

Association of serum resistin with peripheral arterial disease

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KEY WORDS

atherosclerosis, peripheral arterial disease, resistin, risk factor

ABSTRACT

INTRODUCTION Resistin is an inflammatory mediator and a potential biomarker in cardiovascular diseases.

OBJECTIVES We sought to examine its association with peripheral arterial disease (PAD).

PATIENTS AND METHODS We recruited 200 patients with PAD and 100 healthy controls. Patients were divided into 4 subgroups according to the Fontaine classification for PAD, that is, from Stage I to Stage IV. Serum resistin levels were compared between the PAD group and the control group and among 4 PAD subgroups adjusted for selected factors.

RESULTS Serum resistin (Ln-resistin – log scale) levels and high-sensitivity C-reactive protein (hsCRP) levels in patients with PAD were higher than in healthy controls ($P < 0.05$). Moreover, among the 4 PAD subgroups, the value of Ln-resistin in Stage I subgroup was the lowest, and Stage II subgroup had lower Ln-resistin than Stage III subgroup or Stage IV subgroup ($P < 0.05$). There was also a significant difference in hsCRP levels among those 4 subgroups ($P < 0.05$). In PAD patients, Ln-resistin levels correlated inversely with the ankle–brachial pressure index ($r = -0.301$, $P < 0.05$), and positively with total cholesterol levels ($r = 0.228$, $P < 0.01$). Moreover, a multivariate analysis showed Ln-resistin levels to be an independent risk factor for PAD (odds ratio, 1.237; 95% confidence interval, 1.086–1.396; $P < 0.01$).

CONCLUSIONS Ln-resistin levels and hsCRP are elevated in PAD patients, and they rise as the severity of PAD increases. A multivariate analysis suggests that Ln-resistin could be a prognostic biomarker for the presence of PAD.

INTRODUCTION Peripheral arterial disease (PAD) is one of the major atherosclerotic manifestations, displaying progressive lipid, inflammatory cells, and fibrous matter accumulation in peripheral arteries, especially in the lower extremities. Primary risk factors are smoking, hypertension, elevated levels of cholesterol and glucose.^{1,2} PAD is associated with reduced functional capacity³ and increased risk of cardiovascular morbidity and mortality.^{4–6} It is characterized by progressive luminal obstruction in the peripheral arteries and may be less related to thrombosis or plaque rupture than myocardial infarction or ischemic stroke.^{7,8} This raises the possibility that factors with anti-atherosclerotic and anti-inflammatory properties, such as some adipokines, may be of particular importance in the treatment of this type of atherosclerosis.

Resistin, an adipokine, was originally discovered in mice in 2001 and named for its ability to

resist insulin action.⁹ In humans, it is primarily expressed in monocytes and macrophages, but at much lower levels than in adipocytes.¹⁰ Resistin has been found to be predominantly expressed in those inflammatory cells. Moreover, it has been shown to be involved in obesity-related subclinical inflammation, atherosclerosis, and cardiovascular disease.¹¹ Accumulating evidence has demonstrated the association between high circulating resistin levels and the development of coronary heart disease (CAD),¹² acute coronary syndrome,¹³ restenosis in patients undergoing percutaneous coronary intervention,¹⁴ and heart failure.¹⁵ Whether a similar relationship exists for the development of PAD is uncertain. In this study, we compared serum resistin levels in PAD patients with those of healthy volunteers, and investigated whether or not there was an association between serum resistin levels and the severity of PAD.

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PATIENTS AND METHODS **Participants** The study was conducted on 200 consecutive PAD patients who attended the outpatient department of our institution and who did not receive any revascularization treatment for peripheral arteries. The diagnosis of PAD was confirmed by clinical symptoms or signs, ankle-brachial pressure index (ABPI) of <0.9, and atherosclerotic stenosis or occlusion of the arteries in the lower extremities identified by color Doppler ultrasound, computed-tomography angiography, magnetic resonance angiography, or digital subtraction angiography. All PAD patients were then divided into 4 subgroups according to the Fontaine classification for PAD,¹⁶ i.e., Stage I – asymptomatic; Stage II – intermittent claudication; Stage III – resting pain; Stage IV – ischemic ulcers or gangrene. The control group consisted of 100 healthy volunteers who attended an annual checkup at our hospital. The control participants had no cardiovascular or any other organ system disease, and had normal results in their physical examination, chest radiography, electrocardiogram, echocardiogram, and duplex ultrasonography.

The exclusion criteria were: diabetes mellitus, acute coronary syndrome, decompensated heart failure, cardiomyopathy, valvular heart disease, cerebral stroke, Buerger's disease, severe renal dysfunction (serum creatinine >2.5 mg/dl), active malignancy, chronic liver failure, and autoimmune diseases. The study was approved by the local ethical committee and written informed consent was obtained from all patients.

Clinical data Patients' data were collected, including age, sex, body mass index (BMI), smoking habit, systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiovascular disease history, and current medications. SBP and DBP were measured 3 times on the right arm after a 10-minute rest in the supine position using a standard mercury sphygmomanometer and the average reading was calculated. Hypertension was defined as an SBP of greater than 140 mmHg and/or a DBP of greater than 90 mmHg on repeated measurements and/or receiving antihypertensive treatment. CAD was defined as angina and/or electrocardiogram signs of ischemia during the treadmill-exercise test and/or positive findings on coronary angiography.

Laboratory measurements A venous blood sample was collected from each participant under fasting conditions. Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-sensitivity C-reactive protein (hsCRP) levels were recorded. Resistin levels were measured by an enzyme-linked immunosorbent assay (ELISA) using commercially available kits (R&D systems Inc., Minneapolis, MN, United States). The intra-assay and interassay coefficients of variation were 5.1% and 8.6%, respectively. All tests

for each sample were performed in a random order by technicians who were unaware of which group the sample belonged to.

Statistical analysis All numeric variables were expressed as mean \pm standard deviation, and categorical data were expressed as numbers (n) and percentage in parentheses. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Logarithmic (Ln) transformation of serum resistin concentration (ng/ml) was required because the data were not normally distributed. The Student's *t* test was used for the univariate analysis of normally distributed continuous numerical variables, and the χ^2 test for the categorical variables. Ln-resistin values, according to the health status and PAD stage, were compared using multiple regressions adjusted for sex, age, smoking, history of hypertension, history of CAD, and medications with Bonferroni correction for post-hoc testing. Correlations were assessed by the Pearson correlation analysis. We used a multivariable logistic regression analysis, adjusted for age, sex (male), BMI, smoking, history of hypertension, history of CAD, total cholesterol, and hsCRP to determine the significant factors indicating the presence of PAD. All tests of significance were two-tailed. Statistical significance was defined as $P < 0.05$. The SPSS statistical software (SPSS15.0, Inc., Chicago, Illinois, United States) was used in all statistical calculations.

RESULTS The clinical characteristics of the study population were detailed in **TABLE 1**. In the PAD group, 67.5% of the participants were male and in the control group 54% were male ($P < 0.01$). The PAD group contained a higher percentage of smokers, hypertension patients, and CAD patients compared with the control group (56.5% vs. 48%, $P < 0.05$; 58% vs. 0%, $P < 0.001$; 74.5% vs. 0%, $P < 0.001$; respectively). Age, BMI, total cholesterol, low-density lipoprotein cholesterol, SBP, DBP, and hsCRP levels were higher in the PAD group than in the control group ($P < 0.05$). There were no differences between the 2 groups with respect to high-density lipoprotein cholesterol, triglyceride, or fasting glucose levels ($P > 0.05$). Ln-resistin (ng/ml) was higher in the PAD group than in the control group (1.86 ± 0.57 vs. 1.38 ± 0.42 , $P < 0.05$). In the 4 PAD subgroups, the value of Ln-resistin was significantly lower in patients with Stage I than in any of the other 3 subgroups. Although there was no significant difference between Stage III and Stage IV subgroups, both subgroups had higher Ln-resistin than the Stage II subgroup (**FIGURE 1**). Meanwhile, the hsCRP level rose as the grade of PAD increased.

The levels of Ln-resistin correlated inversely with the ABPI ($r = -0.301$, $P < 0.05$; **FIGURE 2**) and positively with total cholesterol levels ($r = 0.228$, $P < 0.01$) in PAD patients but not in controls. Moreover, a multivariable

TABLE 1 Clinical characteristics of the participants

	Controls (n = 100)	Total PAD patients (n = 200)	PAD groups				P ^a	
			Stage I (n = 6)	Stage II (n = 93)	Stage III (n = 82)	Stage IV (n = 19)		
male, (n, %)	54 (54)	135 (67.5)	2 (33.3) ^b	55 (59.1) ^c	66 (80.5) ^{b,c,d}	12 (63.2) ^{c,e}	0.004	
age, y	43.6 (8.7)	65.7 (6.9)	67.4 (7.1) ^b	62.3 (8.0) ^b	66.2 (8.5) ^b	64.7 (9.3) ^b	0.003	
BMI, kg/m ²	21.6 (3.1)	24.1 (4.2)	22.7 (5.6)	24.9 (4.8) ^b	23.2 (5.3) ^b	25.0 (6.1) ^b	0.021	
history of hypertension	0	116 (58)	2 (33.3) ^b	57 (62.0) ^{b,c}	45 (54.9) ^{b,c}	12 (63.2) ^{b,c}	<0.001	
CAD history	0	119 (74.5)	4 (66.7) ^b	61 (65.6) ^b	69 (84.1) ^{b,c,d}	15 (78.9) ^{b,c,d}	<0.001	
smoker (n, %)	48 (48)	113 (56.5)	3 (50) ^b	54 (58.1) ^{b,c}	42 (51.2) ^c	14 (73.7) ^{b,c,e}	0.017	
medications	ASA (n, %)	0	132 (66)	3(50) ^b	62 (66.7) ^{b,c}	57 (69.5) ^{b,c}	10 (52.6) ^{b,d,e}	<0.001
	β-blocker (n, %)	0	97 (48.5)	2 (33.3) ^b	41 (44.1) ^{b,c}	42 (51.2) ^{b,c}	12 (63.2) ^{b,c,d}	<0.001
	ACEI/ARB (n, %)	0	121 (60.5)	4 (66.7) ^b	55 (59.1) ^b	49 (59.1) ^b	13 (68.4) ^b	<0.001
	statin (n, %)	0	84(42)	2(33.3) ^b	30(32.3) ^b	42(51.2) ^{b,c,d}	10(52.6) ^{b,c,d}	<0.001
	CCB (n, %)	0	127(63.5)	3(50) ^b	60 (64.5) ^{b,c}	52 (63.4) ^{b,c}	12 (63.2) ^{b,c}	<0.001
ABI	1.13 (0.11)	0.76 (0.18)	0.86 (0.07) ^b	0.81 (0.19) ^{b,c}	0.74 (0.12) ^{b,c}	0.72 (0.17) ^{b,c}	0.004	
total cholesterol, mg/dl	180.6 (16.2)	214.3 (17.8)	206.7 (11.4) ^b	212.5 (13.9) ^b	215.9 (14.6) ^b	221.4 (13.5) ^b	0.034	
LDL cholesterol, mg/dl	84.3 (15.4)	119.7 (16.1)	118.4 (9.2) ^b	117.2 (10.6) ^b	121.5 (11.7) ^b	120.3 (12.5) ^b	0.005	
HDL cholesterol, mg/dl	45.6 (9.0)	46.8 (7.1)	48.8 (5.9)	47.3 (8.2)	45.4 (7.6)	44.2 (5.8)	0.283	
triglyceride, mg/dl	132.6 (16.2)	136.1 (12.4)	140.3 (8.0)	136.7 (9.3)	140.3 (11.7)	135.4 (7.5)	0.402	
fasting glucose, mg/dl	96.2 (8.3)	94.1 (7.4)	89.3 (6.2)	97.4 (10.3)	93.5 (8.7)	101.3 (7.7)	0.179	
SBP, mmHg	124.6 (7.3)	138.5 (10.2)	130.5 (5.2) ^b	141.6 (8.3) ^{b,c}	135.7 (9.4) ^{b,c}	139.6 (10.7) ^{b,c}	0.001	
DBP, mmHg	78.9 (6.2)	86.1 (9.4)	82.4 (5.8) ^b	87.5 (8.2) ^{b,c}	84.9 (10.3) ^b	84.6 (7.6) ^b	0.006	
hsCRP, mg/l	2.6 (1.8)	11.5 (4.6)	6.2 (1.4) ^b	10.8 (3.6) ^{b,c}	11.7 (4.7) ^{b,c,d}	12.8 (3.1) ^{b,c,d,e}	0.003	
Ln-resistin, ng/ml	1.38 (0.42)	1.86 (0.57)	1.59 (0.35) ^b	1.76 (0.51) ^{b,c}	1.93 (0.40) ^{b,c,d}	1.98 (0.48) ^{b,c,d}	0.015	

- a PAD group vs. control group
- b P <0.05 compared with control, after Bonferroni correction
- c P <0.05 compared with Stage-I subgroup, after Bonferroni correction
- d P <0.05 compared with Stage-II subgroup, after Bonferroni correction
- e P <0.05 compared with Stage-III subgroup, after Bonferroni correction

Abbreviations: ABI – ankle-brachial pressure index, ACEI – angiotensin-converting-enzyme inhibitor, ARB – angiotensin II receptor blocker, ASA – acetylsalicylic acid, BMI – body mass index, CAD – coronary artery disease, CCB – calcium channel blocker, DBP – diastolic blood pressure, HDL – high-density lipoprotein, hsCRP – high-sensitivity C-reactive protein, LDL – low-density lipoprotein, Ln-resistin – logarithmic transformation of serum resistin concentration, PAD – peripheral arterial disease, SBP – systolic blood pressure

logistic regression analysis identified smoking (OR, 1.318; 95% CI, 1.159–1.947; P <0.05), total cholesterol (OR, 1.407; 95%CI, 1.212–3.754; P <0.01), and resistin levels (OR, 1.237; 95% CI, 1.086–1.396, P <0.01) as independent factors associated with the presence of PAD (TABLE 2).

DISCUSSION In the current study, we demonstrated significantly higher Ln-resistin and hsCRP levels in patients with PAD compared with healthy controls. In addition, among the 4 PAD subgroups, the value of Ln-resistin in the Stage I subgroup was the lowest, and the Stage II subgroup had lower Ln-resistin than the Stage III or IV subgroups, which suggested that Ln-resistin levels increased together with the severity of PAD. Finally, a multivariate analysis showed that the Ln-resistin level was an independent risk factor for PAD. To our knowledge, this is the first report showing the relationship between resistin and PAD severity.

Recent clinical research and in vitro experiments have supported the concept that resistin is an inflammatory mediator and a potential

biomarker in cardiovascular diseases, especially in CAD and heart failure. On the one hand, human clinical studies displayed an association between CAD or its equivalents and either increased circulating resistin levels or local resistin expression. On the other hand, in vitro studies displayed the proatherogenic effects of resistin on endothelial cells, smooth muscle cells, and monocytes or macrophages. Furthermore, animal studies have proved the existence of a causal relationship between resistin and atherosclerosis progression.¹⁷ However, there was little data on the relationship between resistin and PAD, which has many features characteristic of a pathobiological process akin to CAD, including chronic inflammation, endothelial dysfunction, lipoprotein deposition, smooth cell dysfunction, and altered fibrin clot formation/degradation,¹⁸ which is why we designed this study to investigate the relationship between resistin and the extent of PAD. However, our study was a clinical observation and did not explore the mechanisms by which resistin levels were increased in PAD patients. Nevertheless,

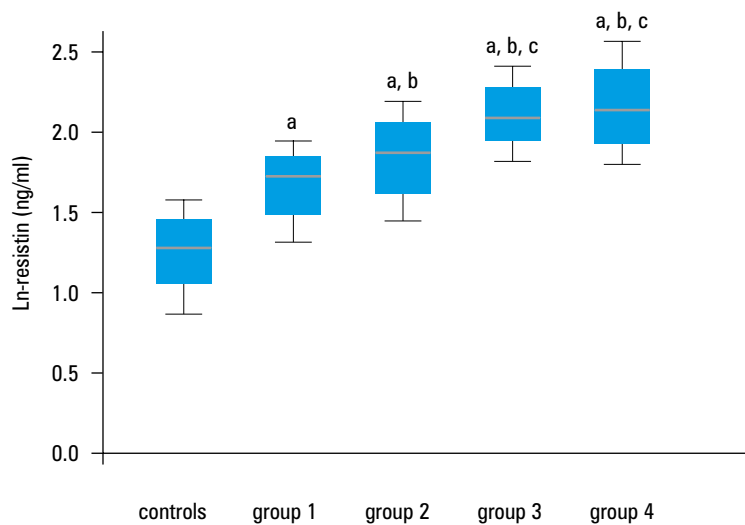


FIGURE 1 Comparison of log-transformed resistin level (ng/ml) between the control group and 4 subgroups with peripheral arterial disease; **a** $P < 0.05$, compared with control group; **b** $P < 0.05$, compared with Stage-I subgroup; **c** $P < 0.05$, compared with Stage-II subgroup; those comparisons were after Bonferroni correction

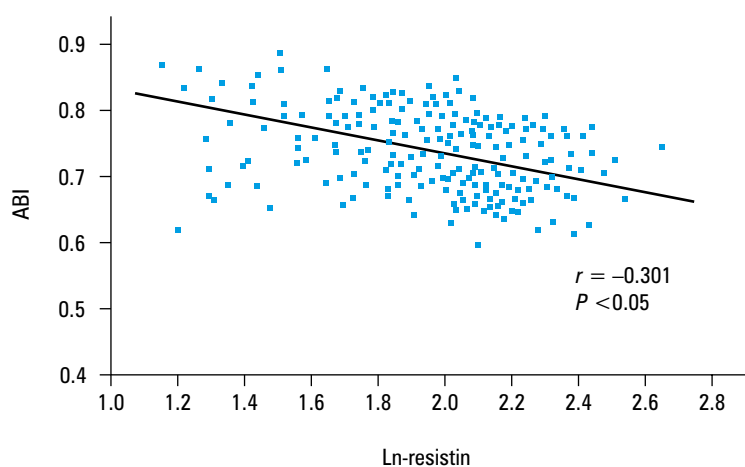


FIGURE 2 Correlation between log-transformed resistin level (ng/ml) and ankle-brachial pressure index in patients with peripheral arterial disease
Abbreviations: see **TABLE 1**

TABLE 2 Multivariable logistic regression analysis of the presence of peripheral artery disease

	OR (95%CI)	P
age	1.126 (0.823–1.591)	0.074
sex (male)	0.753 (0.550–2.436)	0.189
BMI	0.864 (0.613–1.028)	0.054
smoking	1.318 (1.159–1.947)	0.037
hypertension	2.383 (0.641–6.252)	0.483
CAD	0.932 (0.244–3.105)	0.092
total cholesterol	1.407 (1.212–3.754)	0.005
hsCRP	1.604 (0.717–8.263)	0.118
Ln-resistin	1.237 (1.086–1.396)	0.006

Abbreviations: see **TABLE 1**

our results are in line with the viewpoint that resistin plays an important regulatory role in atherosclerosis progression.

PAD is a distinct atherosclerotic syndrome marked by stenosis or occlusion of the arteries, particularly of the lower extremities. Insulin resistance and chronic inflammation have both been implicated in the development of PAD. The first study illustrating the association of PAD and insulin resistance was a cross-sectional study published in 2008 using the National Health and Nutrition Examination Survey, which reported that insulin resistance was strongly and independently associated with PAD and the presence of insulin resistance attenuated the association of inflammation with PAD.¹⁹ In that study, PAD was diagnosed if either leg had an ABPI of ≤ 0.90 . Recently, a study of elderly adults within the Cardiovascular Health Study demonstrated similar findings: insulin resistance was associated with the development of PAD assessed both by the development of a low ABPI and clinical PAD.²⁰ Since resistin was first described in 2001, it was gradually concluded that resistin played an important role in insulin resistance and obesity in diabetic mouse models based on a number of experiments.^{9,21,22} Although human resistin is only 59% homologous to mouse resistin at the amino acid level,²³ which highlights the limitations of using a mouse model to study human metabolism, a growing number of studies has shown a positive correlation between obesity, insulin resistance, and elevated serum resistin in humans. Sheng et al.²⁴ found that resistin was expressed in human hepatocytes with induced insulin resistance. A study performed on 176 obese children and 88 healthy children in China showed that resistin not only played a direct role in metabolic syndrome, but also indirectly contributed to early atherosclerosis in obese children via insulin resistance and hsCRP.²⁵

A high inflammatory burden has been observed in the development of PAD.²⁶ In our study, we observed that the levels of hsCRP, which is a well-known and sensitive marker for prediction of the degree of systemic inflammation, were higher than those in healthy controls and were associated with the severity of PAD. As resistin is expressed by macrophages in response to inflammatory stimuli in humans,¹⁷ it has been the object of intense clinical research that has generally shown high levels of resistin in several atherosclerotic diseases. It was reported that plasma resistin and interleukin-6 concentrations increased significantly in patients with ischemic heart disease with and without diabetes, which indicated there was a possible role of resistin and interleukin-6 in inflammatory processes, especially in atherosclerosis.²⁷ Based on their finding of increased resistin levels being related to inflammation and endothelial activation, Maggio et al.²⁸ hypothesized that interventions aiming to diminish resistin expression might slow down atherogenesis in adolescents. In a recent review, Jamaluddin et al.²⁹ summarized that resistin was involved in pathological processes leading to cardiovascular diseases including inflammation,

endothelial dysfunction, thrombosis, angiogenesis, and smooth muscle cell dysfunction.

We found a positive association between Ln-resistin and total cholesterol. An earlier study demonstrated that resistin directly affected the metabolism of fatty acids by increasing cholesterol esterification into lipids.³⁰ Moreover, there were some reports showing that some drugs, such as statins and antidiabetic drugs, might alter the concentration of resistin,²⁹ so we also applied adjustments for our PAD patients' medications when we compared the levels of Ln-resistin. Additionally, in our multivariate analysis, we identified smoking, total cholesterol, and Ln-resistin as independent risk factors for PAD, which was partly consistent with earlier reports. A well-characterized and prospective study of 44,985 men in the United States with more than 2 decades of follow-up showed that smoking, hypertension, hypercholesterolemia, and type 2 diabetes accounted for the majority of risk associated with the development of clinically significant PAD.³¹ Our observations are promising and prompt further research into robust biomarkers to identify the underlying signaling pathways in PAD.

Our study has several limitations, one of which was the cross-sectional design. Although cross-sectional studies can measure associations, they are not able to prove causality. It would have been ideal to have obtained serial follow-ups and resistin levels in our study to prove causality. Second, our sample size was relatively small, and this study may not be representative of the general population or the community-based population. Third, we have to admit that our case-control study being not age- and sex-matched was faulty, and this lessened its reliability to a certain extent.

Conclusions Our study demonstrated that Ln-resistin values are increased in PAD patients. There was a significant difference among the different PAD-grade subgroups. Furthermore, in a multivariate analysis, the Ln-resistin level was an independent predictor of PAD. It would be necessary to carry out large and long-term prospective studies to confirm that serum resistin is a prognostic biomarker for the extent of PAD, as in other forms of clinically overt atherosclerosis.

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Związek między stężeniem rezystyny w surowicy a chorobą tętnic obwodowych

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SŁOWA KLUCZOWE

choroba naczyń obwodowych, czynnik ryzyka, miażdżycy, rezystyna

STRESZCZENIE

WPROWADZENIE Rezystyna jest mediatorem reakcji zapalnej i potencjalnym biomarkerem chorób sercowo-naczyniowych.

CELE Celem pracy było ustalenie jej związku z chorobą tętnic obwodowych (*peripheral arterial disease* – PAD).

PACJENCI I METODY W badaniu uczestniczyło 200 chorych z PAD i 100 zdrowych osób w grupie kontrolnej. Chorych podzielono wg zaawansowania PAD na 4 podgrupy wyodrębnione zgodnie z klasyfikacją Fontaine'a (okresy I–IV). Porównywano stężenie rezystyny u chorych z PAD i w grupie kontrolnej oraz między 4 podgrupami PAD po wprowadzeniu poprawek na wybrane czynniki.

WYNIKI Logarytm naturalny stężenia rezystyny (Ln-rezystyna) i stężenie białka C-reaktywnego oznaczonego metodą o dużej czułości (*high-sensitivity C-reactive protein* – hsCRP) były większe u chorych z PAD niż u zdrowych osób z grupy kontrolnej ($p < 0,05$). W 4 podgrupach PAD wartość Ln-rezystyny była najmniejsza w podgrupie z etapem I, a ponadto mniejsza w podgrupie z etapem II niż w podgrupach z etapami III i IV ($p < 0,05$). Stwierdzono również znamienne różnice stężeń hsCRP między tymi 4 podgrupami ($p < 0,05$). U chorych z PAD wartość Ln-rezystyny wykazywała korelację ujemną ze wskaźnikiem kostkowo-ramiennym ($r = -0,301$, $p < 0,05$) i korelację dodatnią ze stężeniem cholesterolu całkowitego ($r = 0,228$, $p < 0,01$). Ponadto w dodatkowej analizie wieloczynnikowej wykazano, że wartość Ln-rezystyny jest niezależnym czynnikiem ryzyka PAD (OR = 1,237, 95% CI = 1,086–1,396, $p < 0,01$).

WNIOSKI Wartość Ln-rezystyny i stężenie hsCRP u chorych z PAD są zwiększone i zwiększają się wraz ze wzrostem zaawansowania PAD. Analiza wieloczynnikowa sugeruje, że Ln-rezystyna może być prognostycznym biomarkerem występowania PAD.

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