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Authors
Zahner, Greg J
Ramirez, Joel L
Spaulding, Kimberly A
et al.

Publication Date
2019-06-01

DOI
10.1016/j.jss.2019.01.023

Peer reviewed

HHS Public Access

Author manuscript

J Surg Res. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

J Surg Res. 2019 June ; 238: 48–56. doi:10.1016/j.jss.2019.01.023.

Leptinemia is Associated with Peripheral Artery Disease

Greg J. Zahner[1], **Joel L. Ramirez**[1], **Kimberly A. Spaulding**[1,2], **Sukaynah A. Khetani**[1,2], **Warren J. Gasper**[1,2], **Carl Grunfeld**[3,4], **Nancy K. Hills**[5], **Anne L. Schafer**[3,5,6], and **S. Marlene Grenon**[1]

[1]Department of Surgery, University of California, San Francisco, San Francisco, CA, USA

[2]Vascular Surgery Section, Veterans Affairs Medical Center, San Francisco, CA, USA

[3]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[4]Metabolism Section, Veterans Affairs Medical Center, San Francisco, CA, USA

[5]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

[6]Endocrine Research Unit, Veterans Affairs Medical Center, San Francisco, CA, USA

Abstract

Introduction: Leptin, adiponectin, and resistin are in a class of hormones called adipokines that are produced by adipocytes and have been implicated in the causal pathway of atherosclerosis. We examined the association between adipokine levels and PAD, hypothesizing that after adjusting for fat mass, leptin and resistin would be higher, while adiponectin would be lower, in patients with PAD.

Methods: A cross-sectional sample of 179 predominately male (97%) vascular surgery outpatients were recruited from the San Francisco Veterans Affairs Medical Center (SFVAMC). PAD was defined as either an ankle-brachial index (ABI) <0.9 plus symptoms of claudication, or prior revascularization for symptomatic PAD (n=141). Controls had an ABI ≥0.9 and no history of atherosclerotic disease (n=38). Adipokines were assayed using commercially available ELISA kits and values were log-transformed. Fat mass was measured using bioelectrical impedance.

Results: In an analysis adjusting for body mass index (BMI) and atherosclerotic risk factors, higher serum leptin was associated with PAD (OR 2.54, 95%CI 1.07–6.01, p=.03), while high

Correspondence: S. Marlene Grenon, MD, CM, MMSc, FRCSC, Division of Vascular and Endovascular Surgery, UCSF, 400 Parnassus Avenue, A-501, San Francisco, CA 94143-0957, USA. marlene.grenon@ucsf.edu.

Author Contributions: GJZ, JLR, NKH, and SMG were involved in the conception and the design of the study. KAS and SAK were involved in the collection of the data. All authors were involved in the analysis and interpretation of the data. GJZ, JLR, and NKH were involved in the statistical analysis. GJZ and JLR wrote the initial manuscript and all the authors were involved in critically revising, editing, and giving final approval of the manuscript. GJZ and SMG obtained funding while SMG maintained overall responsibility of the study.

The Author Disclosure Statement: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Note: The abstract was presented at the 2018 Academic Surgical Congress in Jacksonville, Florida.

molecular weight (HMW) adiponectin was inversely associated, though not significantly (OR 0.60, 95%CI .33–1.08, p=.09). Resistin was not associated with PAD. Sensitivity analyses using fat mass/height^2 rather than BMI yielded similar results.

Conclusion: These results indicate that after adjusting for BMI or fat mass, serum leptin levels are positively and independently associated with PAD, while HMW adiponectin might be inversely associated. Using a more representative, non-veteran sample, further investigations should focus on the potential role of adipokines in the pathophysiology of PAD as well as determine whether leptin levels have clinical utility in predicting PAD outcomes.

Keywords

Peripheral artery disease; vascular biology; adipokines; leptin; adiponectin

INTRODUCTION

Peripheral artery disease (PAD) is a progressive atherosclerotic disease of the peripheral arterial system. Although it has been established that inflammation plays a key role in the pathogenesis and outcomes of PAD, less is known about the role of adipokines, a class of hormones released by adipose cells, which includes leptin, adiponectin, and resistin. Specifically, leptin is a peptide hormone originally discovered to play a role in metabolism due to the development of obesity in mice lacking a functioning *ob* gene, which encodes leptin.[1] Normally, leptin is released by adipocytes and acts on receptors in the hypothalamus to reduce hunger and increase energy expenditure.[2] Elevated leptin levels in obese individuals are thought to result from increase adipose tissue combined with hypothalamic leptin insensitivity.[3] In addition to leptin's well-established role in satiety and energy expenditure, it has also been associated with inflammation, endothelial dysfunction, and oxidative stress, as isoforms of leptin's receptor have been found in many peripheral sites including endothelial cells and platelets.[4]

Although studies on the potential cardiovascular effects of leptin remain controversial, leptin has been reported to impair nitric oxide production[5,6] and lipid metabolism[7] in endothelial cells. Additionally, leptin has been reported to modulate platelet aggregation[8,9], smooth muscle cell proliferation[10,11], vascular cell adhesion molecule[12], and several inflammatory markers.[13] These findings suggest that leptin plays a role in inflammation and endothelial injury and has prompted the investigation of leptin's role in the atherosclerotic pathway and in cardiovascular disease. While results of these studies have varied, leptinemia has been reported to be associated with decreased arterial distensibility[14], increased intima-media thickness[15], myocardial infarction[16,17], coronary stent restenosis[18], stroke[19,20], and increased 5-year cardiovascular risk.[21] For example, in one study of 382 CAD patients, high baseline leptin was associated with worse vascular outcomes in adjusted analysis, as measured by the occurrence of death due to cardiac cause, myocardial infarction, stroke, or revascularization (inclusive of percutaneous or surgical coronary revascularization).[22] Additionally, in the large prospective WOSCOPs trial, baseline leptin levels were associated with coronary events independent of body mass index (BMI).[21] More specifically, the study by Wallace et al. found that for each one standard deviation increase in leptin, the relative

risk of the combined endpoint of myocardial infarction, cardiac death, or coronary revascularization, increased by 20%.

Resistin and adiponectin may also play a role in vascular health. Resistin has an unclear role in energy metabolism, but appears to reduce insulin sensitivity and is found at the greatest concentrations in adipose stromal tissue and monocytes.[2] Unlike leptin and resistin, adiponectin levels are lower in obese individuals and it appears to play a counteractive, protective role such as through increasing energy expenditure.[2] In a review of the literature, Fantuzzi & Mazzone note that resistin activates adhesion molecules, induces migration of vascular smooth muscle cells, and increases production of inflammatory cytokines. Adiponectin antagonizes several of these effects and appears to be cardioprotective.[23] For example, elevated levels of resistin have been reported to be correlated with systemic inflammation and to predict coronary artery calcification in a large cohort of asymptomatic nondiabetic patients in the Study of Inherited Risk of Coronary Atherosclerosis.[24] Meanwhile lower levels of adiponectin have been found to predict progression of coronary artery calcification[25] and elevated levels of adiponectin have been reported to be protective against myocardial infarction in men.[26] These characteristics and initial findings indicate that the adipokines are of potential interest to clinicians and researchers working on atherosclerotic disease.

Adipokines vary with the fat mass of an individual; leptin has a strong positive association with fat mass and BMI, whereas adiponectin levels have a negative association.[27] However, there is mixed evidence regarding whether resistin positively correlates with BMI.[27,28] Additionally, at higher levels of fat mass, the variability of adipokine level increases.[3] High BMI has not been associated with prevalent PAD[29] and review of the National Health and Nutrition Examination Survey (NHANES) found that those with PAD were deficient in several macro and micronutrients.[30] Therefore, adipokine levels are associated with BMI, but BMI is not associated with PAD.

We hypothesize that as BMI levels increase, the increased variability of adipokines for a given BMI is associated with the presence of PAD. For two people with the same BMI, we hypothesize that the person with the higher leptin level is more likely to have PAD. Therefore, we propose that by adjusting for BMI, adipokine levels may be independently associated with PAD when controlling for a variety of atherosclerotic risk factors in a cross-sectional sample of vascular surgery outpatients.

METHODS

Participants

Between April 2011 and July 2016, 179 participants (97% male) were recruited from the vascular surgery outpatient clinic at the San Francisco Veterans Affairs Medical Center (SFVAMC) as part of ongoing trials on the use of high-dose fish oil supplementation (NCT 01310270 & NCT 01979874).[31] Participants were defined as having PAD if they had symptoms of claudication and an abnormal ankle-brachial index (ABI <.9). Additionally, participants were considered to have PAD if they had a prior history of peripheral revascularization for symptomatic PAD, regardless of ABI. Finally, participants were

defined as controls if they had no prior history of atherosclerotic vascular disease, which included PAD, CAD, or cerebrovascular disease, and a normal ABI (≥.9). Controls were drawn from the clinic population for the treatment of non-PAD vascular diseases, such as aneurysmal disease and venous disease. To be eligible for inclusion, all participants were at least 35 years of age and had no severe hepatic (Child-Pugh ≥ B), renal (creatinine ≥ 2 mg/dL), or non-vascular inflammatory disease (e.g. requiring immunosuppressive medications). Participants were excluded if they had a severe acute illness within the last 30 days. Each participant gave written, informed consent. The study was reviewed and approved by the University of California, San Francisco (UCSF) Committee on Human Research as well as the SFVA Research and Development Office.

Measures

Demographic variables including age, sex, and race were collected for all study participants. Data on atherosclerotic risk factors including smoking history measured in pack years (i.e., number of years smoking an average of one pack per day) and comorbidities including hyperlipidemia, hypertension, diabetes, and CAD, were also ascertained. Additionally, current use of aspirin, beta-blockers, statins, or ACE-inhibitors was recorded. Data on diet was not systematically analyzed as part of the study because much of the available research has found that the effects of diet on adipokine levels are explained by changes in weight or fat mass,[32,33] with the exception that high protein diets may increase adiponectin relative to a high carbohydrate diet.[34]

Anthropometric data included measurement of waist circumference, height and weight for calculating BMI, brachial artery blood pressure, and an ABI for each lower extremity using established techniques.[35] A subset of participants (PAD = 107, controls = 27) also had fat mass calculated using bioelectrical impedance analysis (RJL Quantum 101Q; RJL Sciences, Clinton Township, MI, USA), however this was later removed from the study protocol in order to reduce the time needed for each participant's visit. Since depression[36] and anxiety[37] have been reported to be associated with alterations in adipokine levels, each participant was also asked to fill out a Patient Health Questionnaire-9 (PHQ-9) and a post-traumatic stress disorder (PTSD) checklist – civilian version (PCL). Thresholds diagnostic of depression and PTSD were set at the standard level of PHQ-9 ≥ 10 and PCL ≥ 40, respectively.[38,39]

Blood was obtained from each participant in a fasting state for measuring lipids, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hsCRP) in the clinical lab. Plasma was isolated from the remaining blood samples and stored at −80°C until thawed and analyzed for adipokine levels by a core research lab. Leptin, high molecular weight (HMW) adiponectin, and resistin were measured using commercially available ELISA kits from RnD Systems according to manufacturer's instructions. To ensure reliability of the data, each of the adipokines were run twice for each participant and average values were recordedThose with a constant of variance greater than the *a priori* cut-off of >20% were excluded from further analysis (leptin n=10; adiponectin n=13; & resistin n=1).

Statistical Analysis

Data were analyzed using STATA version 14 (StataCorp, College Station, Texas). For normally distributed continuous variables, summary statistics were reported using mean and standard deviation while median and interquartile range were reported for skewed variables. Categorical variables were summarized using frequency and percentage. Comparisons between characteristics of subjects with and without PAD were performed using *t*-tests for continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and Fisher's exact tests for categorical variables. Pearson correlations were used to assess the relationship between individual adipokines and BMI.

Unadjusted comparisons between PAD and control subjects were made for all variables of interest using univariate regression models. To improve model fit, right-skewed variables including leptin, adiponectin, resistin, and hsCRP were log-transformed.

Next, three multivariable models were built for examining the association of PAD with the logged levels of leptin, adiponectin, and resistin individually as the primary predictor while adjusting for BMI. Although BMI measures adipose tissue imperfectly,[40] it is readily available in a clinical setting and was therefore used for the primary analyses. Sensitivity analyses were subsequently performed that adjusted for fat mass, as measured by bioelectrical impedance, divided by height^2 (analogous to the calculation for BMI). Covariates for all models were selected *a priori* and included well established atherosclerotic risk factors including age, race (defined as Caucasian vs. other), hypertension, hyperlipidemia, diabetes, pack years, and eGFR. Sex was excluded from the models since 97% of the sample was male. History of prior revascularization, ABI, and CAD were excluded since they were used to define participants as either PAD or controls. Additional models are reported which included statin use, depression, and PTSD as covariates. For leptin, specifically, additional analyses were performed to determine whether leptin was associated with inflammation, as measured by hsCRP. All primary models were assessed for goodness of fit and the presence of potentially influential outliers.

RESULTS

Subjects with PAD (n=141) were more likely to have hypertension, hyperlipidemia, diabetes, and CAD compared to controls (n=38). They were more likely to take aspirin, statins, and beta-blockers. The eGFR was lower in patients with PAD, while the number of pack-years was higher. Diastolic blood pressure was paradoxically lower in PAD as well as LDL levels, which may be due to higher use of beta-blockers and statins among participants with PAD (Table 1). Unadjusted differences between PAD and controls for leptin (median: 9.4 ng/mL, IQR: 6.4–18.9 vs. median: 9.7, IQR: 5.4–17.2, p=.49), adiponectin (median: 3.8 ug/ml, IQR: 2.3–7.7 vs. median: 4.5, IQR: 2.3–12.1, p=.34) and resistin (median: 8.1 ng/mL, IQR: 6.2–10.7 vs. median: 7.7, IQR: 5.7–10.5, p=.51) were all small and not statistically significant. One participant had an outlying resistin level greater than 10 standard deviations from the mean and was excluded from analysis.

To explore the relationship between the adipokines and BMI, Pearson correlations found that leptin (rho=.65, p<.001) and log(leptin) (rho=.70, p<.001) were each strongly correlated

with BMI (Figure 1). The relationship between leptin and BMI demonstrated increased variability at higher levels of BMI, which improved with log-transforming leptin, as confirmed by Cameron & Trivedi's decomposition of IM-test. Adiponectin had a small, inverse correlation with BMI (rho=−.22, $p<.004$) (Supplemental Figure S1), whereas resistin demonstrated no correlation with BMI ($p=.89$) (Supplemental Figure S2).

While a univariate analysis found no relationship between log(leptin) and PAD (OR 1.17, 95% CI .79–1.74, $p=.44$), adjusting for BMI revealed a positive association between log(leptin) and PAD (OR=1.69, 95% CI 0.97–2.95, $p=.06$), which reached statistical significance in multivariable analysis controlling for several atherosclerotic risk factors (OR 2.54, 95%CI 1.07–6.01, $p=.03$) (Table 2). The lack of a statistically significant relationship in the univariate analysis is suggestive of negative confounding from BMI. Including statin use or PTSD and depression as additional covariates did not alter the results. Each one-SD increase in log(leptin) was associated with more than double the odds of PAD (OR=2.35). Using waist circumference in lieu of BMI also did not affect the results. Excluding all PAD patients with comorbid CAD yielded a positive association between increasing log(leptin) and PAD, but with the reduced sample size, these results did not reach statistical significance (OR 1.93, 95%CI 0.80–4.64, p=.14). In sensitivity analyses adjusting for fat mass/height^2, rather than BMI, log(leptin) was associated with PAD when controlling for fat mass (OR 2.34, 95% CI 1.19–4.60, $p=.01$), although this association was slightly attenuated in multivariable analysis (OR 2.30, 95% CI 0.97–5.44, $p=.06$).

A Pearson correlation found a small but statistically significant positive relationship (rho=.16, $p=.04$) between log(hsCRP) and log(leptin). However, unlike leptin, log(CRP) was not independently associated with PAD (OR 0.73, 95% CI 0.45–1.17, $p=.19$). Additionally, adding log(hsCRP) as an additional covariate to the log(leptin) multivariable model did not change the results and log(leptin) maintained its statistically significant association with PAD.

Adiponectin was not associated with reduced odds of PAD with (OR 0.74, 95%CI 0.47–1.16, $p=.19$) or without (OR 0.83 95% CI 0.54–1.28, $p=.39$) adjustment for BMI. In the primary multivariable model, adiponectin was inversely associated with PAD, but it did not reach statistical significance (OR 0.60, 95% CI 0.33–1.08, $p=.09$) (Table 3). When replacing BMI with fat mass/height^2, the results were similar.

Finally, resistin was not associated with PAD in univariate (OR 1.13, 95% CI 0.45–2.84, $p=.80$), bivariate (OR 1.20, 95% CI 0.46–3.13, $p=.71$), or multivariable analysis (OR 0.66, 95% CI 0.19–2.27, $p=.51$). A multivariable sensitivity analysis with fat mass/height^2 had similar results (Table 4).

DISCUSSION

The results of the present study demonstrate in a cross-sectional sample of predominately male Veterans that there is an independent association between leptin and PAD when controlling for either BMI or fat mass/height^2 along with several traditional cardiovascular risk factors. Of note, the seemingly null relationship between leptin and PAD in univariate

analysis became unmasked when controlling for BMI. This finding is consistent with previous studies showing a lack of association between BMI and PAD, but a strong association between leptin and BMI. These results demonstrate that for a given BMI, higher leptin is associated with PAD. Additionally, the models indicate that the more clinically accessible measure of BMI, despite its known limitations,[40] can be used in lieu of more precise fat mass measurements such as bioelectrical impedance. Furthermore, the results also suggest that leptin's association with PAD is independent of systemic inflammation. Higher adiponectin levels may also be independently associated with lower odds of PAD, but data in this sample were too variable to detect a statistically significant association. These results a suggest a potential clinical role for leptin apart from more traditional measures like hsCRP, which was not independently associated with PAD in this study, or total cholesterol, which was already well-controlled through use of statins in this sample.

Currently, limited data exist on the relationship between leptin and PAD, although the presumed mechanisms underlying the development of PAD are like mechanisms underlying coronary artery and cerebrovascular atherosclerosis. Gherman & Mironiuc reported an association between elevated leptin and decreased adiponectin with the presence of PAD in a case-control cohort.[41] However, this analysis did not statistically adjust for comorbidities, BMI, or other potential confounders. In unadjusted analysis, there was no significant association between leptin levels and PAD in our cohort. However, after adjusting for BMI or fat mass/height^2, leptin was independently associated with PAD, suggesting that for a given BMI, higher levels of leptin are associated with PAD. This is notable because there is a wide range in leptin levels for a given BMI, particularly at higher BMI.[3]

Like leptin, studies of the relationship between adiponectin and PAD are limited. Lower levels of adiponectin have been reported to be associated with CAD[42] as well as PAD[41,43–45]. With regards to PAD outcomes, lower levels have been associated with lower ABI, shorter walking distance to claudication,[46] and adverse cardiovascular events.[47] Ho *et al.* reported that in an all-female cohort followed for a median of 13.2 years, adiponectin levels were lower in patients who developed PAD.[48] These results suggest that higher adiponectin may play a protective role against the development of PAD or atherosclerosis. Although lower levels of adiponectin were observed in PAD patients relative to controls in the present study's adjusted analysis, these results did not reach statistical significance. Therefore, this relationship should be explored further in a larger cohort.

Resistin levels have been associated with incident cardiovascular disease, coronary stent restenosis, and heart failure[49–52]. Zheng *et al.* and Gherman & Mironiuc both reported elevated levels of resistin in patients with PAD.[41,53] In this study, resistin did not increase with BMI and resistin levels did not differ between patients with and without PAD. While the reason for the divergence from previous studies is unclear, it is possible that resistin has a greater association with systemic inflammation rather than the presence of PAD itself. Zheng *et al.* and Gherman & Mironiuc both reported significant differences in CRP between their control and PAD groups, whereas this was not the case in the present study[41,53], potentially owing to the large number of risk factors among participants in the control group.

While the current literature on the role of adipokines in atherogenesis is variable, several studies have consistently identified relationships between higher leptin and lower adiponectin levels with PAD. It is currently unclear whether these adipokines play a role in the causal pathway of PAD or if they are simply markers of other unmeasured vascular risk factors. Improved understanding of the relationship between adipokines and PAD could identify new therapeutic pathways or new markers of surgical outcome, functional outcome, disease progression, or disease severity.

Limitations

This study has several limitations. The homogeneity of this Veteran patient population (mostly senior, male, and Caucasian) limits the generalizability of the results. Particularly, the nearly all male sample limits generalizability and there are known differences in adiposity by gender.[40] The sample was also too small to disaggregate the relationship between leptin and PAD versus CAD; therefore, the association may be between leptin and systemic atherosclerosis rather than specifically to PAD. Additionally, a larger sample may have increased the statistical power to detect a significant between-group difference in the level of adiponectin. It is also possible that ceasing to conduct bioelectrical impedance late in study recruitment resulted in failure to detect small inaccuracies arising from adjustment by BMI; however, due to the lack of difference in the sensitivity analysis with fat mass, there is reason to believe this was not the case. Additionally, date on use of fibrates or niacin were not collected along with use of other lipid-lowering medications such as statins. While statin use was found to have no effect in this study, prior research suggests that use of fibrates and niacin may modulate adipokine levels.[54,55] For the 40% of participants in the PAD group that had previously undergone revascularization, this study did not identify whether they had previously experienced critical limb ischemia, therefore the results cannot determine whether adipokine levels have any relationship with a history of chronic limb ischemia. Finally, owing to the cross-sectional nature of the study design, directionality of a potential causal relationship between adipokines and PAD cannot be accurately inferred.

CONCLUSION

The present study demonstrates in a Veteran cohort that elevated serum leptin is independently associated with the presence of PAD after adjustment for BMI or fat mass. Whether leptin is simply an associated biomarker or potentially plays a causal role in the development of PAD remains unknown. Additionally, larger studies in other populations will be needed to make a more conclusive determination with regards to adiponectin and PAD. In conclusion, the study provides intriguing evidence for a potential relationship between leptin and PAD, warranting further research that could potentially reveal new therapeutic pathways or new markers of disease outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number TL1 TR001871 with additional student research support from the Society for Vascular Surgery Student Research Fellowship Award and the American Heart Association Student Scholarship (GJZ, JLR). Furthermore, this work was supported by start-up funds from the University of California San Francisco and the Northern California Institute for Research and Education, by Award Number KL2RR024130 from the National Center for Research Resources, Award Number 1K23HL122446–01 from the National Institute of Health/NHLBI, and a Society for Vascular Surgery Seed Grant and Career Development Award (SMG). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The funding organizations were not involved in the design and conduct of the study, collection, management, analysis, and interpretation of the data, or preparation, review or approval of the manuscript.

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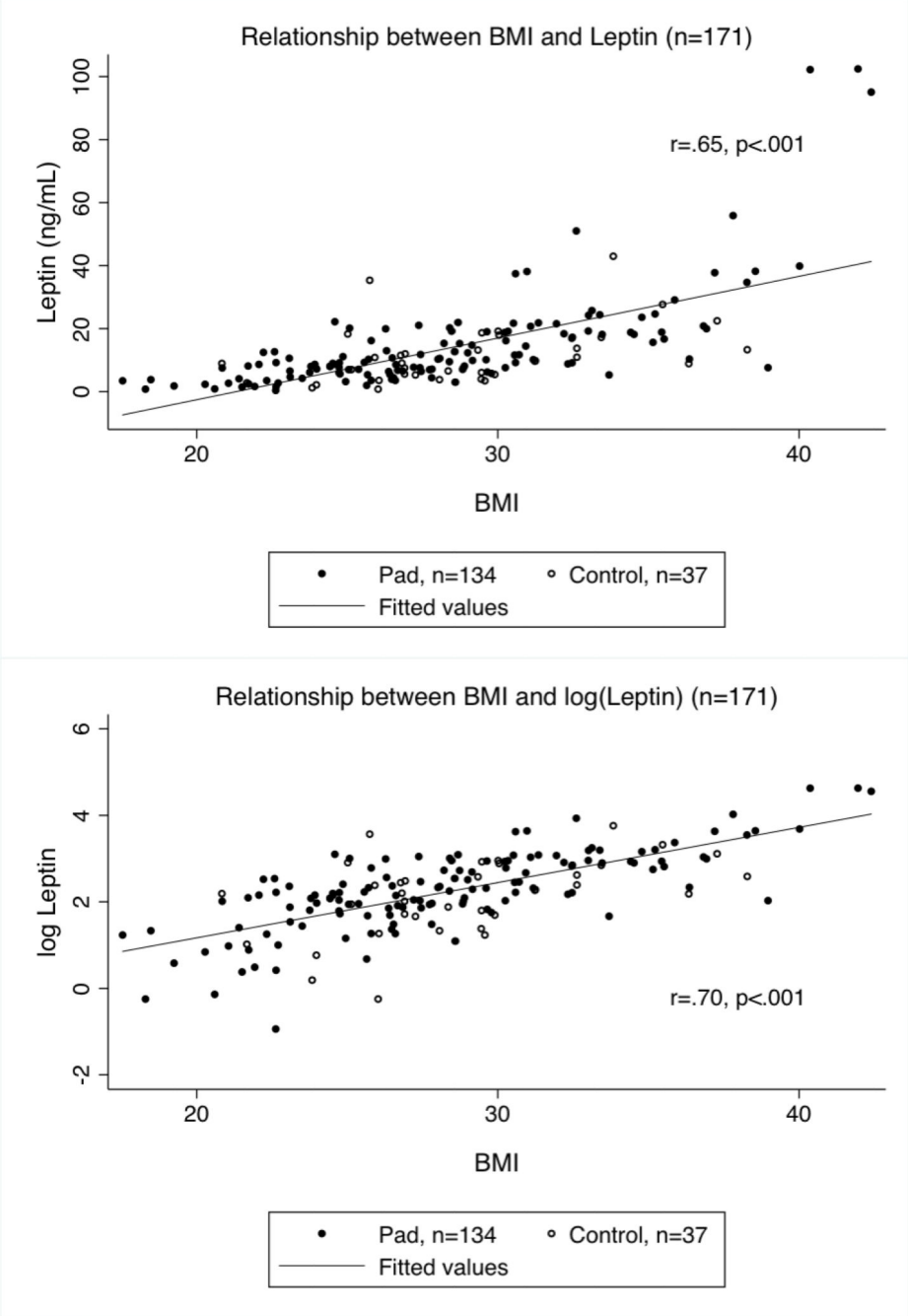

Figure 1.
The relationship between BMI and leptin (n=171).

Table 1.

Characteristics of Patients with PAD and Controls

Characteristics	PAD (n=141)		Controls (n=38)		P-value[a]
	n/mean/median	%/(SD)/ IQR	n/mean/median	%/(SD)/ IQR	
Demographics					
Age	69.0	(7.4)	67.8	(9.1)	.40
Male Sex	138	98%	35	92%	.11
Caucasian	105	74%	26	68%	.54
Comorbidities and Risk Factors					
Body Mass Index (kg/m^2)	28.1	(5.3)	29.2	(4.2)	.23
Waist Circumference (cm)	100	(13)	101	(12)	.60
Pack Years	43	(34)	17	(22)	**<.01**
Hypertension	132	94%	26	68%	**<.01**
Hyperlipidemia	119	84%	26	68%	**.04**
Diabetes Mellitus	51	36%	6	16%	**.02**
Coronary Artery Disease[b]	60	43%	0	0%	**<.01**
Depression (PHQ-9 score ≥ 10)	19	19%	3	11%	.40
PTSD (PCL-C ≥ 40)	22	22%	3	11%	.28
Systolic Blood Pressure (mm Hg)	139	(19)	135	(16)	.23
Diastolic Blood Pressure (mm Hg)	77	(11)	81	(8)	**.02**
Ankle Brachial Index (ABI)[b]	0.72	(0.16)	1.11	(0.12)	**<.01**
History of Revascularization[b,c]	56	40%	0	0%	**<.01**
Medications					
Aspirin	103	73%	20	53%	**.02**
Ace-inhibitor	64	45%	13	34%	.27
Beta-blocker	83	59%	10	26%	**<.01**
Statin	116	82%	23	61%	**.01**
Laboratory Studies					
Leptin (ng/mL)[d]	9.4	6.4–18.9	9.7	5.4–17.2	.49
Adiponectin (ug/ml)[d]	3.8	2.3–7.7	4.5	2.3–12.1	.34
Resistin (ng/mL)[d]	8.1	6.2–10.7	7.7	5.7–10.5	.51
Total Cholesterol (mg/dL)	159	(40)	173	(35)	.05
LDL (mg/dL)	85	(34)	101	(30)	**.01**
HDL (mg/dL)	46	(14)	46	(12)	.82
Triglycerides (mg/dL)	145	(90)	133	(106)	.49
eGFR (mL/min)	75	(24)	87	(24)	**.01**
HbA1C (%)	6.2	(1.3)	5.9	(1.4)	.24
hsCRP (mg/L)[d]	2.4	1.6–5.5	2.9	1.0–5.2	.61

[a]Continuous characteristics are summarized by mean (SD) with between-groups p-values calculated using a ttest. Categorical variables were summarized by number (%) with p-values calculated using Fisher's exact test.

[b] History of CAD, prior peripheral revascularization, and ABI were all used to distinguish participants between PAD and control groups.

[c] History of prior revascularization includes revascularization for PAD as well as CAD

[d] Skewed continuous variables were reported as a median along with the interquartile range (IQR) of 25-75%. Pvalues were calculated using a Wilcoxon rank sum.

Abbreviations: standard deviation (SD), interquartile range (IRQ), patient health question (PHQ-9), PTSD checklist - civilian version (PCL-C), low density lipoprotein (LDL), high density lipoprotein (HDL), estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), and high-sensitivity C-reactive protein (hsCRP).

Table 2.

Multivariable Associations of log(Leptin) with PAD

Predictor[a]	Univariate			Multivariable Analysis w/ BMI			Multivariable Analysis w/ Fat Mass/ Height^2		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
log(Leptin) (n=171)									
log(Leptin)	1.17	(.79–1.74)	.44	2.54	(1.07–6.01)	**.03**	2.30	(.97–5.44)	.06
BMI (kg/ht^2)	0.97	(.90–1.04)	.43	0.76	(.63-.92)	**.01**	-	-	-
Fat Mass (kg/ht^2)	0.97	(.87–1.08)	.59	-	-	-	0.76	(.61-.96)	**.02**
Age	1.02	(.97–1.07)	.43	0.99	(.92–1.06)	.77	1.02	(.94–1.10)	.68
Caucasian	1.41	(.64–3.11)	.39	1.51	(.46–4.98)	.50	1.43	(.43–4.73)	.56
Diabetes	2.98	(1.16–7.64)	**.02**	3.28	(.76–14.3)	.11	2.36	(.57–9.78)	.24
Hypertension	6.67	(2.54–17.5)	**<.01**	10.2	(2.13–49.1)	**<.01**	9.78	(1.62-58.9)	**.01**
Hyperlipidemia	2.28	(.98–5.30)	.06	0.72	(.17–2.93)	.64	0.58	(.11–3.05)	.52
Number of Pack Years (per 5)	1.28	(1.15–1.43)	**<.01**	1.42	(1.20–1.67)	**<.001**	1.35	(1.14-1.60)	**<.001**
eGFR (10mL/min)	0.82	(.70-.96)	**.01**	0.77	(.60-.99)	**.04**	0.78	(.59–1.02)	.07

[a]Predictors were selected a priori and added to the multivariable model after running a univariate analysis for each predictor with PAD.

Abbreviations: odds ratio (OR), confidence interval (CI), body mass index (BMI), and estimated glomerular filtration rate (eGFR).

Table 3.

Multivariable Associations of log(Adiponectin) with PAD

Predictor[a]	**Univariate**			**Multivariable Analysis w/ BMI**			**Multivariable Analysis w/ Fat Mass/ Height^2**		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
log(Adiponectin)(n=166)									
log(Adiponectin)	0.83	(.54–1.28)	.39	0.60	(.33–1.08)	.09	0.57	(.30–1.10)	.10
BMI (kg/ht^2)	0.94	(.87–1.01)	.10	0.84	(.74–.95)	**.01**	-	-	-
Fat Mass (kg/ht^2)	0.96	(.86–1.07)	.45	-	-	-	0.86	(.73–1.01)	.07
Age	1.01	(.96–1.06)	.66	1.00	(.93–1.07)	.91	1.03	(.95–1.11)	.51
Caucasian	1.34	(.58–3.11)	.50	1.77	(.54–5.77)	.34	1.70	(.48–6.00)	.41
Diabetes	2.42	(.93–6.29)	.07	3.06	(.81–11.6)	.10	2.09	(.51–8.46)	.30
Hypertension	5.43	(1.95–15.2)	**<.01**	7.65	(1.75–33.4)	**.01**	12.7	(2.13–76.3)	**.01**
Hyperlipidemia	2.59	(1.07–6.28)	**.04**	1.34	(.35–5.10)	.66	0.52	(.10–2.85)	.45
Number of Pack Years (per 5)	1.23	(1.11–1.37)	**<.01**	1.26	(1.10–1.44)	**.001**	1.34	(1.13–1.59)	**.001**
eGFR (10mL/min)	0.82	(.70–.96)	**.01**	0.78	(.62–.97)	**.03**	0.72	(.55–.95)	**.02**

[a]Predictors were selected a priori and added to the multivariable model after running a univariate analysis for each predictor with PAD.

Abbreviations: odds ratio (OR), confidence interval (CI), body mass index (BMI), and estimated glomerular filtration rate (eGFR).

Table 4.

Multivariable Associations of log(Resistin) with PAD

Predictor[a]	Univariate			Multivariable Analysis w/ BMI			Multivariable Analysis w/ Fat Mass/ Height^2		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
log(Resistin) (n=145)									
log(Resistin)	1.12	(.45–2.84)	.80	0.66	(.19–2.27)	.51	0.94	(.21–4.12)	.94
BMI (kg/ht^2)	0.93	(.86–1.01)	.09	0.88	(.78–1.00)	.06	-	-	-
Fat Mass (kg/ht^2)	0.96	(.86–1.06)	.40	-	-	-	0.90	(.77–1.06)	.20
Age	1.02	(.97–1.07)	.50	1.00	(.94–1.08)	.91	1.02	(.95–1.11)	.52
Caucasian	1.24	(.49–3.11)	.65	1.00	(.28–3.53)	1.00	0.97	(.27–3.43)	.96
Diabetes	2.62	(.92–7.40)	.07	2.32	(.58–9.39)	.24	1.79	(.45–7.19)	.41
Hypertension	4.24	(1.42–12.7)	**.01**	5.41	(.97–30.1)	.05	7.10	(1.17–43.2)	**.03**
Hyperlipidemia	2.50	(.95–6.62)	.07	0.75	(.17–3.35)	.70	0.58	(.11–2.96)	.51
Number of Pack Years (per 5)	1.31	(1.14–1.49)	**<.01**	1.40	(1.18–1.65)	**<.01**	1.37	(1.15–1.63)	**<.01**
eGFR (10mL/min)	0.77	(.64–.92)	**.01**	0.69	(.53–.90)	**.01**	0.70	(.52–.96)	**0.03**

[a]Predictors were selected a priori and added to the multivariable model after running a univariate analysis for each predictor with PAD.

Abbreviations: odds ratio (OR), confidence interval (CI), body mass index (BMI), & estimated glomerular filtration rate (eGFR).