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Authors

Ramirez, Joel L
Khetani, Sukaynah A
Zahner, Greg J
et al.

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Serum Resistin is Associated with Impaired Endothelial Function and a Higher Rate of Adverse Cardiac Events in Patients with Peripheral Artery Disease

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

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

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

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

Abstract

Objective: Resistin is a hormone that has been associated with metabolic syndrome and cardiovascular disease. The role of resistin in patients with peripheral artery disease (PAD) has not been fully explored. The present study seeks to understand the relationship between serum resistin, vascular function, and cardiovascular outcomes in patients with PAD.

Methods: One-hundred and six patients with PAD were recruited between 2011–2016. Patients attended a baseline visit during which a comprehensive vascular physiology assessment including medical and surgical history, radial artery tonometry, and flow mediated-vasodilation (FMD) was completed. A blood sample was drawn and serum resistin was assayed using enzyme-linked immunosorbent assay (ELISA) kits. Using the time of study enrollment as the time of origin, incident major adverse cardiac events (MACE) were identified by subsequent chart review and defined as a composite endpoint of myocardial infarction, coronary revascularization, transient ischemic attack, stroke, or death from a cardiac cause.

Results: Subjects had a mean age of 68±8 years, were largely Caucasian (75%), and had comorbidities commonly associated with PAD including hypertension (92%), hyperlipidemia

Correspondence: S. Marlene Grenon, MD, CM, MMSc, FRCSC, Department of Surgery, University of California, San Francisco & Surgical Services, Veterans Affairs Medical Center, Mail Code 112G, 4150 Clement St, San Francisco, CA 94121, USA, marlene.grenon@ucsf.edu Phone: 415-307-5275 Fax: 415-750-2181.

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(87%), coronary artery disease (37%), and diabetes mellitus (38%). After stratification by resistin quartile, higher resistin quartiles were significantly associated with older age, a greater number of pack years smoked, and lower estimated glomerular filtration rate. Despite similar comorbidities and medication use, endothelial function, as measured by FMD, was significantly lower with increasing resistin quartile (I: 9.1±3.3%, II: 7.1±3.5%, III: 5.8±4.0%, IV: 5.6±3.5%, p=.002). In multivariable linear regression, higher resistin quartiles (III and IV) were associated with lower FMD relative to quartile I after adjusting for several patient characteristics, medications, and comorbidities (III: −2.26, 95% CI: −4.51 to −0.01, p=.05, IV: −2.53, 95% CI: −4.87 to −0.20, p=.03). During a median follow-up period of 36 months (IQR: 29–45), 21 patients experienced the primary endpoint. In a Cox proportional hazards model adjusted for smoking status, coronary artery disease, and age, each 1 ng/mL increase in resistin was associated with a 10% increased risk of MACE (HR: 1.10, 95% CI 1.00 to 1.20, p=.04).

Conclusion: In patients with PAD, higher levels of resistin were associated with impaired endothelial function and an increased rate of MACE. These results suggest that resistin may be a marker or effector of impaired vascular physiology and adverse cardiac outcomes in patients with PAD. Further research is needed to determine the potential mechanisms by which resistin may impair endothelial function and increase MACE in this population.

Keywords

Peripheral artery disease; adipokines; resistin; flow mediated-vasodilation; endothelial function

INTRODUCTION

Resistin is an adipokine, a class of hormones released by adipocytes, that has been positively associated with fat mass[1] and insulin resistance[2,3]. Although the physiologic role of resistin in humans remains unclear, it has been hypothesized to contribute to the well-established link between obesity and diabetes mellitus[4], as well as the development of atherosclerosis[5]. Recent evidence has demonstrated that elevated resistin levels are associated with incidence and severity of coronary artery disease (CAD)[6], heart failure[7], and adverse cardiovascular events[7].

The mechanisms through which resistin could cause atherogenesis and result in poor cardiovascular outcomes have been examined in animal models and in patients without peripheral artery disease (PAD)[5]. Resistin has been reported to be associated with impaired vascular function[5,8], which is associated with the development of atherosclerosis[9], perioperative vents[10], and poor cardiovascular outcomes[11]. While resistin and its effects on vascular pathology are complex, its link to adverse cardiovascular events has been reported in patients with and without a history of cardiovascular disease[12-14].

Although the role of resistin has been explored in patients with cardiovascular disease, literature specific to patients with PAD is sparse. There is limited evidence suggesting that levels of serum resistin are elevated in patients with PAD[15–17]. Additionally, resistin has been associated with PAD severity and reduced amputation free-survival, suggesting that this hormone may play an important role in patients with PAD[18]. Exploration of resistin as a

surrogate marker or effector of impaired vascular function and poor outcomes may identify resistin as a valuable prognostic marker or therapeutic target among patients with PAD.

The objective of this study is to assess the relationship between serum resistin and vascular physiology measures (endothelial function and arterial stiffness) and the rate of major adverse cardiac events (MACE) in patients with PAD. It was hypothesized that elevated serum resistin is associated with increased vascular stiffness, decreased endothelial function, and an increased rate of MACE.

METHODS

Study Subjects

One-hundred and six patients presenting with PAD were recruited between April 2011 and July 2016 from the vascular surgery outpatient clinic at the San Francisco Veterans Affairs Medical Center (SFVAMC). Participants were defined as having PAD if they had symptoms of laudication and an ankle-brachial index (ABI) <0.9 or if they had a prior history of peripheral revascularization for symptomatic PAD, regardless of ABI. Additional inclusion criteria included, at least 35 years of age and had no severe hepatic (Child-Pugh ≥ B), renal (creatinine ≥ 2 mg/dL), or non-vascular inflammatory disease. Patients were excluded if they had a severe acute illness within the last 30 days or were taking any immunosuppressive medications. Several patients included in this study had originally participated in the OMEGA-PAD I trial(NCT01310270), which measured the effects of one month of fish oil supplementation on inflammation, endothelial function, and arterial stiffness[19]. Since this trial assessed inflammatory profiles, several of the inclusion criteria listed above were utilized. Additionally, this trial studied patients with “stable claudication”, which was defined as Rutherford categories 1–3 categories or a history of revascularization for claudication, therefore patients with critical limb ischemia were excluded. Institutional review board approval was granted for this study by the Committee on Human Research at the University of California, San Francisco as well as the SFVAMC Research and Development Office with all participants giving informed written consent.

Measurements

Demographics, Medical Comorbidities, and Anthropometrics—Demographic variables including age, sex, and race were collected for all study subjects through an intake questionnaire. Medical comorbidities including hyperlipidemia, hypertension, diabetes, and CAD were collected using the SFVAMC electronic medical record. Patients provided information regarding their current use of insulin, oral diabetes medications, aspirin, beta-blockers, statins, or ACE-inhibitors. ABI was measured in each lower extremity using previously established techniques[20].

Flow-Mediated Vasodilation—Endothelial function was measured by brachial artery flow-mediated vasodilation (FMD) using previously described methods[21]. A blood pressure cuff was placed on the upper arm and B-mode ultrasound (Philips HD11) with a broadband linear array transducer with a 3–12 MHz range (Philips L12–3) was used to locate the brachial artery. The mean diameter at baseline was then measured. A state of hyperemia was

then induced by inflating the blood pressure cuff until the brachial artery was completely occluded as confirmed by ultrasound. The brachial artery was occluded for five minutes. Then the cuff was deflated and post-hyperemic diameter was recorded for three minutes. Continuous edge-detection software (Brachial Analyzer, Medical Imaging Applications LLC, Coralville, IA) was used to analyze the images and calculate FMD. FMD, which is expressed as a percent and defined as [(hyperemia diameter – baseline diameter)/baseline diameter] multiplied by 100, was calculated.

Radial Artery Tonometry—Arterial stiffness was measured in a subset of patients (n=60) with an applanation tonometer using the SphygmoCor® system (AtCor Medical, Sydney, Australia). Calculation of the augmentation (AIX), as well as more detailed descriptions for tonometry measurements, have been previously described[21,22]. Briefly, radial artery tonometry was measured by applying the SphygmoCor® applanation tonometer to the right wrist. The AIX was then able to be calculated using pulse wave analysis due to the observation that the arterial waveform being examined is a composite of an anterograde pulse wave plus a component of the preceding wave that was reflected backward off of the arterial wall. Stiffer arteries are characterized by higher augmented pressures due to the collision and combination of the anterograde and retrograde pulse waves[23,24]. Calculation of the AIX, which is defined as [augmented pressure/(systolic blood pressure –iastolic blood pressure)], was then completed using the SphygmoCor®'s proprietary software[24]. The peripheral AIX was calculated directly and the central AIX was approximated using previously validated transfer equations[25] that are routinely used[26]. The central AIX was then normalized to 75 beats/min in order to adjust for variations in heart rate.

Laboratory Tests—A blood sample was obtained from each participant while in a fasting state at the initial study visit for measuring lipids, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hsCRP). Resistin was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems according to manufacturer's instructions by a core research lab. Each ELISA was run twice for each participant and for samples with a constant of variance <20%, the average value retained.

Major Adverse Cardiac Events—Subject electronic medical records were retrospectively reviewed for the occurrence of MACE, which were defined as myocardial infarction (MI), coronary revascularization, transient ischemic attack (TIA), stroke, or death from a cardiac cause[27] with enrollment in the study as the time of origin and December 2016 as the end of the study period. MI was defined as a detected rise in cardiac markers >99th percentile with at least one of the following: 1) ischemic symptoms, 2) new ST elevation or left bundle branch block, 3) development of Q waves, 4) imaging evidence of loss of viable myocardium, or 5) coronary thrombus identified by coronary angiography.

Statistical analysis

All statistical analyses were performed using STATA version 15.0 (StataCorp, College Station, Texas). Patients were stratified into groups by resistin quartile to assess differences in baseline characteristics while still providing some granularity in regard to the association

of levels of resistin with endothelial function. Quartiles of resistin were based upon the median level of resistin in the cohort. Summary statistics were reported using mean and standard deviation for continuous variables, along with frequency and percentage for categorical variables. Differences between resistin quartile groups were calculated using analysis of variance (ANOVA) with Bonferroni-corrected post-hoc pairwise comparisons for normally distributed continuous variables, Kruskal-Wallis test for continuous variables without a normal distribution (pack years smoked, hsCRP, and triglycerides), and a Fisher's exact test for categorical variables.

Unadjusted univariate linear regressions were performed in order to measure the relationship between resistin quartiles and FMD, peripheral AIX, and central AIX, normalized to 75 beats/min. Multivariable models were built to adjust for other patient demographics and comorbidities. Bivariate screening was used to select covariates for the multivariable models. In the bivariate analyses, resistin quartiles were used as the primary predictor of FMD, and several demographic characteristics and comorbidities were examined individually as potential covariates. Any covariate associated at the level of $p \leq .20$ was included in the multivariable model. Body mass index (BMI) and diabetes mellitus were included in the model *a priori* due to their previously reported relationship with resistin[1,3].

Cox proportional hazards models were used to calculate hazard ratios for MACE, using enrollment in the study as the time of origin. Due to the small number of events, resistin was modeled as a continuous variable in the Cox models rather than in quartiles. An initial model was built using resistin as the primary predictor of MACE. To determine whether the relationship between resistin and MACE was influenced by inflammatory status, a subsequent model was performed which also adjusted for hsCRP. A final multivariable model was then built in a stepwise fashion using a p-value cut-off of $p < .10$.

RESULTS

Study subjects had a mean age of 68±8 years, were largely Caucasian (75%) and male (97%), and had comorbidities commonly associated with PAD including hypertension (92%), hyperlipidemia (87%), CAD (37%), and diabetes mellitus (38%). Patients were then stratified into groups by resistin quartile (I: 2.6–5.9 ng/mL, II: 6.0–7.8 ng/mL, III: 7.9–10.5 ng/mL, IV: 10.6–24.3 ng/mL). Baseline demographics and patient characteristics are reported by resistin quartile in Table I. The mean age increased and eGFR decreased significantly with increasing resistin quartile. There was no significant difference in comorbidities, medication use, or PAD severity, as measured by Rutherford categories or ABI, between groups.

FMD decreased significantly by increasing resistin quartile (Table II). A Bonferroni post-hoc analysis identified significant differences between resistin quartile I and III ($p=.006$) and I and IV ($p=.004$) (Figure 1). In a univariate linear regression, resistin quartiles II, III, and IV were significantly associated with decreased FMD when compared to the lowest resistin quartile (I) (II: −1.99, 95% CI: −3.96 to −0.02, $p=.05$, III: −3.34, 95% CI: −5.29 to −1.39, $p=.001$, IV: −3.52, 95% CI: −5.48 to −1.55, $p=.001$). Increasing resistin quartiles remained significantly associated with decreased FMD in a multivariable model adjusted for

Caucasian race, BMI, diabetes mellitus, hypertension, eGFR, hsCRP, and beta-blocker and ACE-inhibitor use (Table III). Relative to the lowest resistin quartile (I), quartiles III and IV were independently associated with an absolute difference in FMD of −2.26% and −2.53%, respectively. There was no significant difference in the peripheral AIX or central AIX, normalized to 75 beats/min between resistin quartiles (Table II).

During a median follow-up period of 36 months (IQR: 29–45), 21 patients experienced a MACE (event rate of 20%). These events included: 13 myocardial infarctions or coronary revascularizations, 5 deaths from a cardiac cause, 2 strokes, and 1 TIA. Patients in the fourth quartile of resistin had a higher risk of MACE than patients in the first quartile (Figure 2). A univariate Cox proportional hazards model identified that resistin was associated with an increased rate of MACE (HR: 1.09, 95% CI: 1.01 to 1.18; p=.03), and adjustment for hsCRP did not affect the results. The final multivariable Cox proportional hazards model included CAD, tobacco use status, and age, which was added *a priori*. Other covariates included in the development of the model were Caucasian ethnicity, BMI, FMD, pack years smoked, diabetes mellitus, hyperlipidemia, hypertension, hsCRP, eGFR, and insulin, oral diabetes medications, aspirin, beta-blocker, statin, or ACE-inhibitor use. The resulting multivariable model revealed that serum resistin was independently associated with an increased rate of MACE (HR: 1.10, 95% CI: 1.003 to 1.200, p=.04) (Table IV). These results indicate a 10% higher rate of MACE for every 1 ng/ml increase in serum resistin. This would suggest a nearly 220% higher rate of MACE when comparing the lowest level of resistin with the highest level of resistin in this cohort.

A sensitivity analysis including FMD as a covariate in this model did not significantly alter the association, suggesting that resistin is associated with an increased rate of MACE, independent of its association with endothelial function. An additional sensitivity analysis that only adjusted for CAD and patient characteristics that were significantly different between baseline resistin quartile groups (age, pack years, eGFR, and FMD) yielded similar results as the initial model (HR: 1.13, 95% CI: 1.01 to 1.25, p=.03).

DISCUSSION

This study is the largest assessment of the relationship between serum resistin, vascular function, and incident MACE in patients with PAD. These results demonstrate that in a cohort of subjects with PAD, elevated serum resistin is independently associated with impaired endothelial unction, as measured by brachial artery FMD, and an increased rate of MACE. There was no observed association between resistin and arterial stiffness, as measured by the peripheral AIX and central AIX, normalized to 75 beats/min. These findings suggest that resistin may be a novel biomarker or effector of impaired endothelial function in patients with PAD. Moreover, resistin may be a novel predictor of MACE in a population with a high prevalence of traditional cardiovascular risk factors.

Results of the current study suggest that among patients with PAD serum resistin is not positively associated with fat mass, as BMI was not significantly different between resistin quartiles. Additionally, there were no differences observed in medication use between resistin quartiles, which suggests that these medications may have limited or no effect on

serum resistin levels in patients with PAD. Consistent with results of the current study, previous reports suggest that beta-blocker, ACE-inhibitor, and statin use is not associated with lower levels of serum resistin[28,29]. However, there are currently only a limited number of studies that measure the impact of medication use on serum resistin levels. Prospective studies or randomized clinical trials of patients with PAD would be required to more accurately assess the effect of medication use on resistin levels in this patient population

Studies with small sample sizes have demonstrated that elevated resistin is associated with impaired FMD in healthy subjects[30] and in patients with metabolic syndrome but without ardiovascular disease[31]. To date, only one study has examined this association in patients with PAD. In a cohort of 60 patients with intermittent claudication, Golledge *et al.* reported that serum resistin was not correlated with FMD (r=−0.11, p=.42);[32] however, this study may have been underpowered to detect a significant correlation.

Several mechanisms linking resistin and endothelial function have been described in the basic science literature. Resistin has been reported to increase cellular levels of reactive oxygen species that can impair endothelial dependent vasodilation by decreasing nitric oxide synthesis in porcine[33] and human coronary artery endothelial cells[34]. Resistin has also been reported to increase vasoconstriction of endothelial cells by promoting the release of the local vasoconstrictor endothelin-1[35]. Resistin could further contribute to endothelial dysfunction by upregulating the expression of the adhesion molecules vascular cell adhesion molecule-1[36] and intraellular adhesion molecule-1[36], as well as the chemokine monocyte chemotactic protein-135. The role of resistin in endothelial cell dysfunction has further been implicated with a downregulation of tumor necrosis factor-receptor-associated factor-3[35], which is a potent inhibitor of CD40 ligand-mediated endothelial cell activation. In addition to having several actions that directly affect endothelial cells, resistin has been associated with increased local[37] and systemic inflammation[38], which may further contribute to impaired endothelial function. However, previous reports suggest that inflammation only contributes to a portion of resistin's effects[39]. This is consistent with the results of the multivariable model reported in the current study, which found that adjustment for hsCRP did not affect the results. Additionally, renal dysfunction, as measured by eGFR, was statistically significantly lower with increasing resistin quartiles and independently associated with impaired FMD. Both of these findings are consistent with previous reports[40,41] and suggests that the findings in this study have external validity.

In the context of these proposed mechanisms, the findings of the current study suggest that resistin may be implicated in the pathogenesis of PAD in part by its effects on endothelial dysfunction. However, without a control group, further interpretation of the potential role that resistin may play in the pathogenesis of PAD is limited. Further research is required to determine whether resistin is a true causal determinant of impaired endothelial function in patients with PAD, which has the potential to provide an opportunity for targeted interventions to prevent the progression of disease. Alternatively, resistin may represent a novel biomarker of impaired FMD in this patient population, which would offer a net advantage over the more time-consuming and complex measurement of FMD.

The relationship between serum resistin and MACE in patients with CAD is well supported[42], and consistent with the findings in this cohort of patients with PAD. In a prospective nested case- control study of post-menopausal women, increased resistin was associated with an increased risk of incident stroke, independent of traditional stroke risk factors, endothelial function, and markers of inflammation[12]. The prospective Health, Aging, and Body Composition Study reported that increased resistin was independently associated with an increased risk of nonfatal myocardial infarction and cardiac-related mortality among patients ages 70–79[13]. Similarly, in a study of 140 patients undergoing percutaneous coronary intervention, elevated resistin was associated with an increased risk of MACE at 3-month follow-up[14]. The high prevalence of traditional cardiovascular risk factors typically present in patients with PAD makes existing risk stratification tools less useful in predicting cardiovascular outcomes. The results of this study suggest that resistin may play a role in cardiac risk stratification in this population.

Although the effect size of the reported relationship between resistin and MACE was modest, this association was independent of age and coronary artery disease, which are both strongly associated with MACE. Additionally, the high prevalence of traditional cardiovascular risk factors typically present in patients with PAD makes existing risk prediction tools less useful in predicting adverse cardiovascular events. As such, identification of novel predictors of cardiovascular risk in patients with PAD is important to be able to identify high-risk patients. Future studies should consider examining the incremental predictive benefit of including serum resistin in traditional models of risk prediction. Mechanisms have been proposed to mediate the relationship between resistin and rate of MACE. These hypothesized mechanisms include resistin's ability to increase vascular smooth muscle cell migration[43], plaque instability by the increased expression of CD40 ligand[35,44], adhesion molecule expression[36], and systemic inflammation[45]. However, several studies, including the current study, have identified a significant relationship between resistin and adverse cardiac events even after adjusting for hsCRP[42]. Menzaghi *et al.* recently reported the correlation of resistin with several cytokines that were found to be associated with an increased rate of MACE[46]. Although adjusting for hsCRP did not significantly alter the relationship between resistin and MACE in this cohort, it is possible that hsCRP alone is not representative of the full effects that resistin may have on inflammatory pathways and is not an adequate measurement of systemic inflammation. Given the previous evidence presented, it is likely that resistin affects several pathways that increase the risk of MACE.

Reports on the relationship between resistin and arterial stiffness are heterogeneous. Serum resistin has been significantly positively associated with arterial stiffness in healthy individuals[47]nd patients with CAD,[48] but not in patients with resistant hypertension[49] or patients on hemodialysis[50]. Similar to the association of resistin and endothelial function, studies that have assessed the relationship between resistin and arterial stiffness in patients specifically with PAD are lacking. The results of this study suggest that resistin may not be associated with increased arterial stiffness but is associated with impaired endothelial function in patients with PAD.

As our understanding of the mechanisms underlying PAD improve, it will be important to consider how resistin interrelates with each of these functions. Identifying the roles that resistin may play, may allow for a more thorough understanding of all of the factors that mediate PAD.

Limitations

The small sample size and small number of MACE reduces power. Arterial stiffness was only measured in a subset of the cohort (n=60), which further reduced power in those analyses and might have limited the ability to identify a statistically significant relationship. Determining whether changes in FMD were influenced by alterations in smooth muscle cells was unable to be determined as nitric-oxide independent vasodilation was not examined in all subjects. The patient population is representative of the VA population (mostly male and Caucasian) and might not be generalizable to the rest of the United States population. Furthermore, since this study did not include a control group of patients without PAD, differences in serum resistin between patients with and without PAD were not measured.

CONCLUSION

In summary, resistin was independently associated with impaired endothelial function but not arterial stiffness in patients with PAD. Additionally, resistin predicted an increased rate of adverse cardiac events independent of inflammatory status and endothelial function. Results of this study support the continued exploration of resistin as a predictor of adverse cardiac events and poor operative outcomes in patients with PAD. Further research is needed to determine the potential mechanisms by which resistin may increase MACE or impair endothelial function, and to explore the potential role of resistin in the pathogenesis of PAD. Prospective studies are needed to determine whether decreasing resistin has therapeutic benefit in patients with PAD.

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REFERENCES

1. Azuma K, Katsukawa F, Oguchi S, Murata M, Yamazaki H, Shimada A, et al. Correlation between serum resistin level and adiposity in obese individuals. Obes Res 2003;11(8):997–1001. [PubMed: 12917505]
2. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature 2001;409(6818):307–12. [PubMed: 11201732]

3. Hivert MF, Sullivan LM, Fox CS, Nathan DM, D'Agostino RB, Sr., Wilson PW, et al. Associations of adiponectin, resistin, and tumor necrosis factor-alpha with insulin resistance. J Clin Endocrinol Metab 2008;93(8):3165–72. [PubMed: 18492747]
4. Abate N, Sallam HS, Rizzo M, Nikolic D, Obradovic M, Bjelogrlic P, et al. Resistin: an inflammatory cytokine. Role in cardiovascular diseases, diabetes and the metabolic syndrome. Curr Pharm Des 2014;20(31):4961–9. [PubMed: 24320036]
5. Jamaluddin MS, Weakley SM, Yao Q, Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. Br J Pharmacol 2012;165(3):622–32. [PubMed: 21545576]
6. Sinan UY, Canbolat IP, Baydar O, Oktay V, Imre G, Kocas C, et al. Relationship between increased serum resistin level and severity of coronary artery disease. Angiology 2014;65(3):239–42. [PubMed: 24052521]
7. Muse ED, Feldman DI, Blaha MJ, Dardari ZA, Blumenthal RS, Budoff MJ, et al. The association of resistin with cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2015;239(1):101–8. [PubMed: 25585029]
8. Sabbatini AR, Fontana V, Laurent S, Moreno H. An update on the role of adipokines in arterial stiffness and hypertension. J Hypertens 2015;33(3):435–44. [PubMed: 25502905]
9. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113(5):657–63. [PubMed: 16461838]
10. Biteker M, Duman D, Dayan A, Ilhan E. Increased aortic stiffness can predict perioperative cardiovascular outcomes in patients undergoing noncardiac, nonvascular surgery. World J Surg 2011;35(11):2411–6. [PubMed: 21901323]
11. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2014;15(7):736–46. [PubMed: 24399339]
12. Rajpathak SN, Kaplan RC, Wassertheil-Smoller S, Cushman M, Rohan TE, McGinn AP, et al. Resistin, but not adiponectin and leptin, is associated with the risk of ischemic stroke among postmenopausal women: results from the Women's Health Initiative. Stroke 2011;42(7):1813–20. [PubMed: 21546486]
13. Gencer B, Auer R, de Rekeneire N, Butler J, Kalogeropoulos A, Bauer DC, et al. Association between resistin levels and cardiovascular disease events in older adults: The health, aging and body composition study. Atherosclerosis 2016;245:181–6. [PubMed: 26724528]
14. Momiyama Y, Ohmori R, Uto-Kondo H, Tanaka N, Kato R, Taniguchi H, et al. Serum resistin levels and cardiovascular events in patients undergoing percutaneous coronary intervention. J Atheroscler Thromb 2011;18(2):108–14. [PubMed: 21071880]
15. Gherman CD, Mironiuc AI. Evaluation of serum adipokines in peripheral arterial occlusive disease. Mediators Inflamm 2012;2012:257808. [PubMed: 22547903]
16. Zheng H, Xu H, Xie N, Huang J, Fang H, Luo M. Association of serum resistin with peripheral arterial disease. Pol Arch Med Wewn 2013;123(12):680–5. [PubMed: 24067537]
17. Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet 1971;1(7710):1143–5. [PubMed: 4102857]
18. Owens CD, Kim JM, Hevelone ND, Hamdan A, Raffetto JD, Creager MA, et al. Novel adipokines, high molecular weight adiponectin and resistin, are associated with outcomes following lower extremity revascularization with autogenous vein. J Vasc Surg 2010;51(5):1152–9. [PubMed: 20223619]
19. Grenon SM, Owens CD, Nosova EV, Hughes-Fulford M, Alley HF, Chong K, et al. S Acid-Derived Mediators in Patients With Peripheral Artery Disease (the OMEGA-PAD I rial). J Am Heart Assoc 2015;4(8):e002034. [PubMed: 26296857]
20. Grenon SM, Gagnon J, Hsiang Y. Ankle–Brachial Index for Assessment of Peripheral Arterial Disease. N Engl J Med 2009;361(19):e40. [PubMed: 19890121]
21. Zahner GJ, Spaulding KA, Ramirez JL, Schaller MS, Walker SC, Hills NK, et al. Characterizing the relationship between flow-mediated vasodilation and radial artery tonometry in peripheral artery disease. Journal of Surgical Research 2018;224:121–31. [PubMed: 29506827]

22. Zahner GJ, Gruendl MA, Spaulding KA, Schaller MS, Hills NK, Gasper WJ, et al. Association between arterial stiffness and peripheral artery disease as measured by radial artery tonometry. J Vasc Surg 2017;66(5):1518–26. [PubMed: 28756044]
23. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010;121(4):505–11. [PubMed: 20083680]
24. Butlin M, Qasem A. Large Artery Stiffness Assessment Using SphygmoCor Technology. Pulse (Basel) 2017;4(4):180–92 [PubMed: 28229053]
25. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation 1997;95(7):1827–36. [PubMed: 9107170]
26. Stoner L, Young JM, Fryer S. Assessments of arterial stiffness and endothelial function using pulse wave analysis. Int J Vasc Med 2012;2012:903107. [PubMed: 22666595]
27. Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. Circulation 2009;120(6):502–9. [PubMed: 19635967]
28. Sahebkar A, Giorgini P, Ludovici V, Pedone C, Ferretti G, Bacchetti T, et al. Impact of statin therapy on plasma resistin and visfatin concentrations: A systematic review and meta-analysis of controlled clinical trials. Pharmacol Res 2016;111:827–37. [PubMed: 27468651]
29. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Koh Y, et al. Distinct vascular and metabolic effects of different classes of anti-hypertensive drugs. Int J Cardiol 2010;140(1):73–81. [PubMed: 19059660]
30. Solini A, Stea F, Santini E, Bruno RM, Duranti E, Taddei S, et al. Adipocytokine levels mark endothelial function in normotensive individuals. Cardiovasc Diabetol 2012;11:103. [PubMed: 22938533]
31. Lupattelli G, Marchesi S, Ronti T, Lombardini R, Bruscoli S, Bianchini R, et al. Endothelial dysfunction in vivo is related to monocyte resistin mRNA expression. J Clin Pharm Ther 2007;32(4):373–9. [PubMed: 17635339]
32. Golledge J, Leicht AS, Crowther RG, Glanville S, Clancy P, Sangla KS, et al. Determinants of endothelial function in a cohort of patients with peripheral artery disease. Cardiology 2008;111(1): 51–6. [PubMed: 18239393]
33. Kougias P, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Adipocyte-derived cytokine resistin causes endothelial dysfunction of porcine coronary arteries. J Vasc Surg 2005;41(4):691–8. [PubMed: 15874935]
34. Chen C, Jiang J, Lu JM, Chai H, Wang X, Lin PH, et al. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. Am J Physiol Heart Circ Physiol 2010;299(1):H193–201. [PubMed: 20435848]
35. Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation 2003;108(6):736–40. [PubMed: 12874180]
36. Hsu WY, Chao YW, Tsai YL, Lien CC, Chang CF, Deng MC, et al. Resistin inducesmonocyte-endothelial cell adhesion by increasing ICAM-1 and VCAM-1 expression in endothelial cells via p38MAPK-dependent pathway. J Cell Physiol 2011;226(8):2181–8. [PubMed: 21520070]
37. Jung HS, Park K- H, Cho YM, Chung SS, Cho HJ, Cho SY, et al. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 2006;69(1):76–85. [PubMed: 16271710]
38. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 2005;111(7):932–9. [PubMed: 15710760]
39. Ding Q, White SP, Ling C, Zhou W. Resistin and cardiovascular disease. Trends Cardiovasc Med 2011;21(1):20–7. [PubMed: 22498016]
40. Chong KC, Owens CD, Park M, Alley HF, Boscardin WJ, Conte MS, et al. Relationship between kidney disease and endothelial function in peripheral artery disease. J Vasc Surg 2014;60(6):1605–11. [PubMed: 25441679]

41. Ellington AA, Malik AR, Klee GG, Turner ST, Rule AD, Mosley TH, Jr., et al. Association of plasma resistin with glomerular filtration rate and albuminuria in hypertensive adults. Hypertension 2007;50(4):708–14. [PubMed: 17785630]

42. Fontana A, Spadaro S, Copetti M, Spoto B, Salvemini L, Pizzini P, et al. Association between resistin levels and all-cause and cardiovascular mortality: a new study and a systematic review and meta-analysis. PLoS One 2015;10(3):e0120419. [PubMed: 25793385]

43. Calabro P, Samudio I, Willerson JT, Yeh ET. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation 2004;110(21):3335–40. [PubMed: 15545519]

44. Schonbeck U, Libby P. CD40 signaling and plaque instability. Circ Res 2001;89(12):1092–103. [PubMed: 11739273]

45. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6(10):772–83. [PubMed: 16998510]

46. Menzaghi C, Marucci A, Antonucci A, De Bonis C, Ortega Moreno L, Salvemini L, et al. Suggestive evidence of a multi-cytokine resistin pathway in humans and its role on cardiovascular events in high-risk individuals. Sci Rep 2017;7:44337. [PubMed: 28290549]

47. Windham BG, Griswold ME, Farasat SM, Ling SM, Carlson O, Egan JM, et al. Influence of leptin, adiponectin, and resistin on the association between abdominal adiposity and arterial stiffness. Am J Hypertens 2010;23(5):501–7. [PubMed: 20150891]

48. Wang JH, Lee CJ, Yang CF, Chen YC, Hsu BG. Serum resistin as an independent marker of aortic stiffness in patients with coronary artery disease. PLoS One 2017;12(8):e0183123. [PubMed: 28806778]

49. Sabbatini AR, Faria AP, Barbaro NR, Gordo WM, Modolo RG, Pinho C, et al. Deregulation of adipokines related to target organ damage on resistant hypertension. J Hum Hypertens 2014;28(6): 388–92. [PubMed: 24284384]

50. Liu W, Jiang L, Chen J, Gao C, Zhou J, Zhou J, et al. Association of adipokines with blood pressure, arterial elasticity and cardiac markers in dialysis patients: cross-sectional analysis of baseline data from a cohort study. Nutr Metab (Lond) 2017;14:34. [PubMed: 28491119]

Type of Research:

Single center analysis of prospectively collected cohort data

Key Findings:

In 106 patients with PAD, higher serum levels of the hormone resistin was associated with lower flow mediated-vasodilation and a higher incidence of major adverse cardiac events (MACE) during a mean follow up of 36 months.

Take Home Message:

This study suggests that in PAD patients with a higher serum levels of resistin major adverse cardiac events are more common

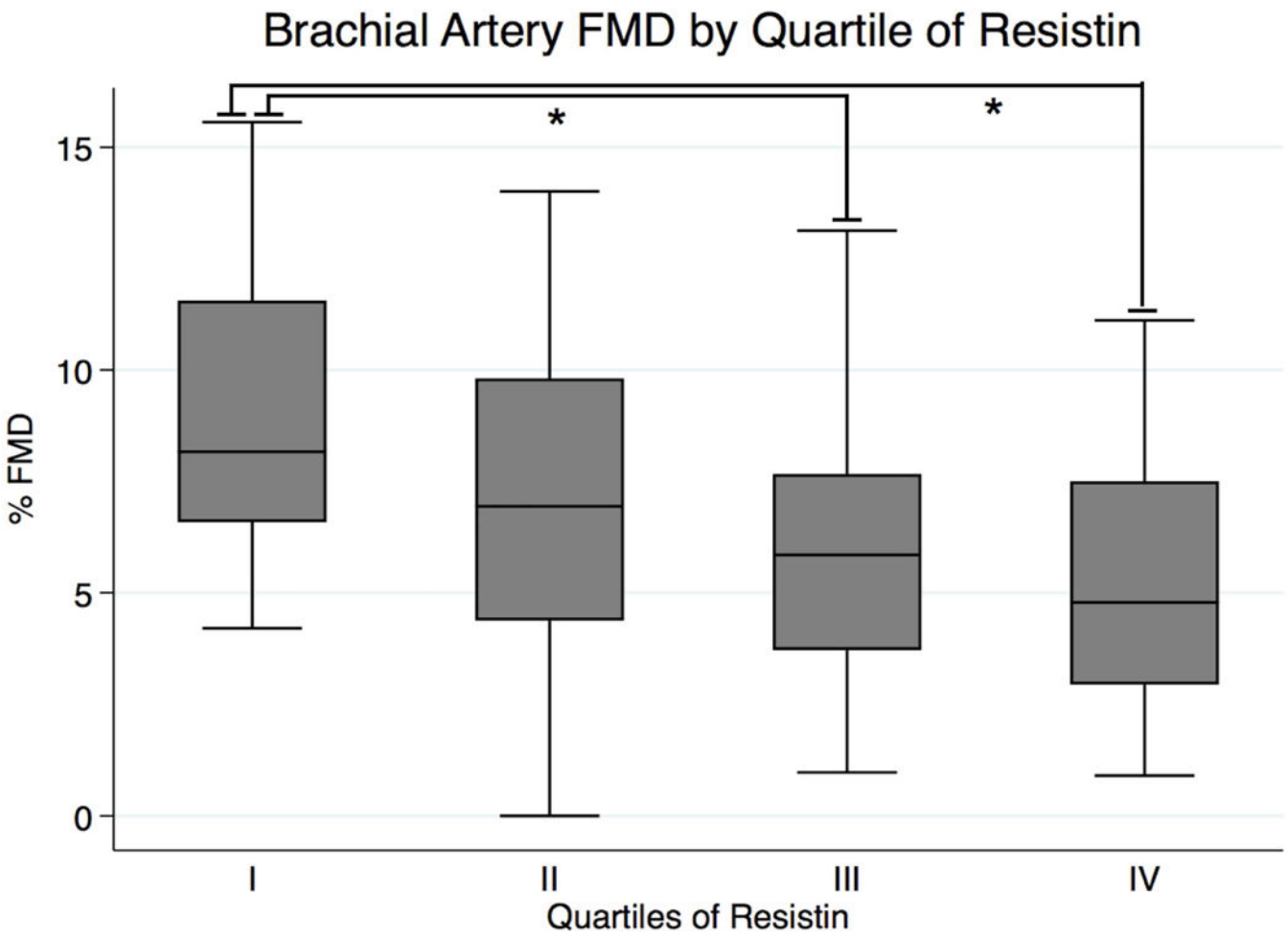

Figure 1.
Brachial artery flow-mediated vasodilation (FMD) decreases with increasing resistin quartile (the asterisks represent a *p*-value <.01).

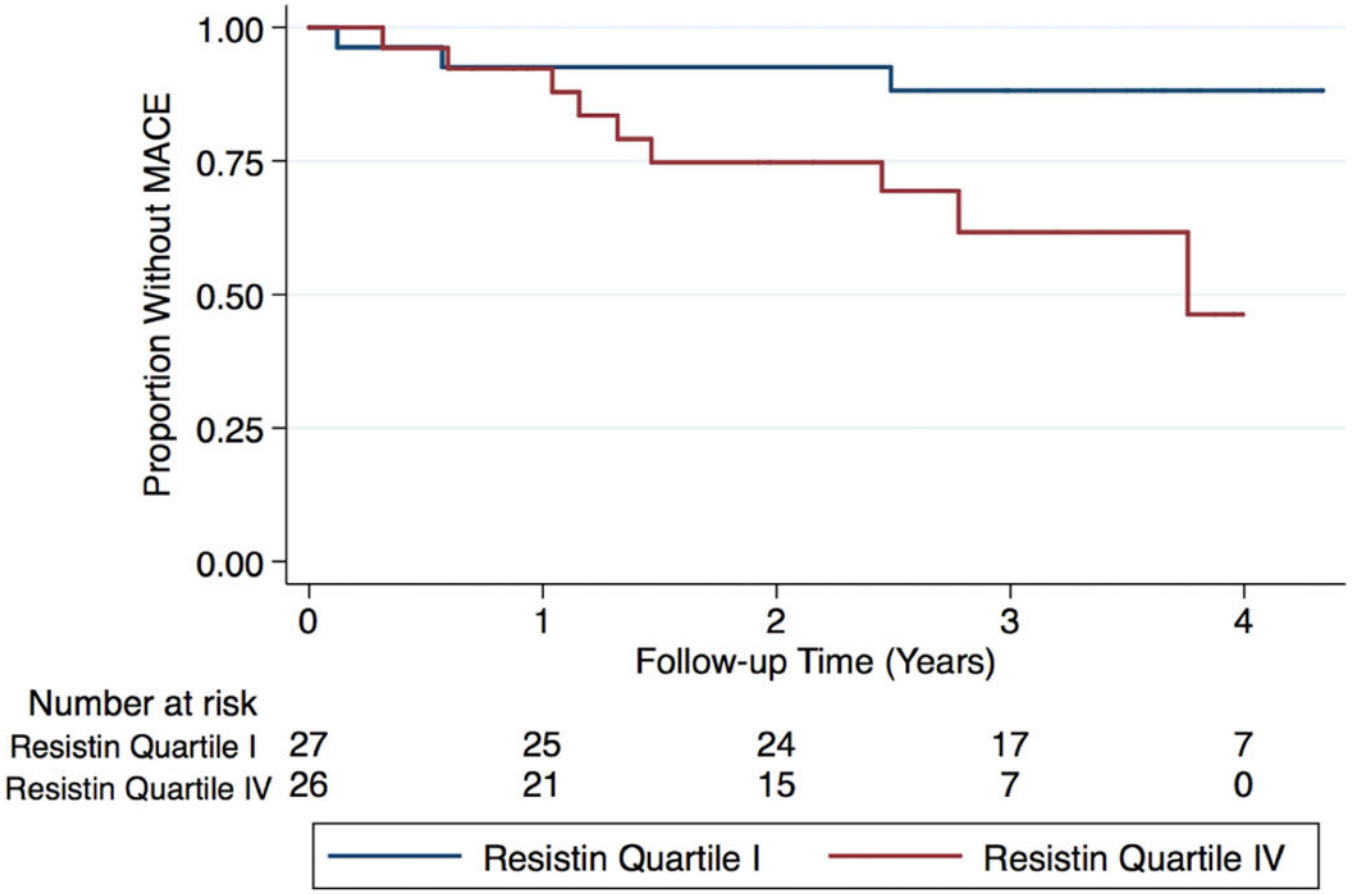

Figure 2.

Kaplan-Meier analysis showing that increased serum resistin is associated with an increased rate of major adverse cardiac events (MACE) in patients with peripheral artery disease (Log-rank: p=.02).

Table I.

Baseline Characteristics of Participants by Resistin Quartile (n=106)

	Quartiles of Resistin[a]				
	I (n=27)	II (n=26)	III (n=27)	IV (n=26)	*P* Value[b]
Characteristics					
Age (years)	65 ± 7.3	67 ± 8.3	69 ± 7.6	71 ± 6.4	**.02**
Male sex	26 (96%)	26 (100%)	26 (96%)	25 (96%)	.80
Caucasian	19 (70%)	20 (77%)	18 (67%)	22 (85%)	.46
BMI (kg/m^2)	28 ± 4.2	28 ± 4.8	29 ± 5.8	28 ± 5.8	.95
Tobacco Use					.41
Never Smoker	2 (7%)	1 (4%)	1 (4%)	4 (15%)	
Former Smoker	13 (48%)	18 (69%)	14 (52%)	12 (46%)	
Current Smoker	12 (45%)	7 (27%)	12 (44%)	10 (39%)	
Pack Years	42 ± 25	41 ± 29	38 ± 19	64 ± 47	.11
Omega-3 index (%)	5.1 ± 1.9	4.5 ± 1.6	5.3 ± 1.7	5.0 ± 1.6	.38
Index ABI	0.73 ± 0.17	0.75 ± 0.13	0.70 ± 0.12	0.74 ± 0.14	.59
Rutherford Category					.38
No Claudication	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Mild Claudication	6 (22%)	10 (38%)	7 (26%)	7 (27%)	
Moderate Claudication	12 (44%)	6 (23%)	9 (33%)	4 (15%)	
Severe Claudication	9 (33%)	9 (35%)	11 (41%)	14 (54%)	
Comorbidities					
Hypertension	24 (89%)	24 (92%)	26 (96%)	24 (92%)	.79
Hyperlipidemia	25 (93%)	22 (85%)	23 (85%)	22 (85%)	.79
Type 2 diabetes mellitus	9 (33%)	8 (31%)	8 (30%)	15 (58%)	.12
Coronary artery disease	11 (41%)	10 (38%)	7 (26%)	11 (42%)	.59
Systolic blood pressure (mmHg)	140 ± 19	135 ± 17	136 ± 20	138 ± 18	.78
Diastolic blood pressure (mmHg)	77 ± 9	79 ± 10	75 ± 10	74 ± 10	.30
Medications					
Aspirin	19 (70%)	19 (73%)	19 (70%)	17 (65%)	.94
ACE-inhibitor	11 (41%)	11 (42%)	14 (52%)	14 (54%)	.71
Beta-blocker	16 (59%)	16 (62%)	15 (56%)	14 (54%)	.94
Statin	21 (78%)	20 (77%)	22 (81%)	22 (85%)	.89
Insulin	2 (7%)	2 (8%)	5 (19%)	6 (23%)	.26
Oral Diabetes Medications	7 (26%)	6 (23%)	6 (22%)	11 (42%)	.33
Laboratory Studies					
Total Cholesterol (mg/dL)	173 ± 47	157 ± 43	164 ± 34	150 ± 34	.18
LDL (mg/dL)	99 ± 42	84 ± 41	88 ± 31	79 ± 29	.25

	Quartiles of Resistin[a]				
	I (n=27)	II (n=26)	III (n=27)	IV (n=26)	*P* Value[b]
HDL (mg/dL)	47 ± 13	44 ± 13	45 ± 14	43 ± 12	.71
Triglycerides (mg/dL)	141 ± 89	157 ± 98	164 ± 124	139 ± 69	.81
HbA1c (%)	6.0 ± 0.9	6.1 ± 1.2	6.4 ± 1.4	6.6 ± 1.7	.35
eGFR (mL/min)	88 ± 19	75 ± 20	70 ± 23	63 ± 14	**<.001**
hsCRP (mg/L)	4.0 ± 3.6	2.4 ± 2.2	4.5 ± 4.5	5.4 ± 5.3	.10

Values as “means ± SD” or “n (%)”. Boldface *p* values were below the .05 level required for statistical significance. ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; BMI = body mass index; Cr = creatinine; eGFR = estimated glomerular filtrate rate; HDL = high-density lipoprotein; HbA1c = hemoglobin A1c; hsCRP = high-sensitivity C-reactive protein; LDL = low density lipoprotein.

[a]Quartile I: 2.6–5.9 ng/mL, Quartile II: 6.0–7.8 ng/mL, Quartile III: 7.9–10.5 ng/mL, Quartile IV: 10.6–24.3 ng/mL.

[b]Calculated using a chi-squared test for categorical variables, analysis of variance (ANOVA) for normally distributed continuous variables, and a Kruskal-Wallis test for continuous variables without a normal distribution (pack years, hsCRP, and triglycerides).

Table II.

Baseline Vascular Function of Participants by Resistin Quartile (n=106)

	Quartiles of Resistin[a]				
	I (n=27)	II (n=26)	III (n=27)	IV (n=26)	*P* Value[b]
Vascular Function Tests					
Flow-mediated vasodilation					
Brachial Artery FMD (%)	9.1 ± 3.3	7.1 ± 3.5	5.8 ± 4.0	5.6 ± 3.5	**.002**
Central Artery Stiffness					
Central Systolic Pressure (mmHg)	142 ± 23	132 ± 17	127 ± 14	133 ± 21	.31
Central Diastolic Pressure (mmHg)	81 ± 13	79 ± 12	80 ± 10	72 ± 20	.26
Central Augmentation Index	34 ± 10	34 ± 9	31 ± 9	29 ± 10	.35
Central Augmentation Index at 75bpm	28 ± 10	26 ± 9	26 ± 10	23 ± 7	.43
Peripheral Artery Stiffness					
Peripheral Systolic Pressure (mmHg)	150 ± 23	140 ± 18	137 ± 15	145 ± 20	.32
Peripheral Diastolic Pressure (mmHg)	150 ± 23	79 ±11	79 ± 10	75 ± 13	.64
Peripheral Mean Pressure (mmHg)	105 ± 14	100 ± 12	99 ± 10	97 ± 13	.40
Peripheral Augmentation Index	105 ± 35	94 ± 10	102 ± 47	85 ± 14	.24

Values as “means ± SD”. Boldface *p* values were below the .05 level required for statistical significance. Bpm = beats per minute; FMD = flow-mediated vasodilation.

[a]Quartile I: 2.6–5.9 ng/mL, Quartile II: 6.0–7.8 ng/mL, Quartile III: 7.9–10.5 ng/mL, Quartile IV: 10.6–24.3 ng/mL.

[b]Calculated using an analysis of variance (ANOVA).

Table III.

Multivariable Model for Resistin Predicting FMD (n=106)

	Bivariate Analysis			Multivariable Analysis[a]		
Predictor	**Coefficient**	**95% CI**	***P* value**	**Coefficient**	**95% CI**	***P* value**
Resistin Quartile[b]: ref I	-	-	-	-	-	-
II	-	-	-	−1.09	−3.29 to 1.10	.33
III	-	-	-	−2.26	−4.51 to −0.01	**.05**
IV	-	-	-	−2.53	−4.87 to −0.20	**.03**
Age (years)	−0.03	−0.13 to 0.06	.50			
Caucasian	1.24	−0.37 to 2.84	.13	1.05	−0.78 to 2.89	.26
Sex	2.27	−1.95 to 6.48	.29			
Body mass index (kg/m^2)	−0.004	−0.14 to 0.13	.96	−0.03	−0.18 to 0.13	.72
Tobacco Use: ref Never Smoker	-	-	-	-	-	-
Former Smoker	0.71	−2.10 to 3.52	.62	-	-	-
Current Smoker	1.34	−1.42 to 4.10	.34	-	-	-
Pack years	0.005	−0.02 to 0.03	.69	-	-	-
Rutherford: ref No Claudication	-	-	-	-	-	-
Mild Claudication	−0.96	−6.25 to 4.33	.72	-	-	-
Moderate Claudication	−2.07	−7.41 to 3.26	.44	-	-	-
Severe Claudication	−0.88	−6.13 to 4.36	.74	-	-	-
Diabetes Mellitus	−0.45	−1.93 to 1.03	.55	−0.39	−2.09 to 1.31	.65
HbA1c (%)	−0.16	−0.70 to 0.38	.57	-	-	-
Hyperlipidemia	−0.01	−2.09 to 2.06	.99	-	-	-
Coronary artery disease	−0.25	−1.72 to 1.21	.73	-	-	-
Hypertension	−2.77	−5.37 to −0.17	**.04**	−1.71	−4.65 to 1.23	.25
Aspirin	−0.22	−1.75 to 1.30	.77	-	-	-
Statin	0.85	−0.90 to 2.60	.34	-	-	-
Beta-blocker	−1.06	−2.46 to 0.35	.14	−0.30	−1.89 to 1.29	.71
ACE-inhibitor	−1.21	−2.60 to 0.18	.09	−0.36	−1.99 to 1.27	.66
Insulin	−0.12	−2.16 to 1.93	.91	-	-	-
Oral Diabetes Medications	−0.71	−2.28 to 0.86	.37	-	-	-
eGFR (mL/min)	0.05	0.01 to 0.09	**.02**	0.05	0.01 to 0.09	**.02**
hsCRP (mg/L)	0.14	−0.03 to 0.32	.11	0.15	−0.08 to 0.38	.19

Boldface *p* values were below the .05 level required for statistical significance. ACE = angiotensin- converting enzyme; eGFR = estimated glomerular filtrate rate; FMD = flow-mediated vasodilation; HbA1c = hemoglobin A1c; hsCRP = high-sensitivity C-reactive protein.

[a]Diabetes mellitus and body mass index were included *a priori* and all variables with a *p* value <.20 in the bivariate analysis were included in the multivariable model.

[b]Quartile I: 2.6–5.9 ng/mL, Quartile II: 6.0–7.8 ng/mL, Quartile III: 7.9–10.5 ng/mL, Quartile IV: 10.6–24.3 ng/mL.

Table IV.

Cox Proportional Hazards for Resistin and Major Adverse Cardiac Events (n=106)

	Multivariable Analysis		
Predictor	**HR**	**95% CI**	***P* value**
Resistin (ng/mL)	1.10	1.003 to 1.200	**.04**
Coronary artery disease	3.30	1.27 to 8.56	**.01**
Tobacco Use: ref Never Smoker	-	-	-
Former Smoker	0.69	0.18 to 2.67	.59
Current Smoker	0.29	0.07 to 1.22	.07
Age (years)	1.02	0.96 to 1.09	.50

Boldface *p* values were below the .05 level required for statistical significance. HR = Hazard ratio