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Serum Level of suPAR and YKL-40, a New Biomarker in Patients with Acute Myocardial Infarction?

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Abstract

Introduction: Low grade inflammation plays an important role in the several development process of coronary artery disease. The soluble urokinase plasminogen activator receptor (suPAR) and chitinase 3-like protein 1 (YKL-40) are the new potential biomarkers of inflammation. We intended to test the hypothesis whether the inflammatory biomarker YKL-40 alone or in combination with suPAR could be the new diagnostic biomarkers for acute myocardial infarction (AMI).

Material and Methods: Fifty-five patients with AMI and seventy control subjects were included in the study. The diagnosis of AMI was based on the current 3rd standard universal definition criteria. Serum YKL-40 and suPAR levels were measured at the first and second days of AMI by using ELİSA method.

Results: Serum YKL-40 levels were significantly higher in the first (69.10±16.58 ng/mL) and second day (60.64±16.01 ng/mL) of AMI patients than those of the control subjects (37.11±4.30 ng/mL) ($p<0.001$). Serum YKL-40 levels in the first day of AMI patients also were significantly higher than those of second day of AMI patients ($p<0.01$). Serum suPAR were significantly higher in the first (6.58±3.24 ng/mL) and second day (5.86±4.56 ng/mL) of AMI patients than those of the control subjects (2.26±1.92 ng/mL) ($p<0.001$).

Conclusion: Serum suPAR and YKL-40 can be considered strong inflammatory markers of AMI. We concluded that serum suPAR and YKL-40 levels at the first day and second day of AMI could be used as a clinically useful marker for diagnosis of AMI.

Key words: Inflammation, the inflammatory biomarker, ischemic heart disease

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Introduction

Acute myocardial infarction (AMI) is the important cause of death worldwide. Systemic and local inflammatory response plays an important role in AMI (1). Atherosclerosis is concerned throughout all stages of the development of AMI, from endothelial dysfunction and plaque formation to plaque disruption with superimposed thrombosis (2-4). Early atherosclerotic lesion development is initiated by endothelial dysfunction and the local deposition of lipids (e.g. low density lipoprotein) (4).

Endothelial dysfunction causes the local inflammatory response. Activation endothelial cells express several adhesion molecules that facilitate leukocyte recruitment to the vessel wall (4,5) via binding of the integrin. Monocytes that take in excess lipids are transformed into macrophages and foam cells (4). These foam cells generate the initial lesions leading to advanced atherosclerosis (5). Foam cells secrete pro-inflammatory cytokines, growth factors, matrix metalloproteinases and tissue factor (3). Neutrophils, lymphocytes, monocytes, and macrophages initiate the inflammatory response through the secretion of numerous growth factors, cytokines (including tumor necrosis factor-α (TNF-α) and interleukin-1β) (2), proteolytic enzymes, integrins and cell adhesion molecules in patients with unstable angina and myocardial infarction (3,4). Proteolytic enzymes, including metalloproteinases and cysteinyl cathepsins can degrade extracellular matrix proteins (4-6) and convert a stable atherosclerotic plaques to unstable plaques called “vulnerable” plaque (2, 5, 7). Acute rupture of vulnerable plaques frequently leads to myocardial infarction or stroke (4).

Chitinase 3-like protein 1 (YKL-40) is a 40 kDa heparin and chitin-binding glycoprotein (8-10). The acute phase protein YKL-40 is an inflammatory biomarker in both early and late phases of the atherosclerotic process and coronary artery disease (CAD) patients, which is produced by macrophages, neutrophils, and vascular smooth muscle cells (9-11). It was demonstrated that YKL-40 levels were elevated in patients with myocardial infarction (8). YKL-40 is association with migration, chemotaxis, remodeling of the extracellular matrix, proliferation,

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differentiation and adhesion of vascular endothelial cells. İt may also participate in angiogenesis, inflammatory processes, tissue destruction/ remodeling, and apoptosis (12-14).

The urokinase-type plasminogen activator receptor (uPAR, CD87) is glycosylphospha tidylinositol (GPI)-anchored cell membrane glycosylated protein (15). uPAR is cleaved from the cell surface by elastase, matrix metalloproteinases, proteases and becomes to the soluble form of the receptor, suPAR, which has been detected in blood, urine and cerebro-spinal fluid (7,16-18). suPAR takes part in various immunological functions, including the plasminogen-activating pathway, inflammation (17), cell adhesion, migration, chemotaxis, proteolysis, tissue remodeling (18). uPAR accumulates in the atherosclerotic lesion, and plasma levels of suPAR have been associated with increased incidence of cardiovascular events (7).

Blood levels of sensitive and specific biomarkers, such as cardiac troponin and the MB fraction of creatine kinase (CK-MB), myoglobin and hsCRP are increased in AMI (19). New biomarkers is need assessed for AMI. YKL-40 and suPAR, which is secreted primarily from inflammatory cells, was associated with increased risk of developing cardiovascular events (7,8). Therefore, YKL-40 and suPAR could potentially be a new useful biomarker of disease severity, prognosis and survival in patients with ischemic heart disease. The inflammatory biomarker YKL-40 has been shown to be significantly increased in patients with ST-elevation myocardial infarction (STEMI) and stable chronic coronary artery disease (CAD) (20). The importance of inflammatory biomarkers in both diagnosing and determining the prognosis for AMI are established. Furthermore, several newer biomarkers have recently been determined and may soon be used clinically. Therefore, in this study we will evaluate whether the inflammatory biomarker YKL-40 alone or in combination with suPAR could be a new biomarker for diagnosis, monitoring the treatment and prognostic biomarker in patients with AMI. Furthermore, the aim was to study whether there were an association between plasma YKL-40 and suPAR markers of inflammation in AMI.

Methods

Participants

The protocol of this study was approved by the Ethics Committee. All of the patients were informed of the details of the study, and the written consent of each patient was received. The ethic number was 2013/89. The diagnosis of AMI was based on the following criteria: 1) Symptoms of ischaemia, 2) New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block, 3) Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL), 4) Development of pathological Q waves in the ECG, 5) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and 6) Identification of an intracoronary thrombus by angiography or autopsy. (21). The exclusion criteria for the cases comprised the following: a) patients with renal disease, b) thyroid disease, c) with a body mass index (BMI) more than 35, d) chronic inflammatory diseases, e) major surgery in last 6 months, f) malignancy. Control subjects were volunteers recruited from the hospital staff. All subjects were assessed by clinical examination and some laboratory tests including electrocardiogram (ECG) and routine biochemical tests. BMI was calculated as kg/m^2. History of smoking and alcohol consumption was noted in details. All participants were also investigated for conventional risk factors (BMI, serum lipid profile).

Sample Collection and Preparation

A venous blood sample was collected simultaneously from each patient on the first 24 hr and first 48 hr after occurrence of AMI. Venous blood samples were obtained from the antecubital fossa of the arm. Serum samples were obtained after suitable centrifugation and samples, stored in aliquots at $-20^{\circ}C$ until the time for analysis.

Biochemical Analysis

We measured serum lipid profile, aspartate aminotransferase (AST), alanine aminotransferase (ALT) activities. High-density lipoprotein cholesterol (HDL-C) levels were determined with direct enzymatic method without precipitation (Randox, UK). Low-density lipoprotein cholesterol (LDL-C) levels were calculated with Friedewald formula. Estimation of other parameters was done by routine methods using autoanalyzer (Synchron LX20 system, Beckman Coulter, CA, USA). The serum concentrations of CK-MB and cTnI were determined by using UniCel DxI 800 analyzer (Beckman Coulter, CA, USA). The cut-off values for CK-MB and cTnI were set at 6. 3 ng/ml and 0.04 ng/ml, respectively. The measurement of all the cardiac markers using the analyzer in each sample was completed within 50 min.

suPAR Analysis

Serum suPAR levels were detected in serum samples using the AssayMax Human Urokinase Receptor (uPAR) ELISA Kit (Assaypro, St. Charles, MO, USA) in accordance with the manufacturer's guidelines. This assay employed a quantitative sandwich enzyme immuno assay technique that measured suPAR. Serum samples were diluted 1: 4 in the supplied buffer and measured. Absorbance was measured at 450 nm on an ELx800 Absorbance Microplate Reader (Biotek, Winooski, VT, USA).

YKL-40 Analysis

Serum YKL-40 levels were detected in serum samples using the Assayprotech Human chitinase-3-like protein 1 ELISA Kit (Assay Biotechnology, USA), in accordance with the manufacturer's guidelines. This assay employed a quantitative sandwich enzyme immuno assay technique that measured YKL-40. Serum samples were diluted 1: 50 in the supplied buffer and measured. Absorbance was measured at 450 nm on an ELx800 Absorbance Microplate Reader (Biotek, Winooski, VT, USA). The results were expressed for serum suPAR and YKL-40 levels as ng/mL for both.

Statistical Analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., IL). To compare the ratio of categorical variables, we used the Chi-squared test. The normality of the variables was evaluated using the one-sample Kolmogorov–Smirnov test. Total cholesterol (TC), LDL-C, BMI and age, were distributed parametrically but HDL-C, triglycerides (TG), AST and ALT were not normally distributed nonparametrically. Independent Samples T-test and Mann–Whitney U test were used for comparing mean and the median values, respectively. We performed (intergroup comparisons) independent samples T-test to compare the difference in the levels of serum suPAR and YKL-40 between healthy subjects and AMI patients. In addition, intragroup comparisons (first day and second day) were performed by paired-sample T-test. The correlations between variables were tested by Pearson's correlation test. All data are expressed as mean ± standard deviations (SDs). Differences were considered significant at a probability level of $p < 0.05$. The YKL-40 and suPAR values were analyzed using ROC (Receiving Operating Characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity, specifisty were presented. While evaluating the area under the curve, a 5% type-I error level was used to accept a statsitically significant predictive value of the test variables.

Results

Clinical characteristics and biochemical parameters of the subjects were presented in table 1. TC, TG, AST, ALT, and LDL-C levels of the AMI patients were significantly higher, whereas HDL-C level was significantly lower than those of the healthy subjects. In addition, no significant differences were observed in age, gender and BMI in AMI patients and healthy subjects.

Serum suPAR and YKL-40 levels of the groups were presented in table 2. Serum suPAR and YKL-40 levels were significantly higher in the first and second day of AMI patients than the healthy subjects ($p < 0.001$ and $p < 0.001$, respectively). In addition, intragroup comparisons (first day and second day) were presented in Table 3. Serum YKL-40 levels were significantly higher in the first day of AMI patients than second day of AMI patients ($p < 0.01$). In addition, there were no different between serum suPAR levels in the first day and second day of AMI patients ($p = 0.34$).

We were presented ROC analyses to compare the diagnosis in the first day and prognosis in the second day value of suPAR and YKL-40 levels of AMI patients in figure 1 and 2. We therefore, tested whether the predictive value of YKL-40 was equal or superior to suPAR by using ROC curve. We found that first day suPAR value is an AUC of 0.92 (cutoff value 3.16 ng/mL, sensitivity 91 %, specificity 81 %) and first day YKL-40 value is an AUC of 0.99 (cutoff value 44 ng/mL, sensitivity 95 %, specificity 94 %). In addition, second day suPAR value is an AUC of 0.81 (cutoff value 3.08 ng/mL, sensitivity 75 %, specificity 83 %) and second day YKL-40 value is an AUC of 0.94 (cutoff value 42 ng/mL, sensitivity 90 %, specificity 93 %). YKL-40 did show superiority compared to suPAR in predicting AMI.

Simple correlation analysis was performed to investigate the association between serum suPAR and YKL-40 levels. There were no correlation between serum suPAR and YKL-40 levels in AMI patients. Serum suPAR and YKL-40 levels in AMI were independent of each other biomarker in diagnosing for AMİ.

Table 1. Clinical and demographic characteristics of the patients and controls.

	Control Subjects n=70	AMI n=55	P Value
Age (years)	54.03 ± 6.89	55.85 ± 11.26	0.321
Sex (male/female)	48M/22F	45M/10F	0.069
BMI (kg/m^2)	26.96 ± 2.57	28.00 ± 3.29	0.062
Hypertension (%)	-	21.66	-
Current smoking (%)	-	80	-
Diabetes mellitus (%)	-	16.66	-
Total Cholesterol (mg/dL) [a]	178.15 ± 16.88	196.86 ± 46.57	<0.01
Triglycerides(mg/dL) [a]	90.55 ± 28.89	170.45 ± 124.54	<0.001
HDL-C (mg/dL) [a]	46.69 ± 9.74	33.01 ± 6.38	<0.001
LDL-C (mg/dL) [a]	115.59 ± 21.14	126.92 ± 30.63	0.032
AST (U/L) [a]	18.60 ± 3.11	72.73 ± 54.46	<0.001
ALT (U/L) [a]	15.95 ± 3.54	29.95 ± 13.99	<0.001
cTnI (ng/mL) [a]	-	30.31 ± 35.83	-
CK-MB (ng/mL) [a]	-	114.17 ± 113.60	-

[a]Serum samples were obtained at the time of hospitalization.
BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; cTnI, cardiac troponin I;
CK-MB, creatine kinase MB.

Table 2. Serum biomarkers of the patients and controls.

	Control Subjects n=70	AMI patients First day n=55	AMI patients Second day n=55	p Value
suPAR (ng/mL)	2.26 ± 1.92	6.58 ± 3.24***	5.86 ± 4.56***	< 0.001
YKL-40 (ng/mL)	37.11 ± 4.30	69.10 ± 16.58***	60.64 ± 16.01***	< 0.001

[1]All values are mean ± standard deviation.
[2] SuPAR: Soluble urokinase plasminogen activator receptor
[3] YKL-40: Chitinase 3-like protein 1
***p<0.001 compared with control group (Independent samples *T*-test;)

Discussion

AMI has high mortality rates, therefore accurate and rapid diagnosis of AMI is essential. Researching new biomarkers that could be more sensitive or shorter time periods for testing. Our results have demonstrated that, both on the first and second day, serum suPAR and YKL-40 levels were increased in patients with AMI compared to the healthy subjects. In addition, serum YKL-40 levels were significantly higher in the first day of AMI patients than second day of AMI patients.

It was shown that highest YKL-40 mRNA expression is seen in macrophages in the early lesion of atherosclerosis (9,14). Serum YKL-40 levels have been increased in patients suffering AMI. YKL-40 could a possible screening or diagnostic marker for coronary atherosclerosis (8,9) and be used for monitoring the efficiency of medical treatment of patients with CAD (8).

Table 3. Serum biomarkers in the first and second day of AMI patients.

	AMI patients First day n=55	AMI patients Second day n=55	p Value
suPAR(ng/mL)	6.58 ± 3.24	5.86 ± 4.56	0.34
YKL-40 (ng/mL)	69.10 ± 16.58	60.64 ± 16.01	< 0.01

[1]All values are mean ± standard deviation.
[2] SuPAR: Soluble urokinase plasminogen activator receptor
[3]YKL-40: Chitinase 3-like protein 1
p; paired sample t test

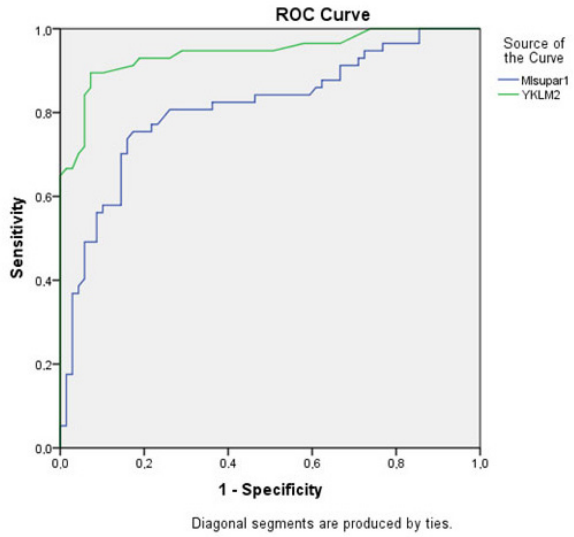

Figure 1: *For first day suPAR and YKL-40 roc curve below.*

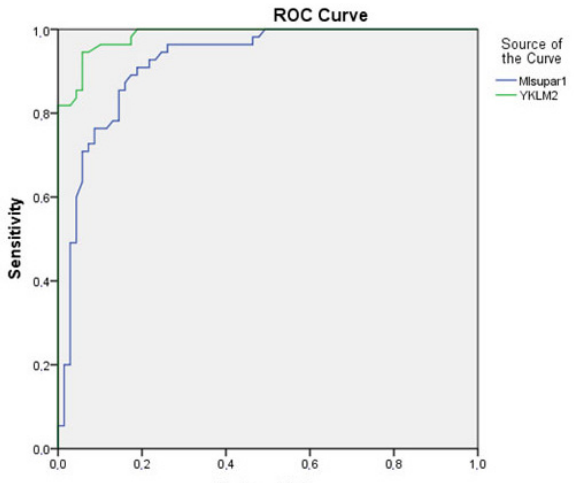

Figure 2: *For second day suPAR and YKL-40 roc curve below.*

Our findings were in agreement with previous studies. Wang et al. (20) and Hedegaard et al. (22) have found that plasma YKL-40 was significantly increased in patients with MI during the first 24 hour after admission compared to controls. The increased YKL-40 level decreased over time, but remained significantly elevated one month after MI compared to controls. Moreover it has been concluded that level of YKL-40 was positively correlated with the severity of patients with non-ST segment elevation acute coronary syndrome. YKL-40 was lower after treatment, when compared with the control group (23). In patients with CAD, it has been reported that plasma YKL-40 was increased (24, 25). In another study, Michelsen AE et al. (26) have found that serum YKL-40 level was significantly elevated in patients with carotid atherosclerosis. Nøjgaard C et al. (27) have found that Serum YKL-40 at the time of admission was higher in patients with AMI than in patients with stable coronary artery disease and healthy participants.

uPAR, known to be present on such inflammatory cells as monocytes and macrophages. When exposed to proteases, metalloproteinases, and elastases released from activated monocytes and macrophages, cell-surface–bound uPAR is cleaved, resulting in the release of suPAR (7). Cytokines released from activated monocytes and lymphocytes stimulate the release of suPAR from neutrophils (IL-8), endothelial cells (IL-1β), and monocytes (TNF-α) (7,28). Enhanced uPAR expression on monocytes from patients with AMI [29] was associated with increased cell adhesion to the uPAR ligand vitronectin (15,29). uPAR has a regulatory role in integrin-mediated cell adhesion (15) in AMI (29). Soluble factors (probably inflammatory cytokines) in plasma from patients with AMI can directly activate integrin-mediated and uPAR-mediated adhesion (29).

In our study, we found that serum suPAR level was increased in patients with AMI compared to the healthy subjects. In the previous studies; Edsfeldt A. et al. (7) reported that plaque levels of uPAR and suPAR correlate with levels of macrophages and lipids in the plaque. Persson M. et al. (30) found that suPAR is associated with increased occurrence of carotid plaque and increased incidence of ischemic stroke and CAD. Lyngbæk S. et al. (31) reported that suPAR is a strong predictor of adverse long-term outcomes and improves risk stratification beyond traditional risk variables in chest pain. Asciutto G. et al. (32) found that the reduced level of suPAR in human carotid plaques of subjects on long-term treatment with beta-blockers suggests their possible

protective role in plaque inflammation. Lyngbæk S. et al. (33) reported that suPAR is a stable plasma biomarker after ST-segment elevation myocardial infarction. Beside these findings same author also found that suPAR provides prognostic information of CVD risk beyond Framingham Risk Score (34). Persson M. et al. (35) found that elevated level of suPAR is, independently of established cardiovascular risk factors, associated with an increased incidence of CVD in elderly subjects. Chavakis T. et al. (36) found that suPAR from vascular cells is upregulated by proangiogenic as well as proatherogenic growth factors and cytokines, is preferentially released towards the basolateral side of endothelial cells and accumulates in the vessel wall. Pawlak et al. (28) found that suPAR correlated with several of the main proinflammatory cytokines and chemokines, in plaque tissue, involved in the atherosclerotic process, including IL-6, IL-1β and TNF-α.

Study Limitations

The present study has some limitations. We did not measure the serum suPAR and YKL-40 levels in the first few hours after the onset of AMI and after second day of AMI. Further studies are needed for the assessment of serum suPAR and YKL-40 levels on the time of admission and in larger study groups.

Conclusion

In the present study, we determined higher serum suPAR and YKL-40 levels on the first and second day of AMI in patients as compared to the healthy subjects. In addition, serum YKL-40 levels were significantly higher in the first day of AMI patients than second day of AMI patients. The increased YKL-40 level decreased on the second day of AMI in patients. We suggest that serum YKL-40 and suPAR are a clinically useful marker for myocardial ischemia, remodelling and may be prognosis.

Funding

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