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The Association between Serum Resistin Levels and Major Adverse Cardiac Events

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Abstract

Resistin is a member of the family of cysteine-rich secretary proteins called resistin-like molecules (RELMs). It is suggested to be involved in inflammatory conditions and atherosclerosis. We have established a significant correlation between serum resistin levels and coronary artery disease (CAD) in a study was performed between 2011 and 2012 in our institute in two hundred fourteen patients (164 CAD patients and 50 controls). Then the CAD patients were followed up to investigate the relationship between increased serum resistin levels and major adverse cardiac events (MACE) between 2012 and 2016. One hundred fifty-five of 164 patients (95%) were followed up and 9 patients lost to follow up. There were 39 MACE (25%) in four years of follow-up. There were 16 in-hospital deaths due to cardiac causes, 8 revascularization procedures, and 15 re-hospitalization due to acute coronary syndrome (ACS) or heart failure (HF). The patients with MACE had similar serum resistin level (median: 71.37 pg/ml) compared to patients without MACE (median: 80.23 pg/ml) ($p > 0.05$).

Keywords

Resistin, Adipokine, Atherosclerosis, Coronary Artery Disease, Major Adverse Cardiac Event

1. Introduction

Adipose tissue acts like an active endocrine organ to synthesize and secrete a number of biologically active molecules called adipokines. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin, adiponectin, and resistin are most

known members of this family.

Resistin is derived from the gene of RSTN. It is a member of the family of cysteine-rich secretory proteins called resistin like molecules (RELMs). Although it is secreted from adipocytes in murine and rat models, monocytes and macrophages are the sources of resistin in humans and rabbits [1] [2]. Resistin affects especially the liver and causes insulin resistance [3]-[8].

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in both developed and developing countries. It is important to diagnose CAD while it is in a subclinical stage to improve prognosis and decrease the complication of the disease. The main cause of the CAD is atherosclerosis of epicardial coronary arteries. Inflammation and endothelial dysfunction play a critical role in atherosclerotic plaque de-stabilization and vulnerability. Inflammatory responses stimulate resistin secretion and resistin also promotes production of pro-inflammatory mediators. It also activates endothelial cells to express endothelin-1, adhesion molecules and chemokines, hence aggravate the pro inflammatory response [4] [9] [10]. These pro-inflammatory mediators have already been implicated in plaque instability. In addition, resistin could also promote lipid accumulation in macrophages [5]. Thus, resistin may have a role in atherosclerosis progression, as well as it can act a plaque de-stabilizer contributing to the occurrence of acute coronary syndrome events [6].

Several studies have reported serum resistin levels to be significantly elevated in CAD patients [6] [11] [12] [13] [14]. Sinan *et al.* has also established the positive correlation between serum resistin level and severity of CAD which was measured by Gensini score [11]. Patients with high serum resistin levels had more severe and complex coronary artery disease. The term major adverse cardiac events (MACE) is used to denote the composite of a variety adverse event related to the cardiovascular system like death, non-fatal myocardial infarction, angina, revascularization, hospitalization due to cardiac events. Patients with more severe and complex CAD are more likely to have MACE. Due to correlation between serum resistin level and Gensini score, we aimed to investigate correlation between MACE and serum resistin levels. We expected to find higher serum resistin levels among patients with MACE which was not the case.

2. Methods

2.1. Study Population

214 patients whom coronary angiography was performed in our hospital between December 2011 and December 2012 with an initial diagnosis of stable angina pectoris (SAP) and ACS without ST segment elevation (NSTE-ACS) were screened for CAD (defined by a plaque in at least 1 major coronary artery). All angiograms were evaluated by two experienced interventional cardiologist blinded to clinical baseline characteristics of the patients. Before coronary angiography, patients with previous history of CAD (myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting), and evi-

dence of significant concomitant diseases, in particular hemodynamically significant valvular heart disease, surgery or trauma within the previous month, known cardiomyopathy, known malignant diseases, or febrile conditions were excluded. CAD was detected in 164 patients by angiography and in 50 patients coronary angiography was completely normal.

Patient's demographics, risk factors, initial diagnosis and laboratory findings were recorded. Blood samples were collected from each patient before coronary angiography and stored −70˚C. Serum resistin concentrations were measured by using a Human Resistin enzyme linked immunoabsorbant assay (Biovendor Company Germany). Other biochemical results were obtained from medical records.

The 164 patients with angiographically proven CAD were included in the actual study group and they were followed up for a period of mean 48 months from 2012-2016 for MACE. MACE (death, non-fatal MI, coronary revascularization, re-hospitalization for any cardiac reason) were recorded. Follow up data was collected from in/outpatient records. When no data was available from medical records, information was obtained through phone calls (either directly from the patient or a first degree relative).

This study was approved by the Ethics Committee of the Istanbul University Cerrahpasa School of Medicine.

2.2. Statistical Analysis

Continuous variables are reported as mean ± standard deviation or as median and inter-quartile range (IQR). Categorical variables are reported as percentages and by the x^2 test. Continuous variables are compared by the t-test or the Mann-Whitney U-test. A P value of <0.05 was considered statically significant. All tests were two-sided. Analyses were performed with SPSS software for windows, version 22.0.

3. Results

Nine patients were lost to follow-up (5%). The final study population consisted of 155 patients (72 patients with SAP, 83 patients with NonSTE-ACS). Study group characteristics and laboratory parameters of this group are given in **Table 1**.

There was 39 MACE (25%) during four years follow-up period. Sixteen in-hospital death due to cardiac causes, 8 revascularizations and 15 re-hospitalizations due to ACS were occurred as MACE. According to basal resistin levels, the patients with MACE had similar serum resistin level (mean: 23.0 ± 11.9 pg/ml) compared to patients without MACE (mean: 27.2 ± 16.4 pg/ml) (P: 0.138). Also, there was no difference between groups according to sex category, risk factors, fasting glucose, LDL-C, HDL-C, GFR, BMI, etc. MACE positive group was significantly older than MACE negative group (64.0 ± 9.1 & 58.1 ± 10.2, p: 0.001). There was much more male in MACE group but it was not significant statistically. According to initial diagnosis at hospital admission, MACE was occurred

Table 1. The characteristics and laboratory parameters of CAD positive patient's.

	CAD (+)
N	155
Male	111 (71.6%)
Female	44 (28.4%)
Age, years	59.5 + 10.4
DM	65 (41.9%)
HT	104 (67.1%)
HL	91 (58.7%)
Smoking	64 (41.3%)
Family history	50 (32.3%)
FBS, mg/dl	122.2 + 53.6
TC, mg/dl	201.2 + 42.6
LDL, mg/dl	123.5 + 35.1
HDL, mg/dl	41.3 + 16.1
TG, mg/dl	196.4 + 104.3
GFR, ml/per minute	86.3 + 26.5
Resistin, pg/ml	26.2 + 15.5
BMI, kg/m^2	29.9 + 3.3

BMI: body mass index, DM: Diabetes mellitus, FBS: Fasting Blood Sugar, GFR: glomerular filtration rate, HDL-C: high density lipoprotein cholesterol, HL: Hyperlipidemia, HT: Hypertension, LDL-C: low density lipoprotein cholesterol, TC: Total Cholesterol, TG: Triglyceride.

in 14 Non-STEMI patients, 10 USAP patients and 15 SAP patients. There was no association between MACE and initial hospitalization diagnosis (p: 0562). Also basal serum resistin levels were similar in all there clinical situation (respectively 25.4 ± 13.4 pg/ml, 25. ± 18.0 and 28.2 ± 16.5 in SAP, USAP and Non-STEMI patients). So there was no correlation between basal serum resistin levels and clinical severity of CAD. 14 of patients with one vessel disease, 12 of patients with two vessel disease and 13 of patients with three vessel diseases had MACE. So there was no association between number of diseased coronary arteries and MACE (p: 0.213). Table 2 is showing characteristics and resistin levels of patients with MACE and patients without MACE.

4. Discussion

In this study, we found there is no association between basal resistin level and MACE. The finding was consistent among both stable/ACS patients. Also number of diseased coronary artery did not predict MACE. The higher levels of serum resistin in CAD was independent of clinical diagnosis. In all three clinical situation (SAP, USAP, Non STEMI) serum resistin levels were similar. Due to association between increased serum resistin levels and presence and complexity

Table 2. Characteristics and resistin levels of MACE (+) and MACE (−) groups.

	MACE (+)	MACE (-)	P value
Age (years old)	64.0 ± 9.1	58.1 ± 10.2	0.001*
Female (%)	12.9	15.5	0.069
Male (%)	40.6	31.0	0.063
Hypertension (%)	38.7	28.4	0.131
Diabetes Mellitus (%)	23.9	18.1	0.611
Hyperlipidemia (%)	30.0	29.0	0.969
Family History (%)	20.0	12.3	0.531
Smoker (%)	25.2	16.1	0.123
Fasting glucose (mg/dl)	126.7 ± 51.3	120.7 ± 54.4	0.548
Total Cholesterol (mg/dl)	199.2 ± 43.7	201.9 ± 42.4	0.729
LDL-C (mg/dl)	124.8 ± 39.5	123.1 ± 33.6	0.800
Triglyceride (mg/dl)	174.6 ± 81.4	203.7 ± 110.3	0.133
HDL-C (mg/dl)	44.7 ± 21.5	40.1 ± 13.7	0.128
GFR (ml/dl)	81.3 ± 26.1	87.9 ± 26.5	0.175
BMI ($kg/m^{2)}$	28.5 ± 4.0	28.9 ± 3.0	0.428
Resistin (pg/ml)	23.0 ± 11.9	27.2 ± 16.4	0.138
Overall	**39**	**116**	

P < 0.05 means the significance when compared with controls. BMI: body mass index, GFR: glomerular filtration rate, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol. The errors are SD.

of CAD, we have also expected to find association between MACE and serum resistin levels, but there was no correlation.

Several studies have reported serum resistin levels to be significantly elevated in CAD patients [6] [11] [12] [13] [14]. In a meta-analysis (by formal searching of PubMed, Web of Science, Google Scholar, the Cochrane Library, Wanfang Data, China Biological Medicine Database and China National Knowledge Infrastructure), Zhang *et al.* showed that the level of serum resistin in the patients with stable angina (SA), unstable angina (UA) or acute myocardial infarction (AMI) were significantly higher than those of normal controls, respectively [15]. They also demonstrated that increased serum resistin level is significantly associated with the severity of CHD [15]. Similarly Sinan *et al.* has also established the positive correlation between serum resistin level and severity of CAD by using Gensini score [11]. Patients with high serum resistin levels had more severe and complex coronary artery disease. Conversely, Mortazavi *et al.* did not find significant association between serum resistin level and presence/severity of CAD [16]. Montazerifar *et al.* [17] has found association between high serum leptin levels (another adipokine) and CAD, but there was no significant serum resistin elevation in CAD patients in their study in contrast to previous studies

[6] [11] [12] [13] [14] [15].

A study by Lee *et al.* showed that high serum resistin levels were dependent predictors for all-cause mortality in patients with AMI [18]. In contrast, Erer *et al.* showed the association of high baseline resistin levels with an increased risk of MACE and resistin was found to be an independent risk factor for predicting MACE in patients with AMI [19]. In a study, systemic review and meta-analysis, Fontana *et al.* analyzed data from Gargano Heart Study (GHS) which was prospective in nature, to investigate the association between resistin and both all cause and cardiovascular (CV) mortality risk [20] [21]. There was 7 studies (n = 4016; 961 events) for all-cause mortality and 6 studies (n = 4187; 961 events) for CV mortality in this meta-analysis. The results provided evidence for an association between circulating resistin and mortality risk among high-risk patients (patients with diabetes and CAD] [21]. Menzaghi *et al.* investigated muti-cytokine resistin pathway in humans and its role on cardiovascular events in high risk individuals [22]. In cells and tissues resistin affects IL-1β, IL-6, IL-8, IL-12 and TNF-α expression, thus suggesting the existence of a multi-cytokine "resistin pathway". Their data indicate the existence of a resistin pathway, which is associated with cardiovascular risk factors and which strongly and independently predicts MACE.

In our study, by contrast with studies by Lee et al, by Erer et al, and by Menzaghi et al there was no association between resistin levels and MACE. Patients with MACE had similar serum resistin level compared to patients without MACE. Basal resistin levels were similar in all three clinical diagnoses (SAP, USAP and Non-STEMI). So unlike these three studies that showed correlation between serum resistin levels and MACE, there was no correlation between basal serum resistin levels and clinical severity of CAD. This may be the negative result of our study. The prognostic importance of resistin in CAD and the association between resistin and MACE remains controversial.

Study Limitations

Our study is small sample size and retrospective in nature. Thus, the role of resistin level in patients with CAD should be investigated by large-scale prospective studies. We compared serum resistin levels of two groups (patients with and without MACE). The another way is dividing patients into groups according to serum resistin levels (high, intermediate and low tertile or high versus low tertile) and follow up to occur MACE.

5. Conclusion

Although the association between increased serum resistin levels and presence and severity of CAD is obvious, the prognostic importance of serum resistin levels in CAD is contradictory. There are studies in the literature that present positive correlation between increased serum resistin and MACE but our study is important to present negative results. Negative studies are important to look at

this relation from different aspect and to prevent from biased results. We need large scale, prospective studies to before final judgment.

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