Soluble Urokinase Plasminogen Activator Receptor as a Diagnostic Biomarker in Coronary Artery Disease Patients

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Abstract

**Introduction:** Atherosclerosis is a leading cause of vascular disease worldwide. This disease’s major clinical manifestations include myocardial infarction and various types of angina. Therefore, we examined the role of the serum level of soluble urokinase plasminogen activator receptor (suPAR), which is generated as a pro-inflammatory marker and may serve as an independent predictor of cardiovascular disease. Additionally, this study was conducted to evaluate the role of suPAR and its relation with troponin I, interleukin-6 (IL-6), creatine kinase-MB (CK-MB), and lipid profiles in coronary artery disease patients. The serum levels of suPAR and IL-6 were measured with ELISA kits in 30 consecutive patients with myocardial infarction admitted for primary PCI, 30 patients with stable angina, and 30 healthy volunteer differentiated by electrocardiogram at baseline. We also examined the cardiac biomarkers troponin I and CK-MB by immunoassay and spectrophotometric methods, respectively. We observed that suPAR level was significantly different between the myocardial infarction group and the control group (p < 0.001) and between the stable angina group and the control group (p < 0.001). ROC curves showed high sensitivity (82) and high specificity (79%) of suPAR level as a biomarker in myocardial patients and moderate sensitivity (80%) and sensitivity (76%) in the stable angina group. Furthermore, this result correlated with the traditional biomarkers troponin I (+ve r = 0.725) and CK-MB (+ve r = 0.421).

Therefore, serum suPAR may be a novel biomarker that reflects a stable biomarker of ST-segment elevation myocardial infarction and stable angina. Moreover, it has a positive correlation with cardiac biomarkers that predict all-cause mortality and recurrent MI.

**Keywords:** suPAR; IL6; CK MB; angina pectoris ; myocardial infarction; troponin I
1. Introduction

Atherosclerosis, the leading cause of death in industrialized countries, is a progressive inflammatory disease [1]. Atherogenesis refers to the development of atheromatous plaques in the inner lining of the arteries [2]. Early atherosclerosis is characterized by the attachment of monocytes to the endothelium of the blood vessel and their infiltration into the sub endothelial space in the intima of the vessel. In the intima, the monocytes differentiate into macrophages [3]. Macrophages in the atheroma may have pro-inflammatory characteristics of M1 macrophages, which produce high levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNFα), or characteristics of M2 macrophages, which are more prominent producers of the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGFβ) [4].

There are many cardiac biomarkers for coronary artery diseases, one of which is troponin. It is a complex comprised of regulatory proteins (troponins C, I and T) that regulate the thin filament system in cardiac and striated muscle [5].

Cardiac troponin I (cTnI) is considered to be exclusive to myocardial tissue. Serum levels increase within 3-12 hours from the onset of chest pain, peak at 24-48 hours, and return to baseline over 5-14 days [6].

Creatine kinase (CK) was first identified as a cardiac biomarker because it is an enzyme that is found primarily in the cardiac muscle and skeletal muscle. This enzyme has 3 isoenzymes. CK-MM is the skeletal muscle fraction, and CK-MB is the cardiac muscle fraction [7].

Recently, soluble urokinase plasminogen activator receptor (suPAR) has been identified as an inflammatory biomarker that is released into the circulation by cleavage of the membrane-bound uPAR from various cells, including inflammatory and endothelial cells [8].
suPAR levels have been reported in ruptured atherosclerotic plaque or segments with severe atherosclerosis due to its role in orchestrating cellular adhesion, migration, and proliferation during tissue remodeling in the atherosclerotic plaque[9]. SuPAR is an emerging biomarker that represents activation of both immunity and inflammation. suPAR accumulates in the atherosclerotic lesion, and plasma levels of suPAR have been associated with increased incidence of cardiovascular events.[10] These findings, together with the knowledge that suPAR is a stable protein, make it interesting as a future biomarker for the diagnosis of coronary artery diseases (CAD) [11].

Interleukin 6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine. Recent studies have shown that elevated levels of serum IL-6 provide valuable information for the risk assessment of long-term cardiovascular mortality in patients with ST-elevation myocardial infarction and are a powerful predictor of cardiovascular and all-cause mortality [12].

We therefore examined the prognostic value and temporal course of suPAR and IL-6 compared to traditional biomarkers in patients with ST-segment elevation myocardial infarction (STEMI), patients with ST-segment depression (angina pectoris), and the correlation between them.

2. Patients and Methods

2.1 Study design

The study group comprised of 60 patients presenting with chest pain due to coronary artery disease and 30 healthy volunteers recruited from the cardiology department of Banha University, Egypt. Blood samples were obtained on admission before revascularization. The study was conducted from July 2015 to June 2016. This study was designed to
determine the prognostic utility of serial measurements of IL-6 and suPAR in high-risk acute coronary syndrome (ACS) patients.

2.1.1 Exclusion criteria

The exclusion criteria were concomitant neoplastic, infectious, connective tissue, inflammatory disease, deep vein thrombosis, pulmonary embolism, and recent (<1 month) surgery or trauma. Patients taking immunosuppressant agents were also excluded. [13]

2.1.2 Inclusion criteria

We included patients who had myocardial infarction, defined by presence of increased cardiac biomarkers of necrosis (usually troponin I) with at least 1 value above the 99th percentile along with evidence of myocardial ischemia with at least 1 of the following: electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block), new pathological Q waves in at least 2 contiguous leads, imaging evidence of new loss of myocardium, or new wall motion abnormality. Myocardial infarction was also established on the basis of current criteria guidelines: ischemic symptoms lasting 10 min and occurring within 72 h before randomization and either ST-segment deviation of 1 mm, deep symmetrical inversion of the T waves in the anterior chest leads, or elevated levels of a biomarker of cardiac necrosis identified by ECG. [14]

Stable angina patients were defined by the following symptoms: retrosternal chest discomfort (pressure, heaviness, squeezing), pain localized primarily in the epigastrium, back, neck, jaw, or shoulders, and pain triggered by eating, lasting for approximately 1-5 minutes and relieved by rest or nitroglycerin.

At admission, patients were randomized into 3 groups using sealed envelopes with assignment codes. Group I consisted of 30 patients, 24 male and 3 female, with ST-segment elevation (myocardial infarction) and with ages ranging between 35 and 85 years. Group II
The STEMI diagnosis, MI and ST-segment depression were confirmed in all 30 patients with angina pectoris. All patients gave written, informed consent for their participation in the study. The study was approved by the national research ethics committee (Banha University Ethical Committee) and was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. Blood samples for analysis of biomarkers were taken at baseline and up to 5 to 8 hours later until the biomarkers of myocardial necrosis (troponin I and/or creatine kinase-MB) consistently decreased.

Sample collection

Blood samples (10 ml) were drawn from each patient and distributed as follows: Two milliliters of venous blood was used for the complete blood count (CBC), which was estimated immediately. Eight milliliters of venous blood was delivered in a vacutainer serum separator tube without anticoagulant. Samples were separated and stored at −80°C until subsequent processing and measurement.

3. Assay Procedures

Biochemical measurements

Levels of IL6 and suPAR were measured using available kits obtained from Assay pro™ ELISA Kits, USA and Cusabio biotech co., Ltd. China, respectively, according to manufacturer protocols. The concentration of troponin I in serum was determined by the lateral flow immunoassay method. This test was performed by ichroma™ Tn-I obtained
from (Boditech Med Incorporated, Republic of Korea) according to manufacturer
protocols.

Serum CK-MB activity was determined by using a spectrophotometric method obtained
from DiaSys Diagnostic Systems (Germany) and performed according to manufacturer
protocols. Plasma was used for the determination of lipid profiles including total
cholesterol (TC), which was measured by enzymatic colorimetric method (Savoldi et al.
1976), triglycerides (TGs) which were measured by an enzymatic-colorimetric method
(Nagele et al. 1984) using commercial kits (Spinreact, S.A, Spain), and high-density
lipoprotein (HDL-C), which was determined by a precipitation method (Austin et al) using
commercial kits (BioMed, Germany). Low-density lipoprotein cholesterol (LDL-C) was
calculated using the Friedewald formula (Friedewald, Levy, & Fredrickson, 1972), where
LDL-C = [TC − HDL-C − (TGs/5)], provided that the TG level was less than 400 mg/dl
(Friedewald et al., 1972).

Hematological measurements

The Sysmex® automated hematology analyzer KX-21N (Sysmex Corporation, Kobe 651-
0073, Japan) was used to determine hemoglobin (Hb) concentration, hematocrit value
(HCT), white blood cell count (WBCs), red blood cell count (RBCs), and platelet count
(PLTs).

4. Statistical analysis

Data were analyzed using the SPSS statistical package version 22.0 (USA). The results
were reported as the mean ± SEM. The Shapiro-Wilk test was used to assess of the
normality of data. Data were analyzed by one-way ANOVA with LSD and Dennett's Post
Hoc tests, Chi-square test, Spearman correlation coefficients and values were considered
significant at $P < 0.05$. The contribution of selected variables (age, gender, hypertension, IL-6, total cholesterol, and troponin I) to variations in baseline suPAR levels was examined using general linear models after appropriate model assessment. Diagnostic accuracy receiver operator characteristics (ROC) curve was used to determine the specificity and sensitivity of traditional markers (troponin I, CK-MB) and new biomarkers (suPAR, IL-6).

5. Results

The patients' medical histories were taken to confirm the absence of any interacting or interfering drugs. Demographic data were collected at baseline using a questionnaire. Information collected included age, sex, hypertension, hemoglobin, and current smoking habits [Table 1]
Table 1 Baseline characteristics of all studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (MI)</th>
<th>Group II (ANGINA)</th>
<th>Normal control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3±2.11</td>
<td>52.1±2.86</td>
<td>47.4±2.57</td>
<td>NS</td>
</tr>
<tr>
<td>Gender male/female</td>
<td>24/6</td>
<td>25/5</td>
<td>19/11</td>
<td>NS</td>
</tr>
<tr>
<td>Current Smoking %</td>
<td>46</td>
<td>60</td>
<td>16</td>
<td>S</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>60</td>
<td>55</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>188±4.49</td>
<td>171±6.53</td>
<td>159±3.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>43.2±0.82</td>
<td>45.8±1.2</td>
<td>43.6±0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>175±6.89</td>
<td>182±8.19</td>
<td>159±3.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>264±6.8</td>
<td>243±4.06</td>
<td>181±3.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (Bpm)</td>
<td>70.23±1.87</td>
<td>74.77±3.15</td>
<td>71.5±0.45</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.71±0.35</td>
<td>12.16±0.3</td>
<td>12.36±0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as the mean (±SEM), BP blood pressure; HDL: high-density cholesterol, Hb: hemoglobin, HR: heart rate, TG: triglyceride, LDL: low-density cholesterol and TC: total cholesterol.
In the myocardial infarction group, there was a significant increase (p < .001) in serum troponin I (1.61± .017 mg/L) compared with the healthy control group (.14 ± 0.01 mg /L). However, there is no significant difference between the angina and healthy control groups.

In the angina group, the serum level was 017 ± .01 mg /L [Table 2]

In the myocardial infarction group, there was a significant increase (p < 0.001) in serum CK-MB (60.8±3.24 mg/L) compared with the healthy control group (12.27±0.81 mg/l).

However, there was no significant difference between the angina and healthy control groups.

In angina group the serum level was (16.4±0.68 mg /L) [Table 2]

There was a significant elevation of both IL-6 and suPAR in the MI group (0.953±0.12 ng /ml and 1.808±0.13 ng /ml, respectively) compared with the healthy control group (0.284±0.06 ng /ml and 1.566±0.14 ng /ml, respectively). While there was no significant difference in IL-6 between the angina group and control group, suPAR was significantly increased in the angina group (1.566±0.14 ng /ml) compared with the control group [Table2]

**Table 2** suPAR and IL-6, CK-MB and Troponin I levels in the studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-6(ng/ml)</th>
<th>suPAR (ng/ ml)</th>
<th>CK-MB (µg/ L)</th>
<th>Troponin I (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (MI)</td>
<td>0.953±0.12&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>1.808±0.13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60.8±3.24&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>1.61±0.17&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group II (Angina)</td>
<td>0.284±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.566±0.14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16.4±0.68&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.17±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group III (control)</td>
<td>0.234±0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.679±0.11&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>12.27±0.81 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.14±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SEM. (n=30 for each group), a: significance vs MI, b: significance vs angina, c: significance vs control.
Serum troponin I showed a significant, positive correlation with both serum IL-6 and serum suPAR (p < 0.001) in the myocardial infarction groups. Serum creatine kinase-MB (CK-MB) showed a significant, positive correlation with both serum IL-6 (p < 0.001) and serum suPAR (p < 0.001) in the MI groups, Table 3.

Table 3: Spearman correlation was assessed between suPAR and IL-6 levels and different lipid profile makers and cardiac biomarkers in all subjects.

<table>
<thead>
<tr>
<th></th>
<th>TC (mmol/l)</th>
<th>TG (mmol/l)</th>
<th>Creatine kinase MB (µg/L)</th>
<th>Troponin I (µg/L)</th>
<th>IL-6 (ng/ml)</th>
<th>suPAR (ng/ml)</th>
<th>LDL (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (ng/ml)</td>
<td>0.351</td>
<td>0.332</td>
<td>0.486</td>
<td>0.675</td>
<td>_</td>
<td>0.520</td>
<td>0.246</td>
</tr>
<tr>
<td>suPAR (ng/ml)</td>
<td>0.430</td>
<td>0.342</td>
<td>0.421</td>
<td>0.725</td>
<td>0.520</td>
<td>_</td>
<td>0.252</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

r: correlation coefficient

Combined ROC curves were constructed for estimating the association between angina pectoris and the semi-quantitative measurements of IL-6 and suPAR. Both variables were significantly associated with angina pectoris P<0.001. (Table IV) (Figure 1). We also determined the association between myocardial infarction and the semi-quantitative measurements of both IL-6 and suPAR. Both variables were significantly associated with myocardial infarctions according to Table 4, Figure 1.
**Table 4** ROC curve, sensitivity, specificity of suPAR levels for determining susceptibility and severity among MI, angina patients and IL-6 levels in MI and angina patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>suPAR levels</th>
<th>IL-6 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI patients</td>
<td>Angina patients</td>
</tr>
<tr>
<td></td>
<td>versus controls</td>
<td>versus controls</td>
</tr>
<tr>
<td>Cut off</td>
<td>0.887</td>
<td>0.825</td>
</tr>
<tr>
<td>Sensitivity%</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Specificity%</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>AUC*</td>
<td>0.908</td>
<td>0.791</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*AUC = Area under the Curve*
6. DISCUSSION

Different pathobiological features, such as inflammation, myocardial stress, structural changes and myonecrosis, play a vital role in the myocardial injury process [15]. Next, generation biomarkers reflect different pathobiological pathways in the complex pathophysiology of acute myocardial infarction (AMI). Measurements of biomarker concentrations may help to measure infarct size, myocardial dysfunction and clinical outcomes and to identify high-risk patients and establish individualized treatments and secondary prevention strategies [16]. Beyond established biomarkers, the improved
The prognostic value of newer generation mediators is of high interest. The aim of the present study was to evaluate novel biomarker levels in patients with different types of AMI compared to controls and to study their role in AMI.

Soluble urokinase plasminogen activator receptor levels correlated with the inflammation markers TnI, CK–MB, and IL-6. Recently, Koller et al introduced suPAR as a promising marker for improved risk prediction in patients with heart failure [17]. SuPAR clearly plays a vital role, as plasma levels of uPA were elevated in patients with stable angina and correlated positively with plaque-positive media and external elastic membrane areas, as determined by intravascular ultrasound, suggesting that the urokinase system is associated with signs of plaque instability. This finding was confirmed in our study, as suPAR was positively correlated with and sensitive for diagnosis of angina [18].

Our results indicated that suPAR is a predictor and diagnostic biomarker for different types of coronary artery disease and recurrent MI. SuPAR adds independent prognostic information to well-established clinical and biochemical prognostic markers in this setting. Previous studies have shown that suPAR is an independent predictor of mortality and cardiovascular disease in healthy subjects [19].

In the present study, suPAR was significantly different between the myocardial infarction group with ST-segment elevation and the control group and between the angina group with ST-segment depression and the control group. Moreover, ROC curves showed high sensitivity (82%) and high specificity (79%) of suPAR as a biomarker in myocardial patients and moderate sensitivity (80%) and specificity (76%) of the biomarker in the angina group.

SuPAR has previously been shown to be a strong marker of mortality in patients with other critical illnesses [20, 21]. In our study, the baseline suPAR levels correlated with the
traditional biomarkers troponin I (+ve r = .725) and CK-MB (+ve r = .421). suPAR provides prognostic information that is not conveyed by traditional cardiovascular risk factors.

Elevated expression of uPA, especially in atherogenic macrophages, leads to accelerated atherosclerosis [22, 23, and 24]. This finding is attributable to the role of the uPA/uPAR system in the pathogenesis of atherosclerosis [25]. There is increasing evidence that cells in the atherosclerotic arterial wall, including macrophages, endothelial cells, and SMC, secrete high levels of uPA in the advanced stages of atherogenesis [26].

By generating transgenic mice with macrophage-targeted overexpression of uPA, Dichek et al. established that uPA has atherogenic activity when it is expressed in macrophages at elevated levels [27].

As there is increasing evidence that the uPA/uPAR system is associated with increased atherogenicity, impairment of uPA and/or uPAR functions, or inhibition of their expression, may provide a novel therapeutic approach to attenuate atherosclerosis. [28]

In this context, it was interesting that suPAR levels did not increase considerably after admission, in contrast to C-reactive protein (CRP) and biomarkers of myocardial necrosis (troponin I and creatinine kinase-MB). Therefore, these biomarker characteristics could make suPAR a strong and suitable candidate in management decisions regarding acute chest pain in patients with suspected non ST elevation acute coronary syndrome (NSTEACS) (29).

SuPAR reflects different pathophysiological pathways compared to the more traditional biomarkers clinically used in this setting, further indicating that suPAR could be a valuable supplement to current risk algorithms [30].

Recently, suPAR has been shown to be a marker of increased albumin/creatinine ratio, a well-established measure of subclinical vascular dysfunction [29]. The extracellular segment of
uPAR can be cleaved and shed from the cell surface into body fluids, thereby serving as a marker for the severity of atheroma progression [25].

In this study, we also examined the role of IL-6 as a biomarker for the diagnosis of coronary artery disease (CAD). Our results showed that IL-6 levels were significantly different between groups of CAD (P >.001) and correlated with the other cardiac biomarkers, troponin I (+ve = .675) and CK-MB (+ve = .482). It has been reported that increased levels of inflammatory agents, including IL-6, are associated with acute ischemic conditions and are predictors of recurrent events in patients with CAD [31].

The serum level of IL-6, along with other cytokines, is also associated with unfavorable clinical outcomes in patients hospitalized for unstable angina and ST-elevated myocardial infarction (STEMI) [32]. Furthermore, many chronic conditions that are common causes of death in the elderly may stimulate and sustain a systemic inflammatory state, which can be measured by increased levels of serum IL-6 or other pro-inflammatory cytokines. The secretion of IL-6, which is a major determinant of the production of acute-phase proteins, is increased in clinical conditions characterized by tissue injury, including infections, malignant neoplasms, ischemic diseases, and trauma [33].

Limitations of the present study deserve mention. The present study was conducted in a single hospital because of the relatively small cohort and a limited number of end points.

7. Conclusions

This study demonstrated that increased circulating concentrations of soluble urokinase plasminogen activator receptor in patients with acute chest pain (angina pectoris) and MI was associated with diagnosis and provided independent prognostic information beyond that of established cardiovascular risk factors. Targeting uPAR with the aim of disrupting its complex with uPA in cardiovascular diseases, similar to its application in cancer, should be considered
to be a possible therapeutic approach in the management of advanced atherosclerosis to prevent plaque rupture and inhibit formation of neointima.

Conflict of interest: None.

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