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Adipokines and Incident Venous Thromboembolism: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Introduction: Obesity leads to adipocyte hypertrophy, adipokine dysregulation and is an independent risk factor for venous thromboembolism (VTE). However, the association between adipokines and VTE is not well established. This study examined whether adipokines are associated with increased risk of incident VTE.

Methods: We studied 1,888 participants of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort who were initially free of VTE and had adipokine (adiponectin, leptin and resistin) levels measured at either exam 2 or 3 (2002-2004 or 2004-2005). During follow up, VTE was ascertained through hospitalization records and death certificates using ICD-9 and 10 codes. We used multivariable Cox proportional hazards regression to assess the association between 1 standard deviation (SD) log-transformed increments in adipokines and incident VTE.

Results: The mean ± SD age was 64.7 ± 9.6 years and 49.8% were women. Median (IQR) of adiponectin, leptin and resistin were 17.3 (11.8-26.2) mcg/mL,13.5 (5.6-28.2) ng/mL and 15.0

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AUTHOR CONTRIBUTIONS

EB designed the study, analyzed and interpreted the data, wrote the first draft of the manuscript and critically revised the manuscript for intellectual content. OO performed statistical analyses, interpreted the data and critically revised the manuscript for intellectual content. RQ, TS, BV, OF, PL, MA and MS interpreted the data and critically revised the manuscript for intellectual content. CN and EM designed the study, interpreted the data and critically revised the manuscript for intellectual content.

CONFLICT OF INTEREST

Dr. Michos is on the advisory boards for Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Esperion, Novartis, Novo Nordisk, and Pfizer. None of the authors report any conflicts of interest.

(11.9 - 19.0) ng/mL, respectively. There were 78 incident cases of VTE after a median of 9.7 (5.0 - 12.4) years of follow-up. After adjusting for socio-demographics, smoking, and physical activity, the hazard ratios (95%) per 1 SD increment of adiponectin, leptin and resistin were 1.14 (0.90-1.44), 1.29 (1.00-1.66) and 1.38 (1.09-1.74), respectively. The associations for resistin persisted after further adjustments for body mass index and computed tomography derived total visceral adipose tissue area.

Conclusion: Higher resistin levels were independently associated with greater risk of incident VTE. Larger prospective cohort studies are warranted to confirm this association.

Keywords

Adipokines; Body mass index; obesity; visceral adipose tissue; venous thromboembolism

INTRODUCTION

Adipokines are endogenous hormones released by adipose tissue and play a role in various metabolic pathways (1). Adipokines have been mechanistically linked with many obesity-related pathologies with higher adiponectin levels considered cardioprotective whereas leptin and resistin are generally considered deleterious to cardiovascular health (2). Obesity leads to adipocyte hypertrophy and dysfunction with concomitant increase in proinflammatory and decreased anti-inflammatory adipokine levels (3).

Venous thromboembolism (VTE) is the third leading cause of vascular mortality worldwide (4) and includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Approximately one million cases of VTE are reported annually in the United States with a 10% case fatality rate (5, 6). Among the known risk factors for VTE, obesity remains the strongest independent risk factor with a reported 6.2-fold increased risk (7). Despite this strong association between excess adiposity and VTE, a couple of prior case control studies linking adipokines to VTE have shown conflicting results (8, 9). Additionally, there were no prior studies on the associations between adipokines and incident VTE. Therefore, in this brief report we evaluated the association between adipokines (adiponectin, leptin and resistin) and incident VTE in a multiethnic cohort to garner further insight into the relationship of obesity-related hormones and VTE risk.

METHODS

Study Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter cohort investigating risk factors for subclinical cardiovascular disease (CVD) in participants who were free of clinical CVD at enrollment (10). At baseline, there were 6,814 participants aged 45 to 84 years recruited from six field centers in Baltimore, MD, Chicago, IL, Forsyth County, NC, Los Angeles, CA, St. Paul, MN and New York, NY.

As part of an ancillary study initially evaluating aortic plaque, a subset of the MESA cohort (n=1,958) underwent an abdominal computed tomography (CT) scan at either exam 2 (2002-2004) or exam 3 (2004-2005), randomly assigned (11). In a subsequent ancillary

study about body composition, the abdominal CTs were overread for measurement of abdominal visceral and subcutaneous adipose tissue, and serum adipokine levels were measured for the participants who underwent abdominal CT (12). For this analysis, we included all MESA participants who had adipokine levels measured. The final sample size for this study was 1,888 after excluding participants with missing data for adipokines, VTE and covariates (Figure 1).

The institutional review boards of the participating institutions approved the study and informed consent was obtained from each participant (10).

Adipokines

Fasting serum samples were obtained at either exam 2 (2002-2004) or exam 3 (2004-2005), at the respective visit of the abdominal CT scan (13, 14), and frozen at −70°C. Adipokines (adiponectin, leptin and resistin) were later measured in 2009 from these stored serum samples using a Bio-Rad Luminex flow cytometry (Millipore, Billerica, MA, USA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA) (15). The adipokine assays were validated against several gold standard ELISAs and the average analytical coefficients of variation across several control samples for the adipokine analytes ranged from 6.0-13.0% (15, 16).

Venous Thromboembolism

Depending on the visit from which their adipokines were measured, participants were followed from either exam 2 or 3 (2002-2004 or 2004-2005) to 2018 for incident VTE events. Specifically, every 9 to 12 months, information on self-reported hospitalization were obtained by telephone from participants and the medical records from these hospitalizations were obtained and reviewed. Incident VTE events were ascertained from the hospitalization records and from death certificates using international classification of diseases (ICD)-9 and ICD-10 codes (17). The included VTE codes were approved by a MESA adjudication committee, but VTE events were not formally adjudicated by chart review.

Body Mass Index (BMI)

At each study visit, using standardized protocol, weight and height were measured twice to the nearest 0.5lb and 0.5cm respectively, and the results were averaged (10). BMI for each participant was calculated from the ratio of weight to height squared (kg/m^2) (12).

Other covariates

Covariates from exams 2 and 3 were used for the analyses except education which was carried forward from exam 1. Demographic and CVD risk factors of age, race/ethnicity, BMI, physical activity (MET minutes /week of moderate or vigorous activity), cigarette smoking status (never, former or current), diabetes (defined as fasting blood glucose ≥126 mg/dl, or non-fasting glucose ≥200 mg/dl or medication use), systolic blood pressure, use of antihypertensive medications, total cholesterol, high density lipoprotein cholesterol (HDL-C), and use of lipid-lowering medications were included in the models. Visceral adipose tissue (VAT) area, measured from abdominal CT slices obtained at L2-L3 adjusted for height, was also included (12).

Statistical analyses

Baseline characteristics of the study population were stratified by VTE status and comparisons were made using the chi-square or Kruskal Wallis tests as appropriate. The adipokines were natural log-transformed because of the skewed distribution and analyzed per 1 standard deviation (SD) increment. Multivariable-adjusted Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) of the association between log transformed adipokines and VTE. The proportional hazards assumption was tested using the Schoenfeld residuals and was not violated.

We used progressively adjusted models. Model 1 adjusted for demographic and lifestyle factors of age, race/ethnicity, smoking and physical activity. Because adiposity might be a mediator of the relationship between adipokines and VTE risk, we performed separate models including these variables as follows: Model 2 adjusted for model 1 covariates plus BMI. Model 3 adjusted for model 1 covariates + VAT. In a supplemental model, we adjusted for age plus the CVD risk factors of diabetes, systolic blood pressure, use of antihypertensive medication, total cholesterol, HDL-C, and use of lipid-lowering medication. In an additional supplemental model, waist circumference was adjusted for in place of BMI. We also examined the association between adipokine tertiles and incident VTE in other supplemental models.

STATA 16.0 version (StataCorp LP, College Station, TX) software package was used to perform the analysis.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 1,888 study participants by VTE status. The mean ± SD age was 64.7 ± 9.6 years and for BMI was 28.2 ± 5.2 kg/m2; 49.8% were women. The participants self-identified as White (40%), Chinese (13%), Black (20%) and Hispanic (26%) Americans.

After a median follow up of 9.7 (5.0-12.4) years, 78 participants developed VTE. Compared to those who did not develop VTE, participants who did were more likely to be older, have a higher BMI, leptin, resistin and systolic blood pressure, as well as be taking antihypertensive medication. There was no significant difference in the levels of adiponectin by VTE status.

Association between Adipokines and Incident VTE

The Kaplan-Meier curves for time to VTE event by adipokine tertiles are presented in Figure 2. There was similar time to VTE events among tertiles of adiponectin and resistin (log rank, p-value >0.05); however, time to VTE event differed among tertiles of leptin (log rank, p-value <0.05). In unadjusted analysis, highest tertiles of leptin and resistin were significantly associated with greater risk of incident VTE (Table S1). This trend persisted for leptin after adjusting for model 1 covariates (Table S2) but not in other models (Tables S3 and S4).

Adipokine levels were then examined as a continuous measure. After adjustment for model 1 covariates of age, race/ethnicity, smoking and physical activity, a 1-SD increment in log-transformed resistin was associated with 38% increase in the hazard of incident VTE [HR 1.38, 95% CI (1.09-1.74)] (Table 2). The magnitude of association was slightly attenuated after further adjusting for BMI in addition to model 1 variables [1.31 (1.04-1.66)] but the association was marginally increased after adjusting for VAT instead of BMI [1.40 (1.09-1.80)]. Conversely, in adjusted analyses, there were no significant associations of adiponectin and leptin with incident VTE. In supplemental analyses, resistin levels remained associated with incident VTE even after adjusting for CVD risk factors and waist circumference (in place of BMI) (Tables S5 and S6, respectively), whereas no significant association was seen for adiponectin and leptin.

DISCUSSION

In this multiethnic cohort free of VTE, higher resistin levels were independently associated with greater risk of VTE, after approximately 10 years of follow up. These associations persisted even after adjusting for demographic and CVD risk factors as well as other measures of adiposity including BMI, waist circumference and CT measures of visceral fat. While higher tertiles of leptin appeared to be associated with a higher incidence of VTE events in unadjusted analysis and in model adjusting for demographic and behavioral risk factors, adiponectin and leptin were not significantly associated with VTE in all other adjusted models.

Prior to this analysis, the relationship with adipokines and VTE had not been well established. The few prior case control studies that examined the association between adipokines and VTE yielded conflicting results (8, 9). Although prior studies have shown that BMI is strongly associated with adipokine levels and VTE (7, 18), no study to the best of our knowledge had investigated these associations with incident VTE. Our results add to the literature by newly demonstrating an association between higher resistin levels and increased risk of incident VTE. Our findings may mirror preclinical studies linking resistin to the pathogenesis of VTE through increased expression of prothrombotic biomarkers such as matrix metalloproteinases-2 and 9 (MMP-2 and MMP-9) and plasminogen activator inhibitor 1 (PAI-1) (19). Additionally, resistin increases the release of endothelin-1, and upregulates chemokine expression and surface adhesion molecules (ICAM-1 and VCAM-1) (20), which are important chemical mediators that have been implicated in endothelial injury. Coupled with endothelial injury, the hypercoagulability and anti-fibrinolytic properties of resistin (21) are essential components of the Virchow’s triad which is vital to the pathogenesis of VTE. It should be noted that in a prior analysis from MESA, higher resistin levels were also associated with incident CVD, coronary heart disease and heart failure events (22).

Leptin is known to potentiate arterial and venous thrombosis through platelet adhesion, activation, and aggregation (23). Additionally, leptin upregulates endothelial cell expression of PAI-1 and may impair fibrinolysis and thrombus resolution (24). Thus it might be anticipated that leptin would be associated with higher VTE risk. We found that higher tertiles of leptin were significantly associated with increased risk of incident VTE in models

adjusting for demographic and behavioral risk factors. However, leptin levels were no longer significantly associated with VTE in models further adjusting for BMI and other measures of adiposity. In a prior analysis from MESA, leptin was also not associated with incident CVD after accounting for BMI (25); other analyses have indicated that associations linking leptin with coronary disease were largely dependent on BMI (26). Prior studies have found a strong correlation between leptin levels and BMI, which may explain why the associations of leptin with vascular outcomes were no longer seen in models that adjusted for BMI. This suggests BMI might be a potential mediator of these relationships (25, 26).

In contrast to resistin and leptin, adiponectin is considered to have vasculo-protective, anti-atherosclerotic and antithrombotic effects and may be associated with reduced risk of VTE (23, 27). However, contrary to hypothesis, we did not find any significant association between higher adiponectin levels and decreased risk of VTE.

Our study has several strengths. We were able to examine the associations of three relevant adipokines with the risk for VTE in a well-characterized multiethnic cohort. Adiponectin, leptin and resistin were measured by standardized and reproducible methods. Additionally, the availability of data on several covariates that were probable confounders of the relationship between the dependent and independent variables allowed for the adjustments of these covariates in our models.

However, our study should also be considered in the context of several limitations. As with any observational study, we cannot rule out residual confounding by unmeasured covariates. Adipokines were measured only once in MESA at either exam 2 or 3 so we could not examine the association between the changes in adipokine levels and the risk for VTE. The sample size of this study was small; therefore, we may not have been sufficiently powered to detect significant associations for the risk of VTE. To avoid overfitting our models, the relatively small number of VTE events precluded the adjustment of sociodemographic and CVD risk factors in our primary model, although we did perform this as an exploratory analysis.

In conclusion, higher resistin levels are associated with increased risk of VTE even after adjusting for demographic and CVD risk factors as well as other measures of adiposity. If the results of our studies are confirmed by cohort studies with a large sample size, quantitative assessment of resistin may add to existing screening and diagnostic modalities for individuals at higher risk for VTE. This may inform clinical risk stratification and aggressive management of patients with VTE for better outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ESSENTIALS

- The association between adipokines and incident venous thromboembolism (VTE) was not well established.
- We studied the prospective association between adipokine levels and incident VTE in the Multi-Ethnic Study of Atherosclerosis (MESA) participants.
- Of the 1,888 participants studied, 78 developed incident VTE events over a median follow up of 9.7 years.
- Higher resistin was independently associated with increased risk of VTE, even after accounting for adiposity indices.

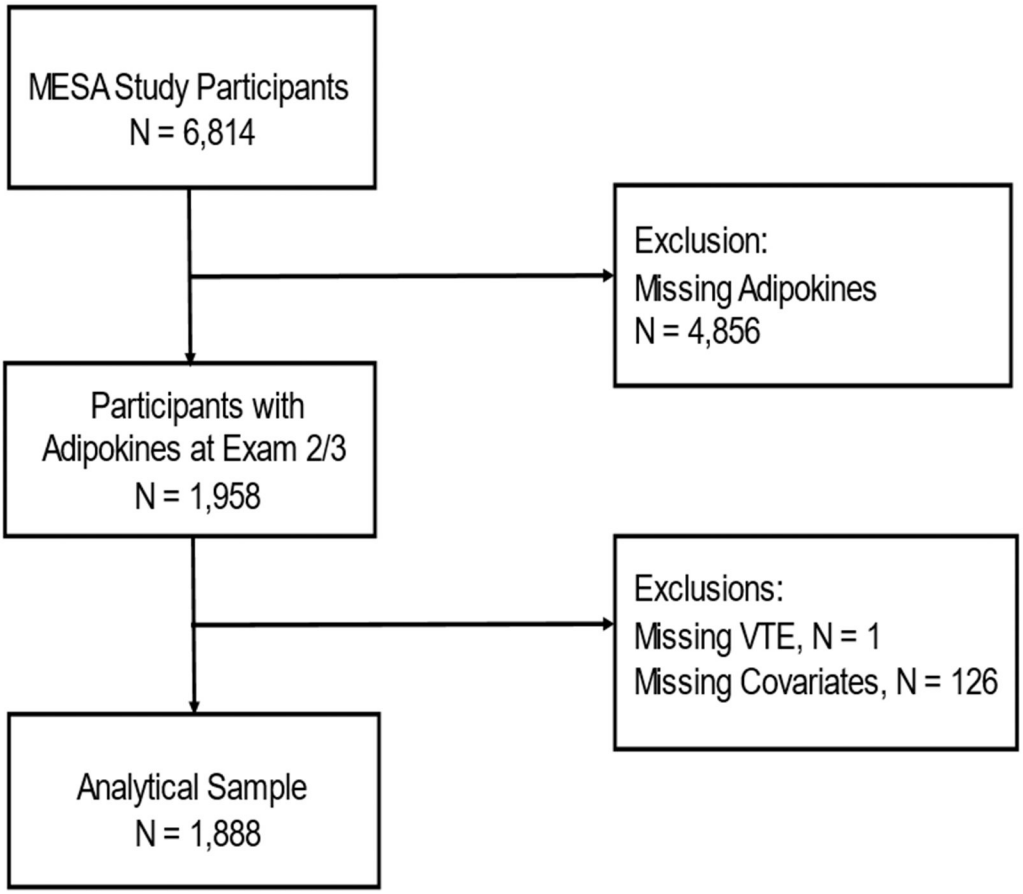

Figure 1.
Flowchart of study participants.

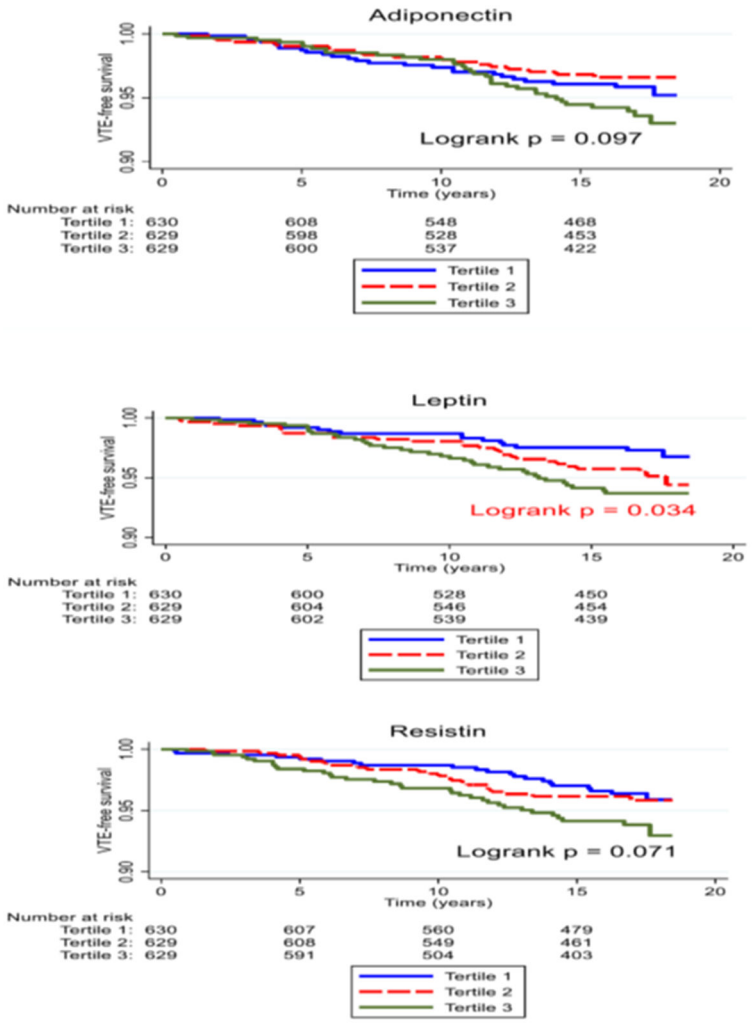

Figure 2.

Kaplan-Meier survival estimates of the unadjusted association between adipokines and venous thromboembolism

Table 1.

Baseline characteristics of study participants

	Total, N = 1,888	VTE, n = 78	No VTE, n = 1,810	P value
Age, years	64.7 ± 9.6	68.1 ± 8.9	64.6 ± 9.6	0.001
Sex				0.157
Women	941 (49.8)	45 (57.7)	896 (49.5)	
Men	947 (50.2)	33 (42.3)	914 (50.5)	
Race/Ethnicity				0.030
White	759 (40.2)	38 (48.7)	721 (39.8)	
Chinese-American	252 (13.4)	4 (5.1)	248 (13.7)	
Black	381 (20.2)	21 (26.9)	360 (19.9)	
Hispanic	496 (26.3)	15 (19.2)	481 (26.6)	
Education				0.233
≥ Bachelor's degree	679 (36.0)	33 (42.3)	646 (35.7)	
< Bachelor's degree	1209 (64.0)	45 (57.7)	1164 (64.3)	
Health Insurance				
Yes	1729 (91.58)	74 (94.9)	1655 (91.4)	0.285
No	159 (8.42)	4 (5.1)	155 (8.6)	
Physical activity, MET-minutes/week	3525.0 (1815.0 - 6387.5)	3105.0 (1470.0 - 5955.0)	3551.3 (1830.0 - 6405.0)	0.290
Smoking				0.070
Never	867 (45.9)	28 (35.9)	839 (46.4)	
Former, or current	1021 (54.1)	50 (64.1)	971 (53.6)	
BMI, Kg/m^2	28.2 ± 5.2	30.7 ± 5.9	28.1 ± 5.2	<0.001
Systolic blood pressure, mmHg	124.0 ± 20.9	131.4 ± 22.3	123.6 ± 20.8	0.001
Use of antihypertensive medication	828 (43.9)	50 (64.1)	778 (43.0)	<0.001
Diabetes	274 (14.5)	16 (20.5)	258 (14.3)	0.306
Total cholesterol	189.8 ± 35.3	183.6 ± 40.3	190.0 ± 35.1	0.111
HDL- C, mg/dl	51.4 ± 15.2	52.2 ± 17.5	51.4 ± 15.1	0.944
Use of lipid-lowering medication	474 (25.1)	22 (28.2)	452 (25.0)	0.519
Adiponectin, mcg/mL	17.3 (11.8 −26.2)	18.1 (12.3 - 31.0)	17.3 (11.8 - 25.8)	0.171
Leptin, ng/mL	13.5 (5.6 - 28.2)	17.4 (8.2 - 43.6)	13.3 (5.5 - 28.0)	0.008
Resistin, ng/mL	15.0 (11.9 - 19.0)	16.1 (12.7 - 21.8)	14.9 (11.9 - 18.9)	0.018
VAT, cm^2	165.2 ± 92.4	182.7 ± 90.1	164.4 ± 92.4	0.064

Abbreviations: BMI, Body mass index; HDL-C, High density lipoprotein cholesterol; MET, Metabolic equivalent of task; VAT, Visceral adipose tissue; VTE, Venous thromboembolism.

Data were presented as mean (SD), frequency (percentages) and median (IQR).

Sample sizes for VAT was 1764.

Table 2.

Hazard Ratio (95% CI) for VTE per 1SD of log-transformed adipokines

	Model 1	Model 2	Model 3
Adiponectin	1.14 (0.90 - 1.44)	1.27 (1.00 - 1.63)	1.27 (0.96 - 1.67)
Leptin	1.29 (1.00 - 1.66)	0.93 (0.68 - 1.26)	1.23 (0.94 - 1.61)
Resistin	**1.38 (1.09 - 1.74)**	**1.31 (1.04 - 1.66)**	**1.40 (1.09 - 1.80)**

Abbreviations: CI, Confidence interval; SD, Standard deviation; VTE, Venous thromboembolism; VAT, visceral adipose tissue.

Adipokines were natural log transformed and expressed as 1 SD for the analyses.

All the analyses were conducted using Cox regression models.

Statistically significant results at $p < 0.05$ are in bold font.

Model 1: Adjusted for age, race/ethnicity, smoking and physical activity.

Model 2: Adjusted for Model 1 covariates + body mass index.

Model 3: Adjusted for Model 1 covariates + VAT.