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Circulating Adipokines and Vascular Function: Cross-sectional Association in a Community-Based Cohort

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Abstract

Adipokines may be potential mediators of the association between excess adiposity and vascular dysfunction. We assessed the cross-sectional associations of circulating adipokines with vascular stiffness in a community-based cohort of younger adults. We related circulating concentrations of leptin and leptin receptor, adiponectin, retinol binding protein 4, and fatty acid binding protein 4 to vascular stiffness measured by arterial tonometry in 3505 Framingham Third Generation cohort participants free of cardiovascular disease (mean age 40 years, 53% women). Separate regression models estimated the relations of each adipokine to mean arterial pressure and aortic stiffness, as carotid femoral pulse wave velocity, adjusting for age, sex, smoking, heart rate, height, antihypertensive treatment, total and high-density lipoprotein cholesterol, diabetes, alcohol consumption, estimated glomerular filtration rate, glucose and C-reactive protein. Models evaluating aortic stiffness also were adjusted for mean arterial pressure. Mean arterial pressure was positively associated with blood retinol binding protein 4, fatty acid binding protein 4, and leptin concentrations (all $P<0.001$) and inversely with adiponectin ($p=0.002$). In fully adjusted models, mean arterial pressure was positively associated with retinol binding protein 4 and leptin receptor levels ($p<0.002$ both). In fully adjusted models, aortic stiffness was positively associated with fatty acid binding protein 4 concentrations ($p=0.02$), but inversely with leptin and leptin receptor levels ($p\leq0.03$ both). In our large community-based sample, circulating concentrations of select

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adipokines were associated with vascular stiffness measures, consistent with the hypothesis that adipokines may influence vascular function and may contribute to the relation between obesity and hypertension.

Keywords

adipokines; biomarkers; epidemiology; obesity; vascular function

Excess adiposity is associated with an increased risk of cardiovascular disease (CVD) events. On a parallel note, aortic stiffness also has been linked to an increased risk of CVD.[1, 2] Other studies, including from our group, have underscored the association of obesity and related comorbidities such as hypertension, dyslipidemia, and diabetes with increased vascular stiffness in community-dwelling individuals.[3, 4] These observations raise the possibility that adiposity may increase CVD risk in part through effects on vascular stiffness. Yet, mechanisms linking adiposity to vascular function are incompletely elucidated.

Toward identifying possible mechanisms, adipose tissue is biologically active, elaborating multiple compounds (often termed as adipokines) such as leptin, leptin receptor (LEP-R), adiponectin, fatty acid binding protein 4 (A-FABP), and retinol binding protein (RBP4). Adipokines may affect arterial structure and function, by multiple mechanisms including hyperglycemia, hyperinsulinemia, inflammation, activation of sympathetic activity, and vascular smooth muscle cell proliferation..[5, 6] The anatomical distribution of various adipose depots may also modulate the metabolic activity of adipokines.[7, 8] Previous work has suggested relations between individual adipokines and arterial stiffness.[9-11] Prior data also indicate adipokines may be altered in patients with hypertension.[12-15]

We hypothesized that higher concentrations of leptin, A-FABP, and RBP4, and lower concentrations of LEP-R and adiponectin would be associated with increased aortic stiffness, as reflected by CFPWV, and with elevated blood pressure, as assessed by mean arterial pressure (MAP). To test this hypothesis, we related circulating concentrations of a panel of adipokines to vascular stiffness in a large community-based sample of young to middle-aged adults.

METHODS

The longitudinal community-based Framingham Third Generation cohort, comprised of the grandchildren of the Original Framingham Cohort, was recruited between 2002 to 2005 to undergo their first examination cycle.,[16] During the examination visit, a targeted physical examination that included measurement of resting blood pressure and anthropometry was performed and a brief medical history that focused on cardiometabolic disease was obtained. Standardized questionnaires were used to assess diet, current smoking, alcohol use, and physical activity. Arterial tonometry was performed during the examination visit (see below). Laboratory evaluation of standard CVD risk factors was performed on venous blood sample obtained after an overnight fast. At the first examination cycle of this cohort, a panel of novel adipokines was measured on biosamples stored at −80° C without prior freeze thaw

cycles. Of the 4095 attendes who were eligible for the present investigation, we excluded 167 for missing tonometry data, 196 for missing adipokine levels, 177 for missing covariate data, and 50 individuals with prevalent CVD, yielding a final sample of 3505 participants for the present analyses, 86% of the eligible Third Generation cohort. All attendees gave written informed consent and the study protocol was approved by the Boston University Medical Center Institutional Review Board.

Adipokine Measurement

Commercially available kits were used to assay blood concentrations of adiponectin, leptin, LEP-R and RBP4 (R&D Systems Inc., Minneapolis, MN) and A-FABP (Biovendor Inc., Candler, NC). Mean interassay coefficients of variation for all adipokines were less than 10% as reported previously.[17]

Applanation Tonometry

After 5 minutes of rest, participants underwent applanation tonometry in a supine position.[2] The timing of the cardiac cycle was determined by electrocardiography, and measurements of systolic and diastolic blood pressures were obtained on the right arm of the supine participant using a semi-automated auscultatory method (Cardiovascular Engineering, Inc. Norwood MA). Arterial tonometry on right-sided carotid, brachial, radial, and femoral arteries was performed using a hand-held customized tonometer. Distances were measured from the suprasternal notch to each pulse measurement site using a caliper for the femoral site and a fiberglass tape measure for other sites. Arterial waveform signals were digitized (1000Hz), transferred to the core laboratory (Cardiovascular Engineering Inc, Norwood MA) and then analyzed blinded to all clinical data.

As previously described, the ECG-derived R wave was used as the reference point for signal averaging and timing waveforms.[3] Tonometry-derived signal averaged brachial waveform was calibrated to the brachial cuff systolic and diastolic blood pressure. The calibrated brachial artery waveform was then integrated to calculate MAP. The carotid waveform was used as a surrogate for central arterial pressure. The carotid waveform was calibrated to brachial waveform by assuming identical diastolic and MAP. Carotid femoral pulse wave velocity (CFPWV) was calculated by dividing the transit distance between carotid and femoral sites by the transit time difference between those sites. Carotid femoral transit distance was adjusted for parallel transmission by using the suprasternal notch as a fiducial point. CFPWV was inverse transformed in order to eliminate skewness and heteroscedasticity. Inverse CFPWV was multipled by −1000 to convert units to ms/m and restore directionality (high value corresponds to higher aortic stiffness).

Assessment of Covariates

Prevalent CVD was defined by the presence of cerebrovascular disease (stroke or transient ischemic attack), coronary heart disease (angina, or acute coronary syndrome, including myocardial infarction), congestive heart failure, or intermittent claudication, as adjudicated by the Framingham endpoints reveiw committee. Hypertension was defined as arm blood pressure ≥140/90 mm Hg or current use of anti-hypertensive medications. Diabetes was defined as fasting glucose concentration ≥126 mg/dl or the use of hypoglycemic

medications. Alcohol use was self-reported and quantified in fluid ounces per month. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. Estimated glomerular filtration rate(eGFR) was calculated by the Chronic Kidney Disease-Epidemiology Collaboration equation.[18] High-sensitivity C reactive protein was measured using the nephelometric method (Dade-Behring BN 100 nephelometer).

Statistical Analyses

The primary exposures of interest (independent variables) were circulating sex-standardized concentrations of the five adipokines. CFPWV, a measure of large artery stiffness, and MAP, a measure of steady-flow arterial pressure, were the primary dependent variables (separate models for each). The cross-sectional associations of adipokines with CFPWV and MAP were examined using sex-pooled multivariable generalized linear regression models, adjusting for age, sex, heart rate, height, diabetes, lipid levels (total cholesterol and HDL), anti-hypertensive treatment, smoking status, and eGFR. CFPWV models were additionally adjusted for MAP in order to account for potential effects of distending pressure on aortic stiffness. In additional analyses, we also adjusted for weight or waist circumference in order to evaluate whether adjustment for adiposity altered any of the observed associations of adipokines with vascular measures. Finally we added adjustment for alcohol intake, high sensitivity C-reactive protein as an index of inflammation, and fasting blood glucose as a continuous measure. Primary analyses treated adipokines as continuous variables. We also conducted analyses using sex-specific quartiles for each adipokine as predictors, with the first quartile serving as the referent and conducting a statistical test for trend across the quartiles. General estimating equations were used to account for the relatedness of individuals in the Third Generation cohort.[19] Statistical significance was indicated by a two-sided P-value of <0.05. SAS 9.1 (Cary, North Carolina) was used for all analyses.

RESULTS

The clinical and vascular stiffness characteristics of our young-to-middle aged adult sample (mean age 40±9 years, range 20 to 72 years, 53% women) are shown in Table 1. While age was similar for men and women, BMI, blood pressure, total cholesterol, smoking prevalence, and waist circumference tended to be higher in men, while HDL-C was higher in women. Leptin and adiponectin concentrations were susbtantially higher in women than in men. CFPWV and MAP were higher in men (p<0.001).

After adjustment for age, sex, anti-hypertensive treatment, total and HDL cholesterol, smoking, and diabetes, a one standard deviation higher value for leptin, RBP4, or A-FABP concentration was associated with approximately a 1-2 mm Hg higher MAP (P<0.0001 for all; **Table 2**), while a similar increment in adiponectin was associated with a 0.6 mm Hg lower MAP (p=0.002). MAP was higher across quartiles of, RBP4, A-FABP, and leptin but was lower across quartiles of adiponectin (P for trend<0.0001 for all, **Figure 1**). Upon adjustment for weight (or alternatively waist circumference; results not shown for latter), RBP4 remained positively associated with MAP while LEP-R emerged as positively related to MAP, (P<0.001 for both). After final adjustment including alcohol intake, C-reactive

protein and blood glucose levels, the associations of RBP4 and LEP-R were essentially unchanged.

Blood leptin and LEP-R were inversely related (p<0.03 for both) to CFPWV whereas A-FABP was positively related (p=0.008;**Table 3**). In comparison by quartile-based models, CFPWV decreased across LEP-R quartiles but rose across RBP4 quartiles (P for trend= 0.02 and 0.05, respectively, **Figure 2**). Upon additional adjustment for weight (or waist), the relations of LEP-R and A-FABP with CFPWV were maintained in terms of directionality and statistical signficance. However leptin emerged also being inversely related to CFPWV (p=0.02;**Table 3**). These associations for FABP, LEP-R, and leptin were largely unchanged by further adjustment for inflammation, alcohol consumption, and blood glucose levels.

DISCUSSION

Principal findings

In this comprehensive cross-sectional analysis of a large, community-based sample of young-to-middle-aged adults, we related circulating concentrations of a panel of five key adipokines to arterial stiffness measures. After multivariable adjustment, higher RBP4, A-FABP, leptin levels and lower adiponectin levels were associated with higher MAP. Upon additional adjustment for weight, the positive association of RBP4 and MAP remained robust, and an additional new positive association of LEP-R and MAP emerged with little change after additional adjustment for inflammation (C-reactive protein), alcohol use, or blood glucose concentrations. Higher A-FABP and lower LEP-R were associated with higher CFPWV. These 2 relations were only modestly attenuated after adjustment for weight and intriguingly an inverse relation of leptin concentrations and CFPWV also emerged, with modest change after additional adjustment for alcohol intake, blood glucose, and inflammation. The observed association patterns support the hypothesis that adipokines are associated with altered small and large artery function, and also suggest that several of the observed relations of adipokines persist after accounting for weight, inflammation, alcohol use, and other confounders.

Circulating adipokines could mediate the well-described relation between obesity and increased vascular stiffness. Underscoring the relevance of vascular stiffness, metaanalysis indicates that 1 SD higher CFPWV is associated with a hazard ratio of 2.04 (1.70-2.44) for major CVD events in younger adults (<61 years of age).[1, 2, 20] Adipokines influence glucose metabolism and insulin resistance, and these relations can vary according to fat quantity and regional location.[21, 22] Therefore studying adipokines also may provide mechanistic insights into the link between glucose intolerance, insulin resistance, and arterial dysfunction.[23] Adipokines can directly modulate endothelial cell and vascular smooth muscle cell activation, proliferation and migration.[24] Indeed, as noted above, prior work has shown that obesity is associated with endothelial dysfunction and increased vascular stiffness.[21, 24, 25] Overall, our findings expand upon prior reports of the relations between adipokines and vascular function. Prior studies relating circulating levels of adipokines and measures of vascular function have been largely focused on a single biomarker and evaluated limited measures of vascular function.

Leptin is a key long-term energy homeostasis signal.[26, 27] Circulating LEP-R binds to leptin and reduces its bioavailability.[26, 28] Both markers have been linked to BMI and fat distribution.[29] In obesity, paradoxical elevation of leptin occurs due to end-organ resistance.[7, 26] Relevant to the present hypothesis, leptin receptors are present on vascular cells and in atherosclerotic lesions, suggesting a role for leptin in vascular physiology.[24] Studies also have shown that leptin increases renal sympathetic activation, which increases arterial pressure.[30] Leptin has been described in youth, young adults, and older adults to be associated with aortic stiffness.[9, 31] These previous investigations also demonstrate the relation between obesity and vascular stiffness is attenuated with the inclusion of leptin, suggesting leptin may mediate the association between adiposity and vascular stiffness. Consistent with these prior studies, our investigation found higher LEP-R, which would lead to lower free leptin signalling, was associated with lower CFPWV and higher MAP. Further adjustment for weight influenced the relations observed for leptin. Paradoxically, after adjustment for weight both higher leptin and LEP-R were associated with lower CFPWV. The associations for leptin and LEP-R may parallel so-called ‘leptin resistance‘ where leptin levels are counterintuitively elevated in obese persons. Despite replete energy stores, altered cell bound leptin receptor signal transduction inadequately senses energy repletion status, while circulating LEP-R activity is largely unaffected. [13, 26] The association of LEP-R with lower CFPWV and higher MAP is complex to reconcile given our cross-sectional analysis. It may be that LEP-R has different effects on small muscular arteries versus larger conduit arteries. For example, normal arterial aging may affect one arterial system (conduit arteries) and spare others (muscular arteries), perhaps due to different tissue constituents.[32, 33] It is unlikely that the LEP-R vascular associations are causally interrelated as the counterregulatory response to lower CFPWV would not engender higher MAP. While our results are generally consistent with a protective role for free leptin in promoting lower arterial stiffness and lower MAP, caution should be exercised in drawing causal inferences from our cross-sectional data.

Adiponectin exerts favorable metabolic and cardiovascular effects by promoting insulin sensitivity and fatty acid oxidization and inhibiting gluconeogenesis.[17, 34, 35] Adiponectin increases nitric oxide availability and suppresses vascular smooth muscle cell proliferation and migration.[36, 37] Endothelial function is diminished in adiponectin knock-out mice.[5, 6] Hypoadiponectinaemia has been associated with impaired endothelial function in patients with hypertension and diabetes.[5, 38] Higher adiponectin levels were associated with lower arterial stiffness and better endothelial function in healthy and clinical samples;[11] however, we were not able to detect a relation between adiponectin level and CFPWV. Data are conflicting regarding the relation between adiponectin and hypertension.[12-14] In metaanalysis, circulating adiponectin concentrations appear to be lower in hypertensive persons.[39] Our data are consistent with these metaanalytic findings as lower adiponectin was associated with higher MAP. Our data are also consistent with the hypothesis that adiponectin may mediate the vascular consequences of excess weight as inclusion of weight in the model attenuated the association of adiponectin with MAP.

RBP4 and A-FABP have been implicated as mediators of insulin sensitivity and lipid metabolism.[40-42] Cross-sectional data from the Framingham Study demonstrated that circulating levels of RBP4 were associated with insulin resistance and elevated blood

pressure but, intriguingly, were not associated with BMI[17] Other investigators also found inconsistent relations between RBP4 and obesity.[28, 43, 44] Despite the inconsistent relation with excess weight, small, patient-based studies support a relation between RBP4 and vascular function as higher circulating and urinary RBP4 concentrations have been associated with carotid intima media thickness and arterial stiffness.[10, 45, 46] Our results demonstrating positive associations of RBP4 and MAP with little attenuation after weight adjustment, are consistent with prior results. Blood A-FABP levels are elevated in persons with insulin resistance and hypertension but lower in treated hypertension.[15, 47] Therefore, our observed positive association of A-FABP with MAP (in models not adjusted for weight) and with CFPWV (models without and with adjustment for weight) are consistent with previous literature.

Our investigation has several limitations including its cross-sectional observational study design, which precludes causal or temporal inferences. Our observations have uncertain generalizability to younger or elderly people of non-white ethnicity due to its constitution with predominantly young and middle-aged adults of European ancestry. While we focused on 5 key adipokines, other adiposity biomarkers may mediate relations of obesity to vascular dysfunction. We used a simple measure of adiposity, body weight, rather than quantitative measures of visceral fat depots, which are known to be more strongly related to adipokine levels.[7, 48, 49] As these analyses are hypothesis-generating, we did not correct for multiple statistical testing. Nonetheless, if we use an overly conservative Bonferroni correction (p of 0.005, i.e., 0.05/10 for relating 5 biomarkers to 2 primary vascular stiffness measures), several observed associations still remain statistically significant.

PERSPECTIVES

Leveraging contemporaneous tonometry and adipokine assays measured in a large well-characterized community-based sample, we observed novel relations of several circulating adipokines with vascular stiffness and MAP. The study findings are consistent with the notion that adipokines may be important mediators of the association of excess adiposity with vascular dysfunction. Additional studies are warranted to examine temporal relation between adipokines, adiposity, and vascular dysfunction.

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Disclosures

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NOVELTY AND SIGNIFICANCE

1) What is new?

- In a large group of younger adults, we studied the relations between five blood proteins and hormones derived from fat tissue and the stiffness of large and small arteries.

2) What is relevant?

- Large and small blood vessel stiffness explains current and predicts future high blood pressure.

3) Summary

- Key fat tissue-produced blood proteins are related to large and small artery stiffness even after accounting for participants‘ weight
- Therefore these fat-tissue related blood proteins may have a role in the presence and/or development of high blood pressure

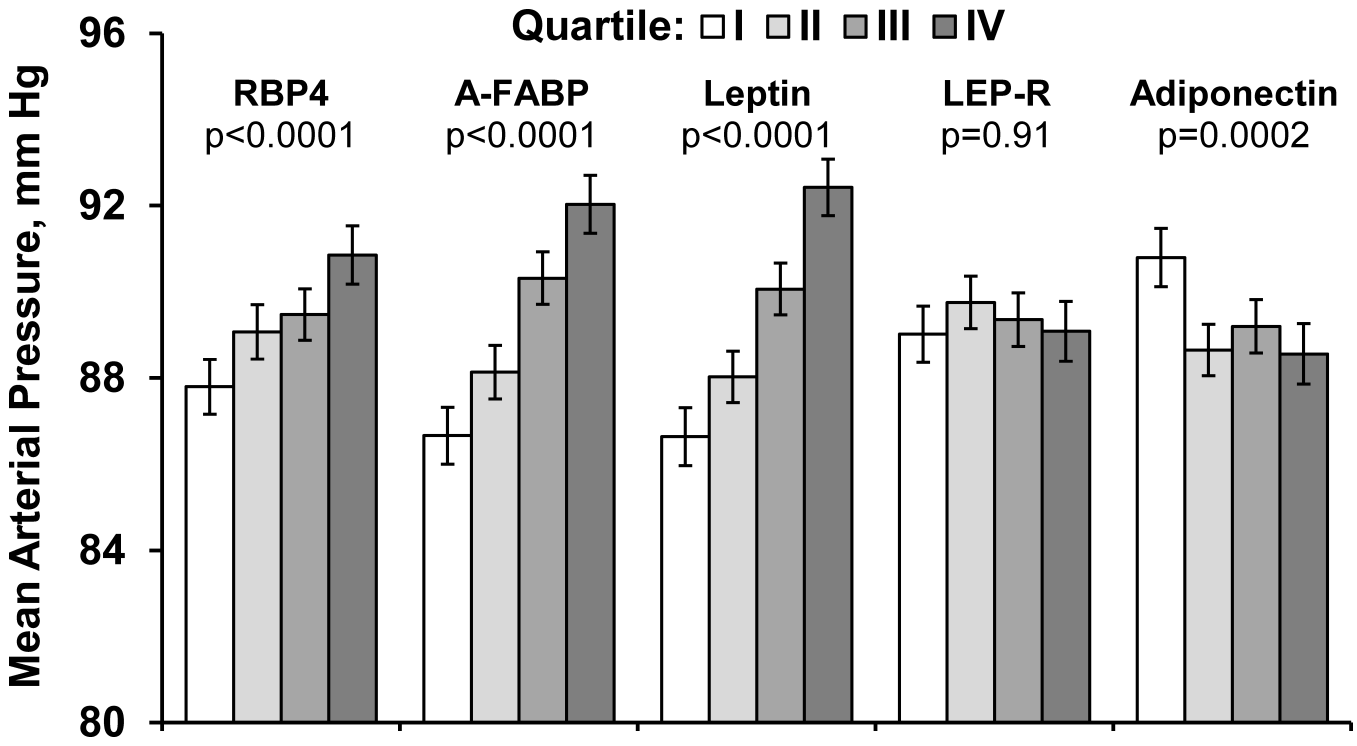

Figure 1.

Shows average mean arterial pressure levels in groups defined according to sex-specific quartiles of each adipokine.

Adjustment covariates included age, sex, heart rate, height, anti-hypertensive treatment, total and HDL cholesterol, smoking, diabetes. Error bars represent 95% confidence intervals.

Abbreviations: MAP- mean arterial pressure, LEP-R- leptin receptor, ug/mL-micrograms per milliliter, A-FABP- fatty acid binding protein 4, RBP4- retinol binding protein 4.

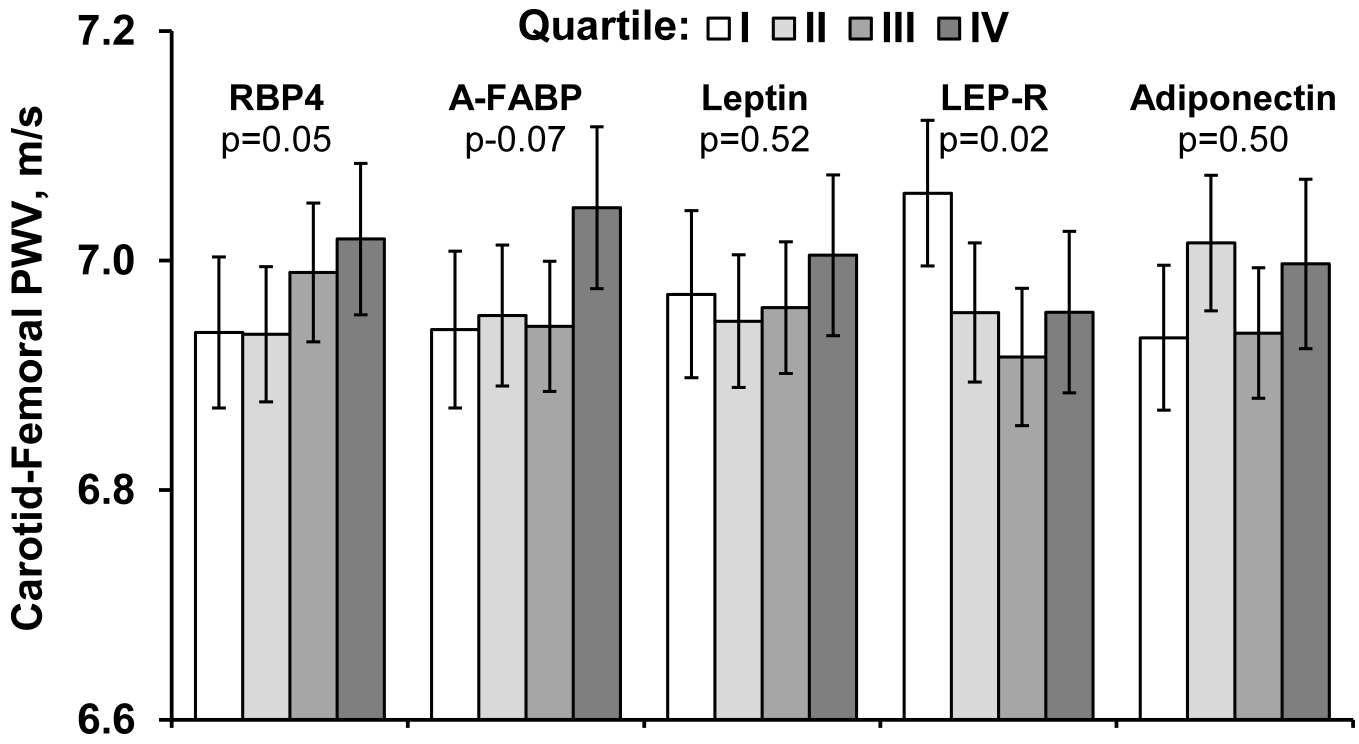

Figure 2.

Shows the average carotid-femoral pulse wave velocity levels in groups defined according to sex-specific quartiles of each adipokine.

Adjustment covariates included adjusted for age, sex, heart rate, height, anti-hypertensive treatment, total and HDL cholesterol, smoking, diabetes and mean arterial pressure. Error bars represent 95% confidence intervals.

Abbreviations: CFPWV- carotid femoral pulse wave velocity, LEP-R- leptin receptor, ug/mL- micrograms per milliliter, A-FABP- fatty acid binding protein 4, RBP4- retinol binding protein 4.

Table 1

Characteristics of the study sample by sex (N=3505)

Characteristic	Men (n=1644)	Women (n=1861)	P value
Clinical			
Age, years	40 ± 9	40 ± 9	0.39
Body mass index, kg/m^2	27.6±4.4	25.4±5.3	<0.0001
Height (meters)	1.78±0.07	1.64±0.06	<0.0001
Heart rate, bpm	61±10	63±10	<0.0001
Systolic blood pressure, mm Hg	120±12	113 ± 14	<0.0001
Diastolic blood pressure, mm Hg	78±9	72±9	<0.0001
Hypertension, %	20 (n=325)	11 (n=199)	<0.0001
Total cholesterol, mmol/L	4.99± 0.96	4.77± 0.86	<0.0001
HDL-C, mmol/L	1.22±0.32	1.59±0.41	<0.0001
Glucose	98±16	92±18	<0.0001
Diabetes, %	3 (n=49)	2 (n=38)	0.07
Current Smoking, %	16 (n=267)	14 (n=259)	0.05
Alcohol (ounces per month)	13.9±19.0	5.9±7.9	<0.0001
Waist circumference, cm	98±12	87±14	<0.0001
eGFR, mL/min per 1.73 m2	99±17	99±19	0.82
C reactive protein()	2.01±4.24	2.85±4.98	<0.0001
Adipokines			
RBP4, ng/ml	43.8±10.0	38.0±10.5	<0.0001
A-FABP, ng/ml	16.4±8.0	20.8±11.9	<0.0001
Leptin, ng/ml	5.7±5.4	16.7±15.6	<0.0001
LEP-R, ng/ml	19.0±8.1	20.1±8.9	<0.0001
Adiponectin, ug/ml	6.1±3.7	11.1±5.7	<0.0001
Tonometry			
CFPWV, m/s	7.4±1.4	6.6±1.2	<0.0001
Mean arterial pressure, mm Hg	92±10	87±11	<0.0001

Values are % (n), or mean± SD

Abbreviations: kg/m^2- kilograms per meters squared, bpm- beats per minute, mmol/L- millimoles per liter, mm Hg- millimeters of mercury, cm- centimeters, eGFR- estimated glomerular filtration rate, ml/min per 1.73 m2- milliliters per minute-1.73 meters squared body surface area, ng/mL- nanograms per milliliter, LEP-R- leptin receptor, ug/mL- micrograms per milliliter, A-FABP- fatty acid binding protein 4, RBP4- retinol binding protein 4, CFPWV- carotid femoral pulse wave velocity, m/s- meters per second

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Table 2

Associations of each adipokine with mean arterial pressure

	Model 1 *		Model 2 †		Model 3 §	
Adipokine	**Regression coefficient per SD (95%CI)**	**P-value**	**Regression coefficient per SD (95%CI)**	**P-value**	**Regression coefficient per SD (95%CI)**	**P value**
RBP4	1.31 (0.94,1.68)	<.0001	1.28 (0.93,1.51)	<0.001	1.15 (0.78, 1.51)	<0.001
A-FABP	1.77 (1.34,2.20)	<.0001	0.35 (−0.08,0.79)	0.11	0.29 (−0.15, 0.73)	0.20
Leptin	2.09 (1.70,2.48)	<.0001	0.16 (−0.32,0.65)	0.50	0.17 (−0.31, 0.65)	0.48
Lep-R	−0.10 (−0.44,0.25)	0.58	0.53 (0.20,0.87)	0.002	0.52 (0.19, 0.85)	0.002
Adiponectin	−0.64 (−1.05,−0.23)	0.0023	−0.09 (−0.49,0.30)	0.64	0.00 (−0.40, 0.39)	0.99

Beta coefficient per standard deviation(SD) of sex-standardized biomarkers as in Table 1.

Abbreviations: Lep-R- leptin receptor, A-FABP- fatty acid binding protein 4, RBP4- retinol binding protein 4

*Model 1: adjusted for age, sex, heart rate, height, anti-hypertensive treatment, total and HDL cholesterol, smoking, and diabetes.

†Model 2: adjusted for Model 1 covariates and body weight.

§Model 3: adjusted for Model 2 covariates plus estimated glomerular filtration, alcohol, glucose, log transformed c reactive protein.

Table 3

Associations of each adipokine with transformed CFPWV (−1000/CFPWV)

	Model 1 *		Model 2 †		Model 3 §	
Adipokine	**Regression coefficient. per SD (95%CI)**	***P* Value**	**Regression coefficient. per SD (95%CI)**	***P* Value**	**Regression coefficient. per SD (95%CI)**	***P* Value**
RBP4	0.58 (−0.08,1.23)	0.09	0.60 (−0.06,1.25)	0.08	0.58 (−0.08,1.25)	0.09
A-FABP	1.14 (0.54,1.73)	0.0002	0.96 (0.25,1.67)	0.008	0.88 (0.16,1.60)	0.02
Leptin	−0.03 (−0.70,0.64)	0.93	−1.06 (−1.95,−0.18)	0.02	−1.22 (−2.12,−0.32)	0.008
LEP-R	−0.79 (−1.35,−0.24)	0.005	−0.65 (−1.21,−0.08)	0.02	−0.65 (−1.21,−0.08)	0.03
Adiponectin	0.22 (−0.54,0.97)	0.57	0.38 (−0.40,1.15)	0.34	0.47 (−0.31,1.25)	0.24

Beta coefficient per standard deviation (SD) of sex standardized biomarkers as in Table 1.

Abbreviations: LEP-R- leptin receptor, A-FABP- fatty acid binding protein 4, RBP4- retinol binding protein 4, CFPWVcarotid femoral pulse wave velocity, m/s- meters per second

*Model 1: adjusted for age, sex, heart rate, height, anti-hypertensive treatment, total and HDL cholesterol, smoking, diabetes and mean arterial pressure.

†Model 2: adjusted for Model 1 covariates and body weight.

§Model 3: adjusted for Model 2 covariates plus estimated glomerular filtration, alcohol, glucose, log transformed c reactive protein.