance, we showed that RC was associated with progression of atheroma in a secondary prevention population,[15] as well as incident events independent of LDL-C and apolipoprotein B levels in a pooled cohort of individuals free of ASCVD.[38] Furthermore, Mendelian randomization studies supported the causal role of RC in the development of atherosclerosis.[14]

To the best of our knowledge, this is the first study evaluating the association between adipokines and RC. In our study, we observed that of the 3 adipokines that we evaluated, only adiponectin continued to be significantly inversely associated with RC in both cross-sectional and longitudinal analyses. Adiponectin is an adipocyte-specific hormone that has been classically shown to be reduced in individuals with obesity, possibly attributable to several mechanisms, including hypoxia, inflammation, and downregulation of β-adrenergic signaling.[39–41] Adiponectin has several systemic insulin-sensitizing and anti-inflammatory properties,[42–44] given that its signaling leads to metabolic health-promoting alterations, such as decreased hepatic gluconeogenesis, increased fatty acid

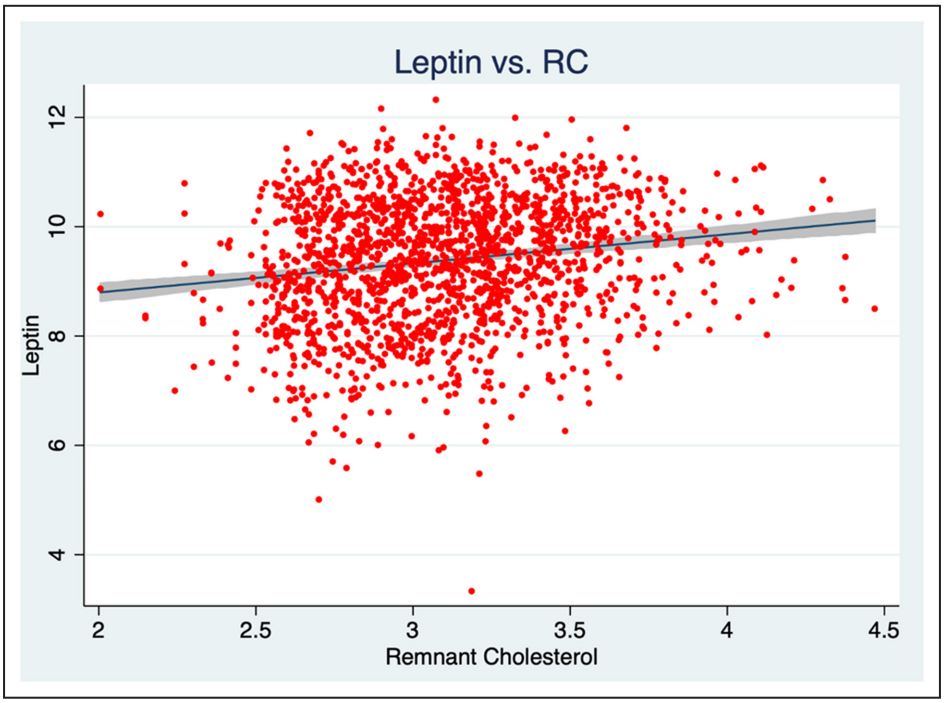

Figure 2. Leptin vs RC levels (log transformed).
Regression line with 95% CI is displayed. RC indicates remnant cholesterol.

oxidation in liver and skeletal muscle, protective effect on pancreatic β-cells, and increased glucose uptake in muscle.[42] Adiponectin has also been shown to have anti-inflammatory properties via its effects on tumor necrosis factor-α and CRP (C-reactive protein),[45] with effects on formation of the atherosclerotic plaque.[46,47] Thus, taken together, adiponectin is generally thought to be a cardioprotective adipokine. Previous studies have shown that adiponectin levels are negatively correlated with markers of TGRL metabolism, such

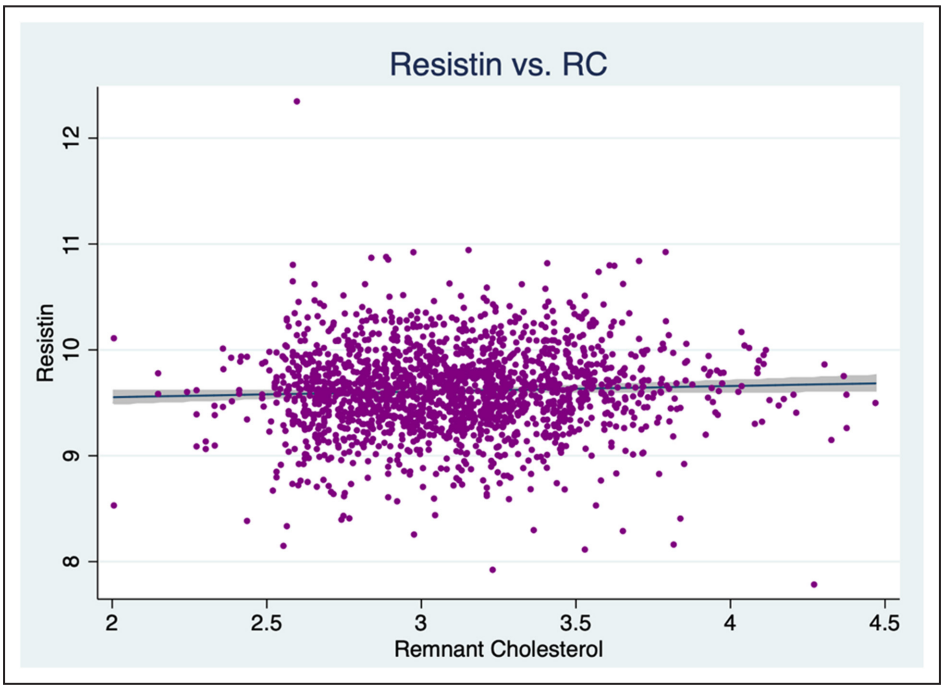

Figure 3. Resistin vs RC levels (log transformed).
Regression line with 95% CI is displayed. RC indicates remnant cholesterol.

Table 4. Linear Regression Models for Associations Between Baseline Adipokines and Levels of RC (n=1791)

Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Adiponectin	–17.2 (–19.6 to –14.6)*	–17.1 (–19.5 to –14.6)*	–15.4 (–17.9 to –12.8)*	–15.0 (–17.3 to –12.6)*	–14.6 (–16.8 to –12.0)*	–14.6 (–16.9 to –12.2)*	–13.6 (–16.0 to –11.1)*	–10.2 (–12.5 to –7.8)*
Leptin	7.7 (5.9 to 9.6)*	7.9 (6.0 to 9.7)*	5.1 (2.8 to 7.5)*	4.8 (2.7 to 7.0)*	4.5 (2.3 to 6.6)*	4.8 (2.7 to 7.0)*	2.6 (0.5 to 4.6)*	2.3 (1.0 to 3.6)*
Resistin	6.0 (1.6 to 10.5)*	5.6 (1.2 to 10.1)*	3.6 (–0.6 to 8.0)	4.4 (0.5 to 8.4)*	5.1 (1.2 to 9.2)*	4.0 (0.2 to 8.1)*	3.6 (–0.7 to 8.1)	3.4 (–0.3 to 7.2)

RC and adipokine levels were log transformed. Results shown are shown as percentage differences [(ε^{β}–1)×100]. Data in parentheses are 95% CIs. Model 1: adjusted for age, sex, race and ethnicity, and study site. Model 2: adjusted for model 1+education, smoking status, and physical activity. Model 3: adjusted for model 2+BMI. Model 4: adjusted for model 3+low-density lipoprotein cholesterol. Model 5: adjusted for model 4+use of lipid-lowering therapy. Model 6: adjusted for model 5+diabetes. Model 7: adjusted for model 6+subcutaneous fat area, in cm^2 (instead of BMI). Model 8: adjusted for model 6+visceral fat area, in cm^2 (instead of BMI). BMI indicates body mass index; and RC, remnant cholesterol.

*Statistically significant (P<0.05).

as apolipoprotein C-III, very low-density lipoproteins–triglycerides, and apolipoprotein B-48 levels.[48–50] Resistance to adiponectin has been described in the setting of insulin resistance in the presence of excess of adipose tissue.[51] However, similar to previous studies,[48–50] our findings showed a negative association with RC that is independent of presence of diabetes. We did not include markers of insulin resistance in the model, and it may be possible that adiponectin resistance may play a role at earlier metabolic stages. We did find an inverse association between adiponectin and levels of RC; these findings could be explained by 3 mechanisms based on previous studies from the literature. First, adiponectin may decrease accumulation of triglyceride in skeletal muscle by enhancing fatty acid oxidation[52]; second, adiponectin can stimulate lipoprotein lipase in adipocytes[53]; and third, adiponectin may decrease the supply of nonesterified fatty acid to the liver for gluconeogenesis, which leads to decreased triglyceride synthesis.[54]

Leptin is an adipokine that is almost exclusively expressed in adipocytes; it has been proposed that the most important physiological role of leptin is via appetite suppression and promoting energy expenditure through receptors in the central nervous system. Circulating leptin levels have been shown to correlate positively with adipose tissue mass,[55] as we observed in our study. Mice studies reported that leptin can stimulate vascular inflammation and oxidative stress that ultimately would lead to atherosclerosis.[56] Other in vivo studies showed that leptin has potent proatherogenic effects on vascular cells (ie, macrophages, endothelial cells, and smooth muscle cells) via an interaction with the long form of leptin receptor that is expressed in atherosclerotic plaques.[57] On the other hand, it has been also suggested that leptin signaling occurs in pancreatic β-cells, with some in vitro studies showing that leptin signaling inhibits insulin secretion and increases survival of β-cells.[58,59] However, these findings have not been confirmed with in vivo studies: mouse models with Leptin Receptor (LepR) knockdown restricted to β-cells found no evidence of hyperinsulinemia or disturbed glucose hemostasis.[60] In a prior MESA analysis, leptin levels were not found to be independently associated with ASCVD after accounting for BMI.[61] In our study, we found an increasing prevalence of diabetes at higher leptin levels, which could be attributable to greater adiposity, as reflected by higher BMI. Higher levels of triglyceride and RC in the highest tertile of leptin could be attributable to the greater prevalence of diabetes rather than a direct effect of leptin; this may also explain why the association between leptin and longitudinal change in RC was rather weak and probably not clinically relevant. To the best of our knowledge,

Table 5. Mixed-Model (Longitudinal) Analyses for Associations Between Baseline Adipokines and Change in Levels of RC

Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Adiponectin	–14.1 (–16.3 to –11.9)*	–14.2 (–16.4 to –12.0)*	–12.0 (–14.2 to –9.7)*	–12.1 (–14.1 to –10.1)*	–11.9 (–13.9 to –9.8)*	–11.6 (–13.6 to –9.5)*	–12.7 (–14.9 to –10.4)*	–9.9 (–11.9 to –7.9)*
Leptin	6.4 (4.8 to 8.0)*	6.5 (4.9 to 8.1)*	1.5 (–0.2 to 3.3)	2.0 (0.4 to 3.6)*	1.9 (0.3 to 3.5)*	1.8 (0.2 to 3.4)*	6.6 (4.5 to 8.6)*	0.2 (–1.3 to 1.7)
Resistin	4.5 (0.7 to 8.3)*	4.1 (0.4 to 7.9)*	1.8 (–1.8 to 5.5)	3.0 (–0.2 to 6.4)	3.2 (–0.1 to 6.5)	2.8 (–0.4 to 6.2)	4.0 (0.3 to 7.8)*	3.6 (0.5 to 6.8)*

RC and adipokine levels were log transformed. Results shown are shown as percentage differences [(ε^{β}–1)×100]. Data in parentheses are 95% CIs. Model 1: adjusted for age, sex, race and ethnicity, and study site. Model 2: adjusted for model 1+education, smoking status, and physical activity. Model 3: adjusted for model 2+BMI. Model 4: adjusted for model 3+LDL-C. Model 5: adjusted for model 4+use of lipid-lowering therapy. Model 6: adjusted for model 5+diabetes. Model 7: adjusted for model 6+subcutaneous fat area, in cm^2 (instead of BMI). Model 8: adjusted for model 6+visceral fat area, in cm^2 (instead of BMI). Time-varying variables were age, smoking status, BMI, LDL-C, and use of lipid-lowering therapy. BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; and RC, remnant cholesterol.

*Statistically significant (P<0.05).

there are no previous studies that have assessed the longitudinal association between leptin and RC.

Resistin, an adipokine released by tissue-resident macrophages rather than adipocytes, accelerates insulin resistance and the development of inflammatory metabolic diseases. It has been suggested that resistin targets toll-like receptor 4 or adenylyl cyclase-associated protein 1, triggering multiple intracellular signal transduction pathways in vascular cell types, inducing proatherosclerotic effects as well as plaque vulnerability.[62,63] We did not identify significant longitudinal associations between resistin levels and triglyceride or RC in models accounting for BMI, for which we hypothesize that the metabolic effect of resistin may not be related to TGRL.

Strengths and Limitations

Our study has several strengths. First, we used the definition of non–HDL-C minus Martin/Hopkins estimated LDL-C given its availability from the standard lipid panel at no extra cost and superiority when compared with RC extrapolated from Friedewald estimated LDL-C.[30] This estimation method has been used by most studies in the literature and includes both atherogenic remnant particles and large nonatherogenic particles, such as large very low-density lipoprotein. Second, we were able to adjust for other markers of adiposity, particularly visceral adipose tissue, which has been proposed to be a more accurate marker of abdominal obesity compared with waist circumference and BMI; furthermore, it has been proposed that visceral adiposity is the primary source of adipokines.[64] Third, 3 of the most important and clinically relevant adipokines were included in this study, and they were measured by standardized and reproducible methods. Fourth, we were able to obtain data from subsequent visits after baseline in a time-varying manner, such as BMI, LDL-C, age, smoking status, and use of lipid-lowering therapies. Fifth, we were able to perform mixed-effect models to model RC change over time, which has more statistical power than cross-sectional analysis.

Our study has some limitations. First, given the observational nature of the study design, we cannot rule out the presence of residual confounding by unmeasured covariates. Second, adipokines were only measured once (either visit 2 or visit 3), for which we were not able to evaluate the association between change in adipokines over time and RC over time. It should be considered that remnant lipoprotein particles can also induce proinflammatory cytokines released from adipocytes and decreased adiponectin secretion by activating nuclear factor-κB and c-Jun N-terminal kinase (JNK) pathways[65] or induce adipogenesis in an apolipoprotein E–dependent manner,[66] leading to an increase in the amount of adipose tissue. Therefore, it may not be possible to fully distinguish the direction of the association between adipokines and RC. Third, the sample size of our study was relatively small, for which stratified analyses were not sufficiently powered to detect significant differences. Fourth, interventions that could have a direct effect on the outcome (ie, lifestyle modifications) may have been started between baseline and follow-up visits and are not taken into account in the present analysis because the data were not available. The negative values for RC associated with adiponectin do not necessarily mean the actual RC levels were decreasing over time but that there was a lesser change in RC compared with the reference group. Fifth, longitudinal studies always carry the risk for attrition bias; however, we used a mixed-effect model, which used individual data from at least 1 and up to 3 follow-up visits, which help to reduce this bias. The study population represents a subset of the overall MESA cohort; however, individuals who were included in this ancillary study were selected randomly, which reduces the risk of selection bias.

CONCLUSIONS

Lower adiponectin and higher leptin levels were associated with worse metabolic profile, and associated with higher levels of RC independent of traditional risk factors, including obesity markers. Additionally, adiponectin levels were significantly independently inversely associated with changes in RC over time, whereas leptin levels were modestly positively associated with longitudinal increase in RC. These findings might help explain the link between obesity and ASCVD pathogenesis. Whether incrementing adiponectin via lifestyle modification or pharmacologic therapies (ie, GLP-1 receptor agonists[67,68]) could be a mechanism to reduce RC levels and ultimately cardiovascular risk warrants further study.

ARTICLE INFORMATION

Received April 22, 2023; accepted March 6, 2024.

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Acknowledgments

The authors thank the other investigators, the staff, and the MESA (Multi-Ethnic Study of Atherosclerosis) participants for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

R.Q. is supported by a National Institutes of Health (NIH) T32 training grant (5T32HL007227). E.D.M. is supported by the Amato Fund for Women's Cardiovascular Health at Johns Hopkins and an American Heart Association grant 946222. The MESA (Multi-Ethnic Study of Atherosclerosis) study is supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the NIH/National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from National Center for Advancing Translational Sciences. The ancillary data used in this analysis were funded by R01 HL088451. C.E.N. and E.D.M. are additionally supported for this work by an American Heart Association Strategic Focused Research Network grant 20SFRN35120152.

Disclosures

Unrelated to this work, Dr Michos served as a consultant for Amgen, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Life Science, Esperion, Medtronic, Merck, New Amsterdam, Novartis, Novo Nordisk, and Pfizer. Outside of this work, Dr Martin reports consulting fees from Amgen, AstraZeneca, Bristol Myers Squibb, Dalcor, Esperion, iHealth, Kaneka, New Amsterdam, Novartis, Novo Nordisk, Sanofi, and 89bio. He was a coinvestigator on a grant funded by Merck. Dr Martin is a coinventor on a patent application filed by Johns Hopkins University for the Martin/Hopkins method of low-density lipoprotein cholesterol and that patent application has since been abandoned to enable use without intellectual property restrictions. The remaining authors have no disclosures to report.

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