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The Association between Serum Resistin Level and Presence or Severity of Coronary Heart Disease

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ABSTRACT

Background: Obesity is a well-known principal risk factor for metabolic disorders and cardiovascular diseases. Resistin is one of adipocyte-derived molecules, which plays important roles in inflammation as well as in endocrine and cardiovascular systems.
Objectives: The present study aimed to determine the association between serum resistin level and presence/severity of Coronary Heart Disease (CHD).
Patients and Methods: This cross-sectional study was conducted on 155 individuals referred for coronary angiography. Information about the patients' age, gender, and cardiovascular risk factors was recorded. Their weight, height, and waist and hip circumferences were measured, as well. Each coronary angiogram was reported for two scoring methods (number of vessel diseases (usual method) and Gensini scoring system) by one cardiologist who was not aware of the participants' serum resistin levels. Then, the relationship between serum resistin level and presence/severity of CHD was evaluated.
Results: The results revealed no significant associations between the mean serum resistin level and the presence of CHD by both methods of evaluation of the coronary angiograms after adjustment for all conventional risk factors for CHD. In addition, no significant association was detected between serum resistin level and the severity of CHD based on the usual method of reporting the coronary angiograms (number of vessel diseases) (P = 0.332). Yet, serum resistin level was positively correlated to body mass index and waist and hip circumferences and negatively related to height and fasting blood sugar level. Moreover, no linear correlation was found between serum resistin level and Gensini score (P = 0.35). Finally, hip circumference (P = 0.002) and height (P = 0.018) were determined as the predictors of serum resistin level.
Conclusions: This cross-sectional study showed no significant associations between serum resistin level and presence/severity of CHD.

►*Implication for health policy/practice/research/medical education:*
Obesity is a well-known principal risk factor for cardiovascular diseases. Resistin is an adipocyte-derived molecule linking obesity and insulin resistance. There is controversy in the literature about the association between serum resistin level and coronary heart disease. This cross-sectional study showed no association between serum resistin level and presence or severity of coronary heart disease.

1. Background

Cardiovascular Diseases (CVDs) are the main cause of death in developed countries and in South Asia, especially India and the Middle East (1-3). Obesity is a well-known principal risk factor for metabolic disorders and CVDs. Recent studies have shown that a number of bioactive molecules secreted from adipose tissue contributed to this connection. Resistin is one of those adipocyte-derived molecules, which was first identified as a pivotal hormone linking obesity and insulin resistance in murine models (4). However, the subsequent

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studies in mouse models and human adipocytes led to a quite different role of resistin in obesity and insulin resistance (5). In contrast to rodents in which resistin is derived exclusively from fat tissue, in humans, peripheral blood mononuclear cells seem to be the major source of this molecule. Resistin, one amongst a family of proteins known as Resistin-Like Molecules (RELMs), may provide insight into links among obesity, inflammation, and atherosclerosis. Resistin may also induce endothelial dysfunction, upregulate adhesion molecules, and promote smooth muscle proliferation (6-8). The involvement of human resistin in inflammation has been well established, as well. Proinflammatory cytokines, such as interleukin-1, interleukin-6, C-reactive protein, and tumor necrosis factor, appeared to be associated with increased resistin expression in monocytes (9). These circulating levels of resistin were predictive of coronary atherosclerosis [10]. Further clinical studies regarding atherosclerosis revealed a multifaceted function of resistin in screening, diagnosis, and prognosis of Coronary Heart Disease (CHD), Peripheral Artery Disease (PAD), and CVDs (10).

Despite its involvement in inflammatory pathways, resistin did not appear to be an independent risk factor for cardiovascular events and mortality in most prospective clinical studies (11).

2. Objectives

The present study aims to assess the association between serum resistin level and presence/severity of CHD.

3. Patients and Methods

This cross-sectional study was conducted on 200 consecutive patients who were referred for coronary angiography to the Cardiac Catheterization Units in Nemazee and Shahid Faghihi teaching hospitals from March to August 2014. The inclusion criteria of the study were aging 30 - 75 years and having a normal kidney function (serum creatinine ≤ 1.4 mg/dL). On the other hand, the exclusion criteria were suffering from diabetes mellitus and having undergone angioplasty or Coronary Artery Bypass Graft (CABG) operation. This study was approved by the local research Ethics Committee of Shiraz University of Medical Sciences. Besides, written informed consents for blood sampling were obtained from all the participants.

Information about the patients' age, gender, and cardiovascular risk factors were asked and recorded. Their weight, height, and waist and hip circumferences were measured, as well. Body Mass Index (BMI) and Waist to Hip (W/H) ratio were also calculated. Then, 10 mL blood samples were taken after a 12-hour fasting. The blood samples were sent to the laboratory of the Endocrinology and Metabolism Research Center where the sera were separated and frozen at -70 ºC. An expert cardiologist, who was blinded to the participants' serum resistin levels, reported all coronary angiograms. Each coronary angiogram was reported through two scoring methods; the usual classical method (number of vessel diseases) and Gensini scoring system. Gensini scoring system is a method that assigns a different severity score depending on the degree of luminal narrowing and the geographical importance of its location, as shown in Figure 1 (12).

Vessel		Stenosis (%)	Score
Lt main (×5)			
LAD	Proximal (×2.5)		
	Mid part (×1.5)		
	Distal (×1)		
D1 (×1)			
D2 (×0.5)			
LCX	Proximal (× 2.5)		
	Mid part (×2)		
	Distal (×1)		
OM1 (×1)			
OM2 (×0.5)			
RCA	Proximal (×1)		
	Mid part (×1)		
	Distal (×1)		
PDA (×1)			
Final score			

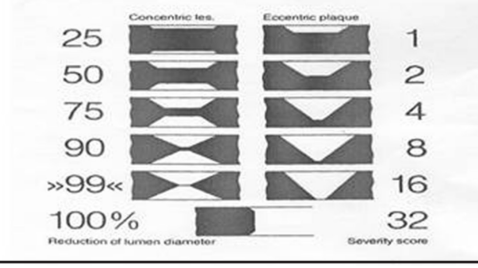

Figure 1. Gensini Scoring System. Gensini Score Calculation: Severity Score × Segment Location Multiplying Factor

Serum resistin level was measured by Enzyme-Linked Immunosorbent Assay (ELISA) using a commercial kit (Mediagnost GmbH, Germany). Inter- and intra-assay coefficients of variation were 5.5% and 2.4%, respectively. Additionally, serum lipid profiles and Fasting Blood Sugar (FBS) level were determined using enzymatic and creatinine level by calorimetric methods. The degree of insulin resistance was also estimated by Homeostasis Model Assessment (HOMA) index that was computed using the following formula: FBS (mg/dL) × serum insulin (μU/mL)/405. Then, the associations between serum resistin level and presence and severity of CHD as well as other variables were evaluated.

3.1. Statistical Analysis

All statistical analyses were performed using the SPSS statistical software for Windows (version 18.0, SPSS Inc., Chicago, IL, USA). Independent Samples t-test was used for comparison of quantitative variables. Besides, distribution of qualitative variables was investigated by chi-square test. Moreover, analysis of covariance was used for comparison of the participants with and without CHD regarding the mean serum resisin level after adjustment for all conventional risk factors of CHD. Spearman's rho test was also used to assess the association between serum resistin level and severity of CHD. Indeed, Pearson's correlation coefficient was used to assess the correlation between serum resistin level and other variables. Logistic regression model was

also employed to determine the independent predictors of CHD. Conventional risk factors for CHD were included in the analysis. Finally, the linear regression analysis was applied for determination of the factors predicting serum resistin level. The variables used in the model were age, sex, smoking, presence of hypertension, weight, BMI, waist and hip circumferences, W/H ratio, FBS, insulin level, insulin resistance (HOMA index), and serum lipid level. $P < 0.05$ was considered to be statistically significant.

4. Results

At the end of the study, the data related to 155 out of 200 patients (103 males and 52 females with the mean age of 58.14 ± 11.70 years) were analyzed. In total, fifteen participants with serum creatinine levels > 1.4 mg/dL, 24 patients with diabetes mellitus, and 6 patients with the history of angioplasty or CABG operation were excluded from the study. The results showed a significant difference between the non-CHD and CHD groups (diagnosed by either usual method or Gensini scoring method of reporting coronary angiograms) regarding the patients' mean age ($P = 0.003$ and $P = 0.001$, respectively). Distribution of the participants with or without CHD based on the usual method of reporting coronary angiograms (number of vessel diseases) has been presented in Table 1. Besides, the participants' demographic, clinical, and biochemical characteristics have been shown in Table 2. Among the demographic factors, age, sex and W/H ratio were significant factors contributing to CHD through both methods of reporting coronary angiograms. Among the biochemical factors also, the mean serum High Density Lipoprotein-Cholesterol (HDL-C) level was significantly higher in the non-CHD group than in the CHD group ($P = 0.047$) as diagnosed by the usual method of reporting coronary angiograms. However, no statistically significant association was observed between serum resistin level and presence of CHD based on the usual method of reporting coronary angiograms after adjustment for all conventional risk factors of CHD ($P = 0.332$). Those risk factors included age, sex, smoking, hypertension, hyperlipidemia, BMI, waist and hip circumferences, W/H ratio, and insulin resistance (HOMA index). Also, the mean serum resistin level in the patients with CHD, as determined by Gensini scoring system, was not significantly different from that in the patients without CHD after adjustment for all conventional risk factors of CHD ($P = 0.628$).

The correlatives of serum resistin levels have been depicted in Table 3. Accordingly, serum resistin level was positively correlated to waist circumference ($r = 0.213$, $P = 0.009$) and BMI ($r = 0.163$, $P = 0.046$), but inversely related to FBS level

Table 1. The Results of the 155 Participants' Coronary Angiograms Based on the Usual Method (No. of Vessel Diseases)

Coronary Status	N (%)	No. of Vessel Diseases	N (%)
Non-CHD [a]	47 (30.32)	-------	47 (30.32)
		One-vessel disease	41 (26.45)
		Two-vessel disease	33 (21.29)
CHD [a]	108 (69.68)		
		Three-vessel disease	21 (13.55)
		Left main disease	13 (8.39)
Total	155 (100)	Total	155 (100)

[a] CHD, coronary heart disease

Table 2. Demographic, Clinical, and Biochemical Characteristics of the Participants Divided by Absence/Presence of Coronary Heart Disease according to the Usual Method (No. of Vessel Diseases) and Gensini Scoring System of Reporting Coronary Angiograms (n = 155)

	Coronary Status (No. of Vessel Diseases)			Coronary Status (Gensini Score)		
Variables	**Non-CHD (47)**	**CHD (108)**	**P value**	**Gensini score = 0**	**Gensini score > 0**	**P value**
Age (years)	53.96 ± 9.88	59.95 ± 12.00	P = 0.003	53.05 ± 9.88	59.96 ± 11.80	P = 0.001
Sex (M/F)	(20/27)	(83/25)	P = 0.0001	(16/25)	(87/27)	P = 0.0001
Smoking, n (%)	21 (44.7)	55 (50.9)	P = 0.475	17 (41.5)	59 (51.8)	P = 0.258
Hypertension, n (%)	22 (46.8)	35 (32.4)	P = 0.087	19 (46.3)	38 (33.3)	P = 0.130
Hyperlipidemia, n (%)	18 (38.3)	34 (31.5)	P = 0.409	15 (36.6)	37 (32.5)	P = 0.631
BMI (kg/m2)	25.61 ± 3.65	25.37 ± 4.20	P = 0.738	25.69 ± 3.74	25.36 ± 4.14	P = 0.653
Waist circumference (cm)	90.64 ± 11.86	91.22 ± 11.84	P = 0.780	89.34 ± 10.73	91.65 ± 12.16	P = 0.284
Hip circumference (cm)	99.48 ± 9.44	97.24 ± 10.92	P = 0.224	98.72 ± 8.65	97.63 ± 11.13	P = 0.572
Waist/hip ratio	0.91 ± 0.06	0.94 ± 0.06	P = 0.008	0.90 ± 0.06	0.94 ± 0.06	P = 0.002
Insulin resistance (HOMA index)	1.99 ± 2.13	2.48 ± 3.00	P = 0.316	1.99 ± 1.97	2.45 ± 3.00	P = 0.362
Resistin (ng/mL)	6.79 ± 3.32	7.44 ± 3.94	P = 0.332	6.99 ± 3.49	7.33 ± 3.87	P = 0.628
Total cholesterol (mg/dL)	175.94 ± 44.19	175.62 ± 47.99	P = 0.969	170.56 ± 40.97	177.57 ± 48.67	P = 0.412
LDL-cholesterol (mg/dL)	118.40 ± 39.19	119.98 ± 40.38	P = 0.822	113.94 ± 35.40	121.52 ± 41.38	P = 0.299
Triglyceride (mg/dL)	96.72 ± 50.79	111.17 ± 67.52	P = 0.191	92.12 ± 48.82	112.06 ± 66.92	P = 0.083
HDL-cholesterol (mg/dL)	38.19 ± 13.56	33.61 ± 12.86	P = 0.047	38.20 ± 13.87	33.84 ± 12.82	P = 0.070

Abbreviations: CHD, coronary heart disease; BMI, body mass index; LDL-cholesterol, low-density lipoprotein-cholesterol; HDL-cholesterol, high-density lipoprotein-cholesterol.

Table 3. The Correlatives of Serum Resistin Level

Variables	r*	P value
Age (years)	-0.090	0.271
Weight (kg)	0.020	0.808
Height (m)	-0.188	0.021
BMI (kg/m2)	0.163	0.046
Waist circumference (cm)	0.213	0.009
Hip circumference (cm)	0.251	0.002
Waist/hip ratio	0.013	0.873
FBS (mg/dL)	-0.228	0.008
Insulin (µU/mL)	-0.104	0.234
Insulin resistance (HOMA index)	-0.128	0.140
Total cholesterol (mg/dL)	0.059	0.474
LDL-cholesterol (mg/dL)	-0.012	0.889
HDL-cholesterol (mg/dL)	-0.148	0.070
Triglyceride (mg/dL)	-0.026	0.753
Gensini score	0.077	0.350

* r = Pearson's correlation coefficient

Abbreviations: BMI, body mass index; FBS, fasting blood sugar; LDL-cholesterol, low-density lipoprotein-cholesterol; HDL-cholesterol, high-density lipoprotein-cholesterol

(r = -0.228, P = 0.008). Height was also inversely related to serum resistin level and was its predictor according to the results of the linear regression analysis (β = -0.188, t = -2.387, P = 0.018). Hip circumference also showed a positive correlation with serum resistin level and was its predictor according to the findings of the linear regression analysis (β = 0.248, t = 3.157, P = 0.002).

5. Discussion

The results of this cross-sectional study showed no significant associations between serum resistin level and presence/severity of CHD. Although a strong relationship exists between low levels of adiponectin and development of metabolic syndrome, some recent publications have expressed doubts on the use of adiponectin as a long-term assessment predictor in patients with CHD (2, 10, 13). Instead, human resistin implicated in the pathogenesis of diabetes has gained attention as a novel biomarker of CHD (14). Among patients with CHD, serum resistin level was associated with renal dysfunction (15). Renal insufficiency, expressed as serum creatinine ≥ 2 mg/dL, has already been considered to be a reliable predictor of all-cause and cardiovascular mortality through univariate cox proportional hazard analysis (16). In the current study, the patients with creatinine levels > 1.4 mg/dL and those with diabetes, as the potential risk factors of CHD, were excluded from the analysis. The results revealed no significant differences between the CHD and control groups regarding serum resistin level using both usual method and Gensini scoring system of reporting coronary angiograms. A bulk of clinical studies have indicated significant associations between high circulating resistin levels and presence and severity of CVDs (2, 4, 5, 9, 17-22) and even atrial fibrillation (23). Krecki et al. (18) also showed a strong correlation between serum resistin level and occurrence of major cardiac and cerebrovascular events in patients with stable multi-vessel Coronary Artery Disease (CAD). As opposed to the studies mentioned above, the present study findings resemble those obtained by Hoefle et al. (15), Lim et al. (24), and Cabrera de León A et al. (25) that did not establish any correlations between development of cardiovascular events and serum resistin levels. Yatura et al. (26) also reported no significant differences between non-diabetic patients with CHD and non-diabetic controls regarding plasma resistin level.

The current study results revealed a significant positive relationship between BMI and serum resistin level. Similar results were also obtained by Steppan and Lazar (27) and Piestrzeniewicz et al. (7). According to the former, high resistin levels in obese individuals were correlated to BMI. Waist circumference was also significantly and positively related to serum resistin level. This was consistent with the findings of the researches performed by Norata et al. (20) and Piestrzeniewicz et al. (7), but in contrast to those of the study by Dominguez Caello et al. (28) that demonstrated no significant relationships between waist circumference and resistin level. Our results also indicated a significant positive relationship between hip circumference and serum resistin level, which is in agreement with the findings of the study by Shams et al. (13).

In this study, height as a routinely measured anthropometric parameter showed a significant inverse correlation with serum resistin level. This is on the contrary to the non-significant correlation between resistin level and height reported by Lim et al. (24). A regulatory role for resistin in somatotrope function has been reported, and administration of resistin to dispersed rat anterior pituitary cells increased GH release (29).

Our findings also revealed a significant inverse correlation between FBS level and resistin level, which is in contrast to the non-significant correlation found by Zhang et al. (9). It is also inconsistent with the positive correlation reported in the studies conducted by Piestrzeniewicz excluding diabetes and liver disease (7) and Ozcan et al. excluding liver, infectious, and inflammatory diseases as well as malignancies and cardiovascular events (23).

5.1. Conclusion

The results of this cross-sectional study showed no

statistically significant associations between serum resistin level and presence/severity of CHD. Moreover, hip circumference and height were determined as the predictors of serum resistin level. Yet, further large-scale studies may be warranted to exactly define the role of resistin in CHD.

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Authors' Contribution

Study concept and design: Shams, Mortazavi, Rasekhi Kazerouni; Acquisition of data: Mortazavi, Rasekhi Kazerouni, Ostovan; Analysis and interpretation of data: Shams, Mortazavi, Omrani; Drafting of the manuscript: Mortazavi; Critical revision of the manuscript for important intellectual content: Shams, Ostovan, Omrani; Statistical analysis: Shams, Mortazavi, Rasekhi, Kazerouni; Administrative, technical, and material support: Omrani, Shams, Mortazavi, Rasekhi Kazerouni, Ostovan; Study supervision: Omrani, Shams.

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