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

Roozbeh Mortazavi 1, Akbar Rasekhi Kazerouni 1, Mohammad Ali Ostovan 2, Gholamhossein Ranjbar Omrani 3, Mesbah Shams 3,*

1 Department of Internal Medicine, Nemazee Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran
2 Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran
3 Endocrine and Metabolism Research Center, Nemazee Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

ARTICLE INFO
Article Type: Research Article

Article History:
Received: 23 Jul 2016
Revised: 05 Oct 2016
Accepted: 22 Oct 2016

Keywords:
Resistin
Coronary Disease
Coronary Angiography
Adipokines

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
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).

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
(Medagnost 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 resistin 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)

<table>
<thead>
<tr>
<th>Coronary Status</th>
<th>N (%)</th>
<th>No. of Vessel Diseases</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CHD</td>
<td>47 (30.32)</td>
<td>One-vessel disease</td>
<td>47 (30.32)</td>
</tr>
<tr>
<td>CHD</td>
<td>108 (69.68)</td>
<td>Two-vessel disease</td>
<td>108 (69.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Three-vessel disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left main disease</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>155 (100)</td>
<td></td>
<td>155 (100)</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coronary Status (No. of Vessel Diseases)</th>
<th>P value</th>
<th>Coronary Status (Gensini Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-CHD (47)</td>
<td>CHD (108)</td>
<td>Gensini score = 0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.96 ± 9.88</td>
<td>59.95 ± 12.00</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>(20/27)</td>
<td>(83/25)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>21 (44.7)</td>
<td>55 (50.9)</td>
<td>P = 0.475</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (46.8)</td>
<td>35 (32.4)</td>
<td>P = 0.087</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>18 (38.3)</td>
<td>34 (31.5)</td>
<td>P = 0.409</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.61 ± 3.65</td>
<td>25.37 ± 4.20</td>
<td>P = 0.738</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.64 ± 11.86</td>
<td>91.22 ± 11.84</td>
<td>P = 0.780</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>99.48 ± 9.44</td>
<td>97.24 ± 10.92</td>
<td>P = 0.224</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.91 ± 0.06</td>
<td>0.94 ± 0.06</td>
<td>P = 0.008</td>
</tr>
<tr>
<td>Insulin resistance (HOMA index)</td>
<td>1.99 ± 2.13</td>
<td>2.48 ± 3.00</td>
<td>P = 0.316</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>6.79 ± 3.32</td>
<td>7.44 ± 3.94</td>
<td>P = 0.332</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>175.94 ± 44.19</td>
<td>175.62 ± 47.99</td>
<td>P = 0.969</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>118.40 ± 39.19</td>
<td>119.98 ± 40.38</td>
<td>P = 0.822</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>96.72 ± 50.79</td>
<td>111.17 ± 67.52</td>
<td>P = 0.191</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>38.19 ± 13.56</td>
<td>33.61 ± 12.86</td>
<td>P = 0.047</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; BMI, body mass index; 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.

Acknowledgements

Hereby, the authors would like to thank the study participants for contribution of their time to this research. They are also grateful for Mr. M. Monjazeb, Mr. M. Moaiedifar, and Mrs. Arefian (personnel of the Endocrine and Metabolism Research Center, Nemazee Teaching Hospital) for their kind technical assistance. Thanks also go to Dr. Najaf Zare, statistician at the Center for Clinical Research Development of Nemazee Teaching Hospital. This paper was extracted from a thesis written by Roozbeh Mortazavi, MD, submitted to the School of Medicine for fulfillment of the degree of specialty in Internal Medicine and financially supported by Shiraz University of Medical Sciences (grant No. 89-2600).

Authors’ Contribution

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

Funding/Support

This study was financially supported by Shiraz University of Medical Sciences (grant No. 89-2600).

Financial Disclosure

The funding organization had no role in the design and conduct of the study, collection, management, and analysis of the data, or p reparation, review, and approval of the manuscript.

References


