Original Article

Relation of resistin levels with C-reactve protein, homocysteine and uric acid in smokers and non-smokers

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Abstract

BACKGROUND: The association between C-reactive protein, homocysteine, uric acid levels and cardiovascular risk have been debated for decades. Resistin is a newly discovered adipocyte derived cytokine. Smoking besides its effect on atherosclerosis, is shown to alter adipocytokine levels. Bearing in mind, these complex relationship of resistin with smoking, C-reactive protein, homocysteine and uric acid, we planned to investigate the association of resistin and these cardiovascular risk factors in smoker and non-smoker subjects.

METHODS: We conducted a cross-sectional randomized study including 52 smoking and 33 non-smoking men. After making comparisons of C-reactive protein, homocysteine, uric acid and resistin between the two groups, we classified the subjects according to their insulin resistance and body mass and made again the comparisons..

RESULTS: Resistin levels were higher in smokers than in non-smokers ($p < 0.001$) and also in insulin resistant than in non-insulin resistant smokers ($p < 0.05$). Resistin levels were indifferent in non-smokers as insulin resistance was concerned and in smoker or non-smokers as body mass index was concerned. As all subjects were grouped based on homeostasis model assesment index and body mass index, neither C-reactive protein nor homocysteine and uric acid levels differred.

CONCLUSIONS: We found that smoking may have influence on resistin levels and in smokers, insulin resistance is related to resistin levels, but in smoker and non-smokers body mass may not have any association with resistin. Resistin also may not have a role in C-reactive protein, homocysteine and uric acid levels both in smokers and non-smokers.

KEYWORDS: CRP, Homocysteine, Uric Acid, Resistin, Smoking.

Atherosclerosis is an inflammatory disease which is initiated in early childhood in the vascular intima.[1] It has been accepted that atherosclerosis has traditional risk factors, such as age, family history, ethnicity, gender, smoking, hypertension, hyperlipidemia, diabetes, obesity, sedantery life and mental stress. Nowadays, new risk factors are considered such as, C-reactive protein (CRP), homocysteine and uric acid.

CRP is a sensitive marker of inflammation.[2] Although it is unknown whether CRP is involved in coronary heart disease pathogenesis,[3,4] elevated serum CRP levels are associated with cardiovascular risk factors and obesity.[5,6] Eversince McCully was the first to draw attention to the relationship between homocysteine and atherosclerosis in 1967, plasma homocysteine levels were widely accepted as an independent risk factor in cardiovascular disease.[7,8] Likewise, the association between increased serum uric acid levels and cardiovascular risk have been debated for decades and studies have provided conflicting results regarding the

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clinical significance of serum uric acid levels in cardiovascular events.[9-11]

It is shown that smoking alters adipo-cytokine levels which are associated with insulin resistance, type 2 diabetes, athero-sclerosis and cardiovascular disease.[12-16] Adipocytokines play a significant role in pathogenesis of low grade inflammation associated with type 2 diabetes, obesity, metabolic syndrome, insulin resistance and in chronic inflammatory and autoimmune diseases.[17-20] Resistin is a recently found adipocytokine.[17,21-23] The subject of its role in insulin resistance, obesity and type 2 diabetes mellitus (T2DM) in human is conflicting.[24-30]

Keeping in mind these complex associations among CRP, homocysteine, uric acid, atherosclerosis, obesity, insulin resis-tance and resistin, we planned to seek the relation between resistin levels and CRP, homocysteine, uric acid after controlling smoking behavior and insulin resistance and body mass index.

Methods
Subjects
A total of 52 male smokers aged 25-45 years (36.8±6.8), were recruited from the outpatient Clinic of Ankara Education and Research Hospital from January 2009 to May 2009. 33 aged matched (36.7 ± 7.2) male subjects formed the control group. This was a cross-sectional study, and subjects were selected randomly. As resistin serum and mRNA levels were significantly higher in females than in males at all ages, in order to obtain an homogenous group we examined only males. Smokers have been smoking at least for 2 years and at least ten cigarettes daily.

Subjects with female gender, hypertension, diabetes mellitus, glucose intolerance, hyperlipidemia, conditions which may affect metabolic parameters (such as tyroid dys-functions in past history or nowadays), chronic diseases, infection and coronary artery disease were excluded.

After detailed physical examination, in all subjects body weight and height were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood was withdrawn after 12 h of overnight fasting, at 08.30 a.m. for CRP, homocysteine, uric acid and resistin levels.

This study was performed according to the Helsinki decleration 2008. The local ethics committee approved this study and all the subjects gave written informed consent .

Methods
An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μunite/ml) x fasting plasma glucose (mmol/l)/22.5 formula as homeostasis model assessment of insulin resistance (HOMA-IR). As in normal person HOMA-IR level was stated to be < 2.7, it was chosen a cut-point for insulin resistance.[31]
High sensitivity C-reactive protein (CRP) was measured by immunnoflowmetric tests by Beckman-Cutler device. Homocysteine concentrations were determined according to the method of HPLC using Agilend 1100 device. Uric acid was measured by calorimetric methods.

For the measurements of resistin, after fasting blood samples were drawn, they were put into a dry tube, and were santrifuged, 5000 cycle/min in 10 minutes. Serum was then seperated and placed in another dry tube before storing at -80°C. Serum resistin levels were evaluated by a commercial resistin ELISA kit.

Statistical analysis
Calculations were performed using SPSS version 11.5 (Customer ID 30000105 930). Data were presented as mean ± SD. Student t-test was used to compare the groups in a parametric way. A p value of < 0.05 was considered as statistically significant. Pearson correlation coefficient was used for the correlation analysis.

Resutls

In smoker group, resistin levels were statistically found higher than in non-smoker group (p<0.001). There were no difference in CRP, homocysteine and uric acid levels between the two groups (Table 1).

As smoker group was grouped according to their HOMA-IR levels, subjects with HOMA-IR<2.7 had lower resistin levels than subjects with HOMA-IR 2.7 (p < 0.05). CRP, homocysteine and uric acid levels were not different (Table 2). When non-smoker group was grouped as HOMA-IR, subjects with HOMA-IR<2.7 and HOMA-IR 2.7 did not show any statistically different parameters (Table 2).

If smoker group was classified based on their BMI, neither CRP, homocysteine and uric acid nor resistin levels were found statistically different between the subgroups (Table 3). In non-smoker group no difference in any parameter was found when BMI was used to divide it into subgroups. (Table 3).

When we made the correlation analysis of smoker and non-smoker group, we did not find any positive or negative correlations between CRP, homocysteine, uric acid and resistin.

Discussion

We planned to find out if the interesting adipocytokine, resistin is associated with newly accepted atherosclerotic markers such as CRP, homocysteine and uric acid in subjects who smoke or do not. We found that in smokers with insulin resistance serum resistin levels were high, but between the two groups who smoked or did not smoke, who had insulin resistance or did not have, and who were obese or were not obese, CRP, homocysteine and uric acid levels were not different.

Cardiovascular disease accounts for nearly 40% of all deaths each year.[6] The factors that make up the Framingaham risk score (age, sex, blood pressure, serum total or low density lipoprotein cholesterol level, high density lipoprotein cholesterol level, smoking and diabetes) account for most of the excess risk for incident coronary heart disease.[32] However, these factors do not explain all of the excess risk,[33] so some markers have received attention as new or emerging risk factors that could account for some of the unexplained variability in cardiovascular heart disease, such as CRP, homocysteine or uric acid.

Table 1. Results of tests in smoker and non-smoker groups

	SMOKER n:52	NON-SMOKER n:33	P
CRP (mg/dl)	3.32±4.20	2.34±1.85	NS
Hcy (mmol/ml)	14.60±10.35	11.86±3.76	NS
Uric acid (mg/dl)	4.62±1.35	4.37±1.27	NS
Resistin (ng/ml)	5.79±2.58	3.25±1.40	<0.001

CRP: C- reactive protein, Hcy: Homocysteine, Homeostasis model assessment-Insulin resistance index. NS: Statistically non-significant. The results are presented as Mean ± SD.

Table 2. Characteristics of smoker and non-smoker group whose Homeostasis model assessment-Insulin resistance index was <2.7 vs. HOMA-IR≥2.7.

	Smoker			Non-smoker		
	HOMA-IR<2.7 N:22	HOMA-IR≥2.7 N:30	P	HOMA-IR<2.7 n:19	HOMA-IR≥2.7 n:14	P
CRP (mg/dl)	2.63±2.58	3.83±5.06	NS	2.49±2.21	2.13±1.26	NS
Hcy (mmol/ml)	14.23±9.33	14.88±11.18	NS	11.51±3.50	12.32±4.17	NS
Uric acid (mg/dl)	4.57±1.27	4.66±1.42	NS	4.06±0.82	4.80±1.64	NS
Rezistin (ng/ml)	4.84±2.04	6.48±2.74	<0.05	3.05±1.41	3.53±1.38	NS

CRP: C- reactive protein, Hcy: Homocysteine, HOMA-IR: Homeostasis model assessment-Insulin resistance index. NS: Statistically non-significant. The results are presented as Mean ± SD.

Table 3. Characteristics of smoker and non-smoker groups when body mass index was < 27 vs. BMI≥27.

	Smoker			Non-smoker		
	BMI<27 n:33	BMI≥27 n:19	P	BMI<27 n:14	BMI≥27 n:19	P
CRP (mg/dl)	3.39±4.83	3.21±292	NS	1.86±1.65	2.68±1.96	NS
Hcy (mmol/ml)	12.72±5.76	17.88±15.05	NS	12.16±4.31	11.63±3.40	NS
Uric Acid (mg/dl)	4.34±1.18	4.11±1.51	NS	4.02±0.74	4.63±1.52	NS
Resistin (ng/ml)	4.72±2.55	5.90±2.69	NS	3.33±1.58	3.20±1.29	NS

CRP: C- reactive protein, Hcy: Homocysteine, BMI: Body mass index. NS: Statistically non-significant. The results are presented as Mean ± SD.

CRP, a pentameric protein produced by the liver, has emerged as the golden marker for inflammation. When measured in blood, CRP proved to be a strong and independent predictor of cardiovascular disease even in healthy asymptomatic subjects.[33-34] A direct comparison of CRP and low density lipoprotein cholesterol (LDL-C) showed that CRP is a more valuable predictor for cardiovascular events and death, compared to LDL-C.[35]

Although the casual relationship between hyperhomocysteinemia and cardiovascular mortality and morbidity is not so clear, consistent findings from a large number of studies strongly support an association between homocysteine level and cardiovascular events.[7,8] However, in some studies a positive correlation between plasma homocysteine levels and severity of coronary lesions was also determined.[36,37]

Uric acid is a novel cardiovascular risk factor, but its use as an independent risk factor for so-called disease still remains controversial.[9-11] In concordance with the studies claiming that increased uric acid levels were associated with an increase in coronary heart disease risk, use of allopurinol has been shown to be related with reduced mortality risk and with reduced blood pressure in some trials.[38,39].

Smoking is well established as a casual factor in coronary heart disease and stroke. Furthermore, large studies suggested that smoking is associated with the development of type 2 diabetes in men and women consistent with evidence linking smoking and insulin resistance.[12-16] Smoking subjects with impaired glucose tolerance and diabetes appeared more insulin resistant than their non-smoking counterparts.[12,40] Smoking also alters levels of adipocytokines.[16,41,42]

Adipocyte related resistin is a circulating protein implicated in insulin resistance in rodents, but the role of human resistin is uncertain because it is produced also by macrophages.[24-30] Besides its role in inflammation,[43-45] some papers reported that in humans, plasma resistin levels correlate with obesity, insulin resistance and type 2 diabetes, while other authors failed to observe any correlation of plasma resistin levels with metabolic or anthropometric parameters. Different explanations could account for these discrepancies including the use of different assay methods, low number of patients enrolled in the different studies and the definition used to select patients. Bearing in mind the relationship of atherosclerosis with inflammation, a number of studies investigated the association of resistin with inflammatory markers such as CRP[44-46] and also resistin was found to be related to coronary artery calcification.[47-49]

The results of current study may have several important implications. First, our findings confirm that smoking elevates the levels of resistin. Second, in smokers resistin levels are associated with insulin resistance, but in non-smokers resistin does not differ when insulin resistance is present or absent. Third, in smoker or in non-smoker subjects if obesity exists or not, resistin levels are not significantly different. Fourth, disputatious

atherosclerotic markers such as CRP, homocysteine or uric acid are not statistically high in smokers than in non-smoker counterparts. Also, in smoker subjects, insulin resistance or obesity did not alter the levels of these markers. In non-smokers, the result is the same. Fifth, CRP, homocysteine or uric acid are not correlated with serum resistin concentrations neither in smokers nor in non-smokers.

Smoking is associated with increased plasma homocysteine levels, and both are associated with an increased risk of cardiovascular disease.[50] It was also determined that passive smoke exposure in never-smokers is positively and independently associated with plasma homocysteine levels in a dose-dependent manner, probably pointing out the link between passive smoking and cardiovascular events.[50] It was also shown that male gender was independently associated with elevated homocysteine levels.[51] Aging was also demonstrated to be accompanied by elevated homocysteine.[52] Having two risk factors about hyperhomocysteinemia, such as male gender and smoking we awaited to find higher levels of homocysteine in our smoking male subjects, but we could not find any statistically significant difference between the groups. Homocysteine levels of our smoking group was nonsignificantly high. Perhaps if we had formed a larger group, we would have find a satisfying result. We may also explain our results by the apparently low age of our subjects.

In discordance with previous data on the relation of resistin with inflammatory markers such as CRP.[44-47] we failed to observe any correlation between CRP, homocysteine, uric acid and resistin. We can explain the difference in our results by a number of conditions. Primarily, our groups comprised apparently healthy men. Second, our subjects were young having the mean age of 36.8±6.8 in smokers and 36.7± 7.2 in non-smokers. Third, we measured each marker at study enrtry and thus could not evaluate the effects of changes in the levels of these markers over time. The discrepancy of previous results with ours may be related to the time of the measurement of the markers. We think that variation over time in levels of these markers may change the correlations.

In conclusion, we want to speculate that smoking may have influence on resistin levels and in smokers insulin resistance is related to resistin levels. Furthermore, we suggest that in smoker and non-smokers, body mass may not have any association with resistin. Our results also makes us think that this small group of atherosclerotic markers are not associated to resistin levels when the subjects smoke or not. Larger and longer studies with subjects having greater range of age and two sexes may enlighten the idea of the association of CRP, homocysteine and uric acid with resistin either in smokers or non-smokers.

Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
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