Elevated resistin opposed to adiponectin or angiogenin plasma levels as a strong, independent predictive factor for the occurrence of major adverse cardiac and cerebrovascular events in patients with stable multivessel coronary artery disease over 1-year follow-up

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Summary

Background:
Adipokines such as adiponectin and resistin, as well as angiogenin, may be associated with inflammation and atherosclerosis. The relationship between their levels and prognosis in high risk patients is, however, still unclear. The aim of this study was to evaluate the prognostic value of these adipokines in patients with stable multivessel coronary artery disease (MCAD).

Material/Methods:
The study group comprised 107 MCAD patients (74% males, mean age 63±8 years). Adiponectin, resistin and angiogenin plasma levels were measured at admission and after 1-year follow-up. Primary end point (major adverse cardiac and cerebrovascular events – MACCE) was defined as cardiac death, nonfatal myocardial infarction, stroke, and hospitalization for angina or heart failure over a 1-year period.

Results:
After 1-year follow-up, 9 (8%) patients died, all from cardiovascular causes. Primary end point was experienced by 32% of patients. Surgical treatment (CABG) was received by 51% of patients, while 49% were treated medically alone. Total cholesterol concentration levels ≥173 mg/dl were associated with a 7-fold increase (OR 7.3; 95% CI, 1.6–33.0); LDL ≥93.5 mg/dl with a 16-fold increase (OR 16.3; 95% CI, 2.8–93.8), and resistin ≥17.265 ng/ml with a 13-fold increase in MACCE risk (OR 13.5; 95% CI, 2.3–80.3). In multivariate analysis, a medical treatment strategy (p=0.001), a higher CCS class (p=0.004), resistin levels (p=0.003) and a higher Gensini score (p=0.03) were independent predictors of MACCE.

Conclusions:
In stable patients with MCAD, elevated plasma resistin (as opposed to adiponectin or angiogenin) is a strong, independent predictive factor for the occurrence of MACCE over 1-year follow-up.

key words: multivessel coronary heart disease • dipocytokines • angiogenesis • prognosis

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**BACKGROUND**

Coronary artery disease (CAD) is the main cause of death in developed countries [1]. Despite recent progress in cardiology, global cardiovascular mortality is still very high, exceeding 7 million in 2002 [2]. Multivessel coronary artery disease (MCAD), defined as subcritical or critical stenosis (cross-section area decreased by >75%) of at least 2 of the 3 main coronary arteries supplying the myocardium, is a common manifestation of advanced coronary atherosclerosis [2]. It has been estimated to represent as much as 50% of all the cases of CAD. Such severity of coronary atherosclerosis leads to common atherothrombotic complications resulting in exceptionally high mortality rate, ranging from 10% to 60% in 5-year follow-up, depending on the extent of atherosclerotic lesions, as well as concomitant risk factor profile [3]. However, this wide range suggests an inhomogeneity of this clinical group.

The commonly unfavorable clinical course and poor prognosis in this particular group of patients attracts the attention of current cardiological research, including the search for markers that improve prognostic stratification in MCAD patients. Adipocytokines and angiogenesis factors are the substances of particular interest.

Adipose tissue has recently been recognized as an endocrine organ. Adiponectin, an adipocytokine, is a recently discovered protein that modulates and suppresses inflammatory response in atherosclerotic lesions [4]. Hypoadiponectinemia has been observed in patients with metabolic syndrome, diabetes mellitus and coronary artery disease [5,6]. Published data support a strong association between plasma adiponectin levels and risk stratification in CAD patients [7]. Despite potential protective function, there are no clear data on whether high or low serum concentrations of adiponectin are associated with poor prognosis. Recently published studies unexpectedly have shown that high plasma adiponectin concentrations were independent risk factors in short- and long-term observations in CAD patients [8,9].

Resistin belongs to a novel family of cysteine-rich proteins called resistin-like molecule or FIZZ (found in inflammatory zone) proteins [10]. Resistin appears to be involved in inflammatory pathways, vascular endothelial cell activation and stimulation of smooth muscle cell proliferation, suggesting its potential role in atherosclerosis [11,12]. Recently, resistin and its mRNA have been detected in atherosclerotic lesions [13]. This is consistent with the finding of elevated circulating resistin in patients with coronary artery disease. Thus, resistin can be considered as an inflammatory marker of atherosclerosis and atherosclerotic complication in humans [14,15].

Angiogenin is a soluble protein, one of the angiogenic factors involved in the creation of capillaries, leading to the formation of new vessels from pre-existing vascular structures [16]. Several studies have suggested that angiogenin and other angiogenic factors can promote atherosclerosis, and potentially destabilize coronary plaques by promoting intralosomal angiogenesis [17,18]. Moreover, angiogenin has been shown to be an independent predictor of poor prognosis in coronary heart disease [19].

The aim of this study was to evaluate the prognostic value of adiponectin, resistin and angiogenin in patients with stable multivessel coronary artery disease.

**MATERIAL AND METHODS**

**Study group**

The study involved a consecutive group of 107 patients with coronary artery disease undergoing angiography at the 2nd Department of Cardiology, Medical University in Lodz in 2007 and meeting the following criteria:
1. Coronary artery disease with >75% diameter stenosis in 3 main coronary branches (right coronary artery, circumflex branch and left anterior descending branch of left coronary artery) as confirmed on coronary angiography. Stenosis of the left main coronary artery exceeding 50% represented an exclusion criterion due to need for urgent revascularization.
2. Stable coronary heart disease (Canadian Cardiovascular Society – CCS I–III*).
3. Absence of significant acquired valve disease resulting in predicted survival below 1 year.
4. Qualification for surgical or medical treatment strategy (qualification to percutaneous angioplasty at baseline was an exclusion criterion)

Following discharge from the department, all patients remained under the care of the outpatient clinic and were followed prospectively for the development of clinical events during 12 months after index coronary angiography. Four patients withdrew their consent to participate in a follow-up visit at 12 months (all the clinically important data were collected via telephone calls; there were no significant events during the investigated time period), and as a result of this, 103 patients were included in final analysis. All the patients were treated pharmacologically according to the current guidelines of the European Society of Cardiology. The choice of treatment strategy (coronary artery bypass graft – CAGB or medical strategy) was made during joint consultations of cardiologists and cardiac surgeons. The main factors determining treatment strategy were clinical severity of the disease, angiographic presentation, as well as the patient’s preferences. All the patients qualified for CAGB were treated in I Department of Cardiosurgery, Medical University in Lodz, receiving left internal mammary artery grafting of the left descending branch (LIMA to LAD) and at least 2 saphenous vein grafts to other coronary vessels. All patients included in the study signed an informed consent form to participate; the study was also approved by the regional Bioethics Committee at the Medical University in Lodz.

**Baseline biochemical tests**

All the patients had additional laboratory tests including: complete blood count, complete lipid profile, fasting blood glucose (and, in non-diabetic patients, an oral glucose tolerance test with blood glucose measurement after 2 hours), CKMB, ura, creatinine, glomerular filtration rate (GFR – measured with the Cockroft-Gault formula), hepatic transferases, C-reactive protein and NT-proBNP levels. Beside the standard biochemical parameters, we examined novel markers such as adiponectin, resistin, angiogenin, tumor necrosis factor alpha (TNF-alpha) and interleukin 8 (IL-8).
proposed as related to the severity of pathophysiological processes promoting atherothrombosis.

**Methodology of cytokine measurement**

Cytokines were assessed in blood samples drawn at baseline and after 12 month follow-up visit. Aliquots plasma samples stored at −70°C were thawed, the concentrations of angiogenin, adiponectin, resistin, TNF-alpha and IL-8 were measured using commercially available ELISA kits (R&D Systems, MN, USA).

**ECG, echocardiography, exercise stress test and coronary angiography**

Transthoracic echocardiography, resting ECG, and electrocardiographic exercise test were performed at baseline in all patients. Based on coronary angiographic results, severity of atherosclerotic changes was semiquantitatively with Gensini score. Lesions formed (involving lesion severity and location) in left main and proximal segments of left descending artery, circumflex and right coronary artery were grouped to calculate proximal Gensini score and distal lesions located in the remaining coronary segments yielded distal Gensini score.

**12-month follow-up measurements**

After 12 months, we stored blood samples to assess serum levels of angiogenin, adiponectin and resistin in all patients. During a follow-up visit, we performed an electrocardiographic exercise test (10 patients due to ischemic changes or/and clinical symptoms not capable to do the test) and transthoracic echocardiography.

**Clinical endpoints**

Patients were followed for at least 12 months for the occurrence of death (all-cause and cardiac), stroke and myocardial infarction (MI). We defined a cumulative major adverse cardiac and cerebrovascular event (MACCE) as composition of death, stroke, MI and hospitalization due to the progression of ischemic and/or heart failure (HF) symptoms. MI during follow-up was defined according to recent universal definition [20]. Death was classified as cardiac if the predominant and immediate cause was related to ischemia, arrhythmia, refractory HF, or if death was sudden and unexpected in nature. Information regarding death was obtained by review of the death certificate and conversation with the family.

**Statistical analysis**

The Shapiro-Wilk’s test was used to determine the normality of the analyzed variables distribution. Continuous variables showing normal distribution were presented as means ± standard deviations, whereas those with distribution different from normal and ordinal variables were expressed as medians with interquartile range (25th–75th percentile). Variance analysis and the Wilcoxon non-parametric test were applied to compare the differences in the presence of particular features in patient groups. The results were considered statistically significant if the p value was <0.05.

In univariate analysis, due to lack of normality of distribution of the majority of the analyzed variables, the Mann-Whitney U test was used to compare continuous variables in the study group, and the chi-square test for independence was applied to compare constant variables. For selected parameters, receiver operating characteristic curves (ROC) were plotted.

In multivariate analysis we tried to build a logistic regression model in the study group using the variables that significantly influenced MACCE in univariate analysis. However, due to lack of significance of these models, we then used step-wise logistic regression analysis. Chi-square statistic with the number of degrees of freedom equal was used to measure variables to assess the fit of the model.

Kaplan-Meier analysis was used to compare the survival in groups defined by treatment strategy or values of cytokine concentrations.

**RESULTS**

**Baseline characteristics**

A total of 107 patients were enrolled in the study and followed-up for 12 months. One year follow-up data were available for 100% of the patients (in 4 patients we did not perform a 12-month follow-up control test, but we received information about their medical history during the studied time period). Out of 107 patients, 80 (74%) were male, the mean age in the group was 62.5. All the patients complained of chest pain – the mean CCS class in the study group was 2.5 (2–3), mean the angina history duration was 71 ± 64 months. The mean Gensini score in the study group was 91 (66–132), with the proximal Gensini score being 45 (20–90) and the distal one 49 (20–70). The baseline demographic, clinical, laboratory and angiographic characteristics of the study population stratified by the treatment strategy are shown in Tables 1, 2. Fifty-five patients (51%) were treated surgically (CABG), while 52 (49%) were treated medically. Patients qualified for medical therapy had a significantly longer history of angina duration, more severe heart failure symptoms, higher serum LDL cholesterol and lower values of the proximal Gensini score.

**Clinical endpoints**

Among the 107 patients followed-up over 12 months there were 9 deaths (8%, all from cardiovascular reasons), including 6 (11.5%) in medically treated patients (2 deaths due to MI, 2 due to stroke and 2 sudden cardiac deaths at home) and 3 (5.5%) in the CABG group (2 periprocedural deaths, 1 due to stroke). Patients treated pharmacologically were more commonly hospitalized due to the progression of angina symptoms (20 vs. 5; p=0.003). Six patients (11.5%) developed MI in the CABG group and 1 (1.3%) in the CABG group (p=NS). In 7 patients (13.5%) from the pharmacologically treated group, a palliative percutaneous procedure (PTCA) was performed on 1 diseased vessel with drug eluting stent implantation (without complete revascularization). All events during a 12-month follow-up are summarized in Table 3.

**Survival analysis**

Predictors of MACE in the study group of patients, revealed by univariate logistic regression analysis were: total
cholesterol (p=0.01), LDL-cholesterol (p=0.009) and resistin (p=0.01) plasma levels. The total cholesterol concentration level \( \geq 173 \text{ mg/dl} \) was associated with a 7-fold increase in MACCE risk (OR 7.3; 95% CI, 1.6–33.0); LDL \( \geq 93.5 \text{ mg/dl} \) with a 16-fold increase in MACCE risk (OR 16.3; 95% CI, 2.8–93.8) and resistin \( \geq 17.3 \text{ ng/ml} \) with a 13-fold increase in MACCE risk (OR 13.5; 95% CI, 2.3–80.3), as shown in Figures 1, 2.

In multivariate analysis, medical treatment strategy (p=0.001), a higher CCS class (p=0.004), resistin level (p=0.003) and a higher Gensini score (p=0.03) were independent predictors of MACCE.

**DISCUSSION**

The investigation of novel circulating serum biomarkers in patients with coronary heart disease has been accelerating at a remarkable pace. This expanding body of research has established firm evidence for the value of several biomarkers, such as those for diagnosis, treatment efficiency and risk assessment, among patients with CAD.

Our study showed that among patients with multivessel coronary heart disease, application in clinical practice of some novel inflammatory and angiogenesis factors would allow for risk stratification, thus limiting the incidence of numerous cardiovascular adverse events in this group of patients. In light of the above, novel biochemical markers, such as resistin (the marker of atherogenesis activity), have shown promising results. However, we did not find that knowledge of the serum levels of adiponectin, angiogenin (the marker of angiogenesis activity), as well as novel inflammatory markers (IL-8 and TNF alpha) helps in the assessment of prognosis.

The understanding of mechanisms underlying the atherosclerotic process, from a pathologist’s point of view being a form of inflammatory response to factors damaging the vessel wall, has made it possible to identify many markers of inflammatory response crucial in atherogenesis. A new, recently revealed inflammatory marker, closely connected with atherosclerosis, is the fat cell protein product resistin. There are many studies showing elevated serum resistin levels in CAD patients that indicate the severity of the inflammatory response connected with atherogenesis [20].

| Males n (%) | CABG group N=55 | Medical group N=52 | P |
|-------------|-----------------|-------------------|---|
| Age (mean ±SD) | 43 (77%) | 36 (72%) | NS |
| Duration of angina (months, mean ±SD) | 61.5±8.5 | 64.6±8.1 | NS |
| History of myocardial infarction n (%) | 40 (73%) | 33 (63%) | NS |
| NYHA Class | 2 (1–2) | 2 (1–3) | 0.03 |
| CCS Class | 2.5 (2–3) | 2.5 (2–2.5) | NS |
| Kidney failure n (%) | 0 (0%) | 3 (6%) | NS |
| Hypertension m (%) | 53 (96%) | 51 (98%) | NS |
| Diabetes mellitus n (%) | 27 (49%) | 24 (46%) | NS |
| Impaired glucose tolerance n (%) | 18 (33%) | 16 (31%) | NS |
| Obesity n (%) | 17 (31%) | 20 (38%) | NS |
| Body mass index (mean ±SD) | 28.3±3.9 | 29.1±3.9 | NS |
| Smoking n (%) | 20 (36%) | 14 (27%) | NS |
| Positive family history n (%) | 14 (25%) | 14 (27%) | NS |
| Atrial fibrillation n (%) | 1 (2%) | 4 (8%) | NS |
| Atherosclerosis of peripheral arteries n (%) | 6 (12%) | 12 (23%) | NS |
| Stroke n (%) | 3 (5%) | 2 (4%) | NS |
| METS during exercise test | 5.7 (4.6–7) | 5.5 (4–7) | NS |
| EF (%) | 47±10 | 44±13 | NS |
| ST depression >1mm in resting ECG | 17 (31%) | 13 (25%) | NS |
| Q wave in resting ECG | 31 (56%) | 31 (60%) | NS |
| LBBB | 1 (2%) | 2 (4%) | NS |

NYHA – New York Heart Association; CCS – Canadian Cardiovascular Society; METS – Metabolic equivalents; EF – ejection fraction; LBBB – Left bundle branch block.
reports published so far have shown a strong relationship between resistin levels and the progression, severity and prognosis of patients with CAD. Reilly et al. demonstrated a relationship between resistin levels and the degree of coronary artery calcification (“calcium score”) computed on the basis of the interpretation of imaging from computed tomography performed in asymptomatic patients [20]. In addition, based on angiographic evaluation, Ohmeri et al. came to the conclusion that there is a correlation between resistin levels and the number of stenoses in coronary arteries [11]. Hu et al. also documented significantly different concentrations of resistin in stable and unstable CAD, thus confirming the role of resistin in risk stratification of atherosclerotic plaque destabilization in CAD patients [21]. Lubos et al. showed in a group of over 1500 patients that serum resistin levels are significantly higher in patients with ACS than in stable patients (p<0.001). High resistin levels were associated with a 1.22-fold (95% CI 1.04–1.43; P=0.02) increased risk for future fatal cardiovascular events in a model adjusted for risk factors and clinical and therapeutic variables during a 3-year follow-up [22]. The same conclusion came from a study conducted by Weikert C et al., showing that individuals in the highest quartile of plasma resistin levels, compared to those in the lowest quartile, had a significantly increased risk of MI (relative risk 2.09;
95% CI 1.01–4.31; p=0.01) [14]. In our study, serum resistin levels higher than 17.265 ng/ml were associated with a 13-fold increase in MACE risk.

Another recently detected substance useful in risk stratification in CAD is diponectin, the insulin-sensitizing, anti-inflammatory anti-atherosclerotic protein. The pleiotropy of adipokine activity is the reason for performing a number of clinical studies investigating its usefulness in everyday medical practice. Our findings with respect to the lack of correlation between adiponectin levels and risk stratification in coronary heart disease are in contrast to many other studies that have reaffirmed a strong relation between the serum levels of adiponectin and prognosis assessment. However, reports published so far give contradictory information. According to Inoue et al., in a group of 149 patients with confirmed CAD, low adiponectin levels were an independent predictor of cardiovascular events (RR 2.79, 95% CI 1.49 to 5.24, p=0.0014) [23]. Pischon et al. drew similar conclusions – in a group of over 1800 patients, participants in the highest quintile of adiponectin levels, as compared with the lowest quintile, had a significantly decreased risk of MI (RR 0.39; 95% CI, 0.23–0.64; p=0.001) during a 6-year follow-up [24]. On the other hand, Cavusoglu et al., in group of 325 male patients with CAD, showed that high plasma adiponectin levels independently predict the individual endpoints of all-cause mortality, cardiac mortality, and MI. Twenty-four-month survival rates for patients in the lower (< or =4.431 mg/L), middle (>4.431 and < or =8.008 mg/L), and upper (>8.008 mg/L) tertiles of plasma adiponectin values were 95.0, 90.4, and 83.5%, respectively (p=0.02) [8]. The same conclusion came from a study conducted by Laughlin at al., who found that in a group of over 1500 patients, adiponectin levels in the highest sex-specific quintile, as compared with lower levels, were associated with almost 40% higher risks of cardiovascular disease death and death from all causes, independent of age, sex, waist girth, lipid levels, and glucose level (both p<0.001) [9]. These conflicting observations may relate, at least in part, to the markedly different risk profiles of the populations in the presented studies, as well as in our study. Our patient population consisted of a relatively high-risk cohort, as manifested not only by the clinical, angiographic, and laboratory data, but also by the high incidence of heart failure. Indeed, it is well-established that patients with CHF have higher baseline levels of adiponectin, which may be a consequence of resistance at the level of the adiponectin receptor, a mechanism potentially akin to that seen in diabetics with elevated insulin levels [8,25,26]. This is why a significant lowering of plasma adiponectin concentrations after 12 months (better expressed in the CABG group), observed in our study, might be the result of the improvement of systolic left ventricular function and heart failure symptoms.

The presence of coronary collateralization improves the prognosis for patients with advanced coronary artery disease. Collateral improve ventricular function and overall perfusion in ischemic myocardium [27]. The development of coronary collaterals appears to be initiated by ischemia resulting in the opening of preexisting anastomotic channels through an increase in shear forces and pressure, or by formation of new capillary sprouts (angiogenesis). On the other hand, there is strong evidence that the development of human atherosclerotic plaques is associated with the formation of new macrovessels within the plaque [28–30]. Therefore, the role of angiogenesis remains a highly contentious issue, and no consensus exists as to whether angiogenesis is the key causative factor in the pathogenesis of atherosclerotic plaque formation, or as to the best treatment of coronary artery disease. There are some reports showing correlation between angiogenin levels and risk stratification in coronary heart disease. Tello-Montoliu et al. demonstrated in a group of 516 patients that “acute coronary syndrome” patients had significantly elevated plasma angiogenin levels as compared with both disease controls (stable CAD) and healthy controls (p<0.001). However, the authors did not find any correlation between angiogenin and the severity of atherosclerosis expressed as Gensini score, and raised angiogenin levels were independently associated with more adverse events at a 6-month follow-up [19]. These observations are in contrast to our findings, with no
correlation between serum angiogenin levels and prognosis after 12 months, probably due to high heterogeneity of the investigated group of patients.

This study is limited by the relatively small study group and a high variety of risk profiles in the study group. Finding a more homogenous group of patients, especially as regards heart failure symptoms, might help to better understand the complex chain of relationships between inflammation, atherosclerosis and angiogenesis.

CONCLUSIONS

In conclusion, in stable patients with multivessel coronary artery disease, high plasma resistin is a strong independent predictive factor for the occurrence of MACE over 1-year follow-up. This initial demonstration of prognostic potential of the novel biomarkers warrants further studies on their practical usefulness and relationship with established clinical factors.

REFERENCES:

1. American Heart Association. Heart Disease and Stroke Statistics – 2008 Update. American Heart Association, Dallas, Texas 2008
2. Morrow A, Gersh J, Braunwald E: Chronic Coronary Heart Disease [In:] Zipes DR, Libby P, Bonow RO, Braunwald E (eds.). Braunwald’s Heart Disease – a textbook of cardiovascular medicine 7th Edition. 2005; 50: 354-365
3. Solomon AJ, Gersh BJ: Management of chronic stable angina: medical therapy, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. Lessons from the randomized trials. Ann Intern Med. 1998; 128: 216-23
4. Ouchi N, Kihara S, Arita Y et al: Novel modulator for endothelial adhesion molecules: Adipocytederived plasma protein adiponectin. Circulation, 1999; 100: 2473-76
5. Koenig W, Khuseyinova N, Baumert J et al: Serum concentrations of adiponectin and resistin in type 2 diabetes mellitus and coronary heart disease in apparently healthy middle aged men: results from the 18-years follow-up of a large cohort from southern Germany. J Am Coll Cardiol, 2006; 48: 1369-77
6. Nakamura Y, Shimada K, Fukuda D et al: Implications of plasma concentrations of adiponectin in patients with coronary artery disease. Heart, 2004; 90: 528-53
7. Pietrzeniewicz K, Luczak K, Maciejewski M, Goch JH: Impact of obesity and adipokines on cardiac structure and function in men with first myocardial infarction. Arch Med Sci, 2008; 4(2): 152-60
8. Cavusoglu E, Ruwende C, Chopra V et al: Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. Eur Heart J, 2006; 27: 2300-9
9. Laughlin GA, Barrett-Connor E, May S, Langenberg C: Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study. Am J Epidemiol, 2007; 165: 164-74
10. Steppan CM, Brown EJ, Wright CM et al: A family of tissue specific resistin-like molecules. Proc Natl Acad Sci, 2001; 98: 592-6
11. Ohmori R, Monizyama Y, Kato R et al: Associations between serum resistin levels and insulin resistance, inflammation, and coronary artery disease. J Am Coll Cardiol, 2005; 46: 379-90
12. Verma S, Li SH, Wang CH et al: Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation, 2003; 108: 736-40
13. Burnett MS, Lee CW, Kinnaird TD et al: The potential role of resistin in atherogenesis. Atherosclerosis, 2003; 182: 241-48
14. Weikert C, Westphal S, Berger K et al: Plasma resistin levels and risk of myocardial infarction and ischemic stroke. J Clin Endocrinol Metab, 2008; 93: 2647-53
15. Pietrzeniewicz K, Luczak K, Goch JH: Value of blood adipose tissue hormones concentration-adiponectin, resistin and leptin in the prediction of major adverse cardiac events (MACE) in 1-year follow-up after primary percutaneous coronary intervention in ST-segment elevation acute myocardial infarction. Neuro Endocrinol Lett, 2008; 29: 581-88
16. Tabbibazar R, Rockson SG: Angiogenesis and the ischaemic heart. Eur Heart J. 2001; 22: 903-18
17. Khurma R, Simons M, Martin FJ, Zachary IC: Role of Angiogenesis in Cardiovascular Disease: A Critical Appraisal. Circulation, 2005; 112: 1813-24
18. Moreno PR, Purushothaman KR, Fuster V et al: Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: implications for plaque vulnerability. Circulation, 2004; 110: 2032-38
19. Tello-Montoliu A, Marín F, Patel J et al: Plasma angiogenin levels in acute coronary syndromes: implications for prognosis. Eur Heart J, 2007; 28: 3006-11
20. Thygesen K, Alpert JS, White HD: on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal Definition of Myocardial Infarction. Circulation, 2007; 116: 2634-53
21. Reilly MP, Lehrke M, Wolfe ML et al: Resistin is an inflammatory marker of atherosclerosis in humans. Circulation, 2005; 111: 932-39
22. Hu WL, Qiao SB, Hou Q, Yuan JS: Plasma resistin is increased in patients with unstable angina. Chin Med J, 2007; 120: 871-75
23. Lubos E, Messow CM, Schnabel R et al: Resistin, acute coronary syndrome and prognosis results from the AtheroGene study. Atherosclerosis, 2007; 193: 121-28
24. Inoue T, Kotsuka N, Morooka T et al: High molecular weight adiponectin as a predictor of long-term clinical outcome in patients with coronary artery disease. Am J Cardiol, 2007; 100: 569-74
25. Puchon T, Girmian CJ, Hotamisligil GS et al: Plasma adiponectin levels and risk of myocardial infarction in men. JAMA, 2004; 291: 1730-37
26. Tamura T, Furukawa Y, Taniguchi H et al: Serum adiponectin level as an independent predictor of mortality in patients with congestive heart failure. Circ J, 2007; 71: 623-30
27. George J, Papal S, Wexler D et al: Circulating adiponectin concentrations in patients with congestive heart failure. Heart, 2006; 92: 1420-24
28. Werner SG, Janeti E, Krack A et al: Occlusions: Relation to Duration of Occlusion and Collateral Function Growth Factors in the Collateral Circulation of Chronic Total Coronary Occlusion. Circulation, 2004; 110: 1940-45
29. Moulton KS, Heller E, Konerding MA et al: Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E - deficient mice. Circulation, 1999; 99: 1813-24
30. Tenaglia AN, Peters KG, Sketch MH Jr, Annex BH: Neovascularization of human tumor xenografts in vivo by microscopic three-dimensional computed tomography technique. J Am Coll Cardiol, 1998; 32: 2072-79