

Original Article**Relation of resistin levels with C-reactive protein, homocysteine and uric acid in smokers and non-smokers**

Onur Esbah<sup>1</sup>, Gül Gürsoy<sup>2</sup>, Nazli Gulsoy Kirnap<sup>1</sup>, Hacer Cetiner<sup>1</sup>,  
Berrin Demirbaş<sup>3</sup>, Yasar Acar<sup>1</sup>, Murat Bayram<sup>1</sup>

**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 differed.

**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.

J Res Med Sci 2011; 16(10): 1273-1279

**A**therosclerosis is an inflammatory disease which is initiated in early childhood in the vascular intima.<sup>1</sup> 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.<sup>2</sup> Although it is unknown whether CRP is

involved in coronary heart disease pathogenesis,<sup>3,4</sup> elevated serum CRP levels are associated with cardiovascular risk factors and obesity.<sup>5,6</sup> 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.<sup>7,8</sup> 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

1- Department of Internal Medicine, Ministry of Health Ankara Education and Research Hospital, Ankara, Turkey.

2- Associate Professor, Department of Internal Medicine, Ministry of Health Ankara Education and Research Hospital, Ankara, Turkey.

3- Associate Professor, Departement of Endocrinology, MESA Hospital, Ankara, Turkey.

Corresponding Author: Gül Gürsoy

E-mail: gulgursoyyener@yahoo.com

clinical significance of serum uric acid levels in cardiovascular events.<sup>9-11</sup>

It is shown that smoking alters adipocytokine levels which are associated with insulin resistance, type 2 diabetes, atherosclerosis and cardiovascular disease.<sup>12-16</sup> 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.<sup>17-20</sup> Resistin is a recently found adipocytokine.<sup>17,21-23</sup> The subject of its role in insulin resistance, obesity and type 2 diabetes mellitus (T2DM) in human is conflicting.<sup>24-30</sup>

Keeping in mind these complex associations among CRP, homocysteine, uric acid, atherosclerosis, obesity, insulin resistance 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 ( $36.8 \pm 6.8$ ), were recruited from the outpatient Clinic of Ankara Education and Research Hospital from January 2009 to May 2009. 33 aged matched ( $36.7 \pm 7.2$ ) 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 thyroid dysfunctions 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 declaration 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 ( $\mu\text{unit/ml}$ ) x fasting plasma glucose ( $\text{mmol/l}$ )/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.<sup>31</sup>

High sensitivity C-reactive protein (CRP) was measured by immunofluorescent tests by Beckman-Cutler device. Homocysteine concentrations were determined according to the method of HPLC using Agilent 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 centrifuged, 5000 cycle/min in 10 minutes. Serum was then separated and placed in another dry tube before storing at  $-80^{\circ}\text{C}$ . 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  $\pm$  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.

## Results

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  $\geq 2.7$  ( $p < 0.05$ ). 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  $\geq 2.7$  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.<sup>6</sup> The factors that make up the Framingham 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.<sup>32</sup> However, these factors do not explain all of the excess risk,<sup>33</sup> 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  $\pm$  SD.

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

	Smoker		P	Non-smoker		P
	HOMA-IR $< 2.7$ N:22	HOMA-IR $\geq 2.7$ N:30		HOMA-IR $< 2.7$ n:19	HOMA-IR $\geq 2.7$ n:14	
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
Resistin (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  $\pm$  SD.

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

	Smoker		P	Non-smoker		P
	BMI<27 n:33	BMI≥27 n:19		BMI<27 n:14	BMI≥27 n:19	
CRP (mg/dl)	3.39±4.83	3.21±2.92	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.<sup>33-34</sup> 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.<sup>35</sup>

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.<sup>7,8</sup> However, in some studies a positive correlation between plasma homocysteine levels and severity of coronary lesions was also determined.<sup>36,37</sup>

Uric acid is a novel cardiovascular risk factor, but its use as an independent risk factor for so-called disease still remains controversial.<sup>9-11</sup> 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.<sup>38,39</sup>

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.<sup>12-16</sup> Smoking subjects with impaired glucose tolerance and diabetes appeared more insulin resistant than their non-smoking counterparts.<sup>12,40</sup> Smoking also alters levels of adipocytokines.<sup>16,41,42</sup>

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.<sup>24-30</sup> Besides its role in inflammation,<sup>43-45</sup> 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<sup>44-46</sup> and also resistin was found to be related to coronary artery calcification.<sup>47-49</sup>

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.<sup>50</sup> 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.<sup>50</sup> It was also shown that male gender was independently associated with elevated homocysteine levels.<sup>51</sup> Aging was also demonstrated to be accompanied by elevated homocysteine.<sup>52</sup> 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 found a satisfying result. We may also explain our results by the apparently low age of our subjects.

### **Conflict of Interests**

Authors have no conflict of interests.

### **Authors' Contributions**

Design: Gül Gürsoy, Onur Eşbah

Analysis and interpretation of the data: Gül Gürsoy, Onur Eşbah, Berrin Demirbaş.

Final approval of the article: Gül Gürsoy, Onur Eşbah, Nazlı Gülsoy Kırnay, Hacer Çetiner, Berrin Demirbaş, Yaşar Acar, Murat Bayram.

Statistical expertise: Onur Eşbah, Yaşar Acar.

Collection of data: Onur Eşbah, Murat Bayram, Nazlı Gülsoy Kırnay, Hacer Çetiner.

In discordance with previous data on the relation of resistin with inflammatory markers such as CRP.<sup>44-47</sup> 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  $36.8 \pm 6.8$  in smokers and  $36.7 \pm 7.2$  in non-smokers. Third, we measured each marker at study entry 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.

### **Acknowledgements**

We thank the patients.



## References

1. Luomala M, Paiva H, Thelen K, Laaksonen R, Saarela M, Mattila K, et al. Osteopontin levels are associated with cholesterol synthesis markers in mildly hypercholesterolaemic patients. *Acta Cardiol* 2007; 62(2): 177-81.
2. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003; 111(12): 1805-12.
3. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. *Circulation* 2006; 113(17): 2128-34.
4. Hingorani AD, Shah T, Casas JP. Linking observational and genetic approaches to determine the role of C-reactive protein in heart disease risk. *Eur Heart J* 2006; 27(11): 1261-3.
5. Miller M, Zhan M, Havas S. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2005; 165(18): 2063-8.
6. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; 151(7): 483-95.
7. Tarkun I, Cetinarlan B, Canturk Z. Lipoprotein(a) concentrations in patients with type 2 diabetes mellitus without cardiovascular disease: relationship to metabolic parameters and diabetic complications. *Nutr Metab Cardiovasc Dis* 2002; 12(3): 127-31.
8. Oudi ME, Aouni Z, Mazigh C, Khochkar R, Gazoueni E, Haouela H, et al. Homocysteine and markers of inflammation in acute coronary syndrome. *Exp Clin Cardiol* 2010; 15(2): e25-e28.
9. Wu YQ, Li J, Xu YX, Wang YL, Luo YY, Hu DY, et al. Predictive value of serum uric acid on cardiovascular disease and all-cause mortality in urban Chinese patients. *Chin Med J (Engl)* 2010; 123(11): 1387-91.
10. Krishnan E, Sokolove J. Uric acid in heart disease: a new C-reactive protein? *Curr Opin Rheumatol* 2011; 23(2): 174-7.
11. Rodrigues TC, Maahs DM, Johnson RJ, Jalal DI, Kinney GL, Rivard C, et al. Serum uric acid predicts progression of subclinical coronary atherosclerosis in individuals without renal disease. *Diabetes Care* 2010; 33(11): 2471-3.
12. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007; 298(22): 2654-64.
13. Ronnema T, Ronnema EM, Puukka P, Pyorala K, Laakso M. Smoking is independently associated with high plasma insulin levels in nondiabetic men. *Diabetes Care* 1996; 19(11): 1229-32.
14. Nakashita Y, Nakamura M, Kitamura A, Kiyama M, Ishikawa Y, Mikami H. Relationships of cigarette smoking and alcohol consumption to metabolic syndrome in Japanese men. *J Epidemiol* 2010; 20(5): 391-7.
15. Al Mutairi SS, Mojiminiyi OA, Shihab-Eldeen AA, Al SA, Abdella N. Effect of smoking habit on circulating adipokines in diabetic and non-diabetic subjects. *Ann Nutr Metab* 2008; 52(4): 329-34.
16. Al-Daghri NM, Al-Attas OS, Hussain T, Sabico S, Bamakhramah A. Altered levels of adipocytokines in type 2 diabetic cigarette smokers. *Diabetes Res Clin Pract* 2009; 83(2): e37-e39.
17. Stofkova A. Resistin and visfatin: regulators of insulin sensitivity, inflammation and immunity. *Endocr Regul* 2010; 44(1): 25-36.
18. GURSOY G, KYRNAS NG, ESBAB O, ACAR Y, DEMIRBAS B, AKCAYOZ S. The relationship between plasma omentin-1 levels and insulin resistance in newly diagnosed type 2 diabetic women. *Clin Rev Opin* 2010; 2(4): 49-54.
19. GURSOY G, ALAGOZ S, ACAR Y, DEMIRBAS B, CETINER H, KILIC Z. Osteopontin a new probable marker for atherosclerosis in obese women. *Clin Rev Opin* 2010; 2(3): 35-40.
20. GURSOY G, AKCAYOZ SS, ACAR Y, DEMIRBAS B. Visfatin in hyperlipidemic female patients. *J Medicine Medical Sciences* 2010; 1(4): 120-5.
21. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. *Nature* 2001; 409(6818): 307-12.
22. Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *J Biol Chem* 2001; 276(14): 11252-6.
23. Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, et al. FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* 2000; 19(15): 4046-55.
24. Al-Harithy RN, Al-Ghamdi S. Serum resistin, adiposity and insulin resistance in Saudi women with type 2 diabetes mellitus. *Ann Saudi Med* 2005; 25(4): 283-7.
25. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, et al. Resistin / Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. *Diabetes* 2001; 50(10): 2199-202.
26. Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, et al. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration:

- cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab* 2003; 88(10): 4848-56.
27. Vozarova de Court, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. *Diabetes* 2004; 53(5): 1279-84.
  28. Rea R, Donnelly R. Resistin: an adipocyte-derived hormone. Has it a role in diabetes and obesity? *Diabetes Obes Metab* 2004; 6(3): 163-70.
  29. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, et al. Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia* 2005; 48(11): 2330-3.
  30. Makimura H, Mizuno TM, Bergen H, Mobbs CV. Adiponectin is stimulated by adrenalectomy in ob/ob mice and is highly correlated with resistin mRNA. *Am J Physiol Endocrinol Metab* 2002; 283(6): E1266-E1271.
  31. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27(6): 1487-95.
  32. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97(18): 1837-47.
  33. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* 2003; 290(7): 891-7.
  34. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336(14): 973-9.
  35. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347(20): 1557-65.
  36. Agoston-Coldea L, Mocan T, Seicean A, Gattfosse M, Rosenstingl S. The plasma homocysteine concentrations and prior myocardial infarction. *Rom J Intern Med* 2010; 48(1): 65-72.
  37. Clarke R, Halsey J, Bennett D, Lewington S. Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials. *J Inherit Metab Dis* 2011; 34(1): 83-91.
  38. Nam GE, Lee KS, Park YG, Cho KH, Lee SH, Ko BJ, et al. An increase in serum uric acid concentrations is associated with an increase in the Framingham risk score in Korean adults. *Clin Chem Lab Med* 2011; 49(5): 909-14.
  39. Tan Z, Dai T, Zhong X, Tian Y, Leppo MK, Gao WD. Preservation of cardiac contractility after long-term therapy with oxypurinol in post-ischemic heart failure in mice. *Eur J Pharmacol* 2009; 621(1-3): 71-7.
  40. Targher G, Alberiche M, Zenere MB, Bonadonna RC, Muggeo M, Bonora E. Cigarette smoking and insulin resistance in patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997; 82(11): 3619-24.
  41. Al Mutairi SS, Mojiminiyi OA, Shihab-Eldeen AA, Al SA, Abdella N. Effect of smoking habit on circulating adipokines in diabetic and non-diabetic subjects. *Ann Nutr Metab* 2008; 52(4): 329-34.
  42. Efstathiou SP, Skeva II, Dimas C, Panagiotou A, Parisi K, Tzanoumis L, et al. Smoking cessation increases serum adiponectin levels in an apparently healthy Greek population. *Atherosclerosis* 2009; 205(2): 632-6.
  43. Gomez-Ambrosi J, Fruhbeck G. Evidence for the involvement of resistin in inflammation and cardiovascular disease. *Curr Diabetes Rev* 2005; 1(3): 227-34.
  44. de Luis DA, Sagrado MG, Conde R, Aller R, Izaola O, de la Fuente B, et al. Relation of resistin levels with cardiovascular risk factors, insulin resistance and inflammation in naive diabetes obese patients. *Diabetes Res Clin Pract* 2010; 89(2): 110-4.
  45. Straburzynska-Lupa A, Nowak A, Pilaczynska-Szczesniak L, Straburzynska-Migaj E, Romanowski W, Karolkiewicz J, et al. Visfatin, resistin, hsCRP and insulin resistance in relation to abdominal obesity in women with rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28(1): 19-24.
  46. Kopff B, Jegier A. Adipokines: adiponectin, leptin, resistin and coronary heart disease risk. *Przegl Lek* 2005; 62 (Suppl 3): 69-72.
  47. Chen BH, Song Y, Ding EL, Roberts CK, Manson JE, Rifai N, et al. Circulating levels of resistin and risk of type 2 diabetes in men and women: results from two prospective cohorts. *Diabetes Care* 2009; 32(2): 329-34.
  48. Chen C, Jiang J, Lu JM, Chai H, Wang X, Lin PH, et al. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. *Am J Physiol Heart Circ Physiol* 2010; 299(1): H193-H201.
  49. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. *Eur J Endocrinol* 2007; 156(2): 279-84.
  50. Kim DB, Oh YS, Yoo KD, Lee JM, Park CS, Ihm SH, et al. Passive smoking in never-smokers is associated with increased plasma homocysteine levels. *Int Heart J* 2010; 51(3): 183-7.
  51. Selhub J. Homocysteine metabolism. *Annu Rev Nutr* 1999; 19: 217-46.
  52. Dominguez LJ, Galioto A, Pineo A, Ferlisi A, Ciaccio M, Putignano E, et al. Age, homocysteine, and oxidative stress: relation to hypertension and type 2 diabetes mellitus. *J Am Coll Nutr* 2010; 29(1): 1-6.