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ORIGINAL ARTICLE

Soluble urokinase-type plasminogen activator receptor as a measure of treatment response in acute exacerbation of COPD

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ABSTRACT

Objective: To evaluate the value of soluble urokinase-type plasminogen activator receptor (suPAR) in the diagnosis of acute exacerbation of COPD (AECOPD) and in monitoring treatment response, analyzing the relationship between suPAR and fibrinogen in AECOPD. AECOPD leads to increased airway inflammation, contributing to an exaggerated release of inflammatory mediators. **Methods:** We recruited 45 patients with AECOPD and 20 healthy control subjects. Medical histories were taken, and all subjects underwent clinical examination, chest X-ray, pulmonary function tests, and blood gas analysis. On day 1 (treatment initiation for the AECOPD patients) and day 14 (end of treatment), blood samples were collected for the determination of serum suPAR and plasma fibrinogen. **Results:** Serum levels of suPAR were significantly higher in the AECOPD group than in the control group. In the AECOPD patients, there was a significant post-treatment decrease in the mean serum suPAR level. The sensitivity, specificity, and accuracy of suPAR were 95.6%, 80.0%, and 93.0%, respectively. The Global Initiative for Chronic Obstructive Lung Disease stage (i.e., COPD severity) correlated positively and significantly with serum levels of suPAR and plasma levels of fibrinogen. **Conclusions:** Monitoring the serum suPAR level can be helpful in the evaluation of the COPD treatment response and might be a valuable biomarker for determining the prognosis of AECOPD. Because serum suPAR correlated with plasma fibrinogen, both markers could be predictive of AECOPD.

Keywords: Pulmonary disease, chronic obstructive/complications; Pulmonary disease, chronic obstructive/diagnosis; Receptors, urokinase plasminogen activator; Fibrinogen.

INTRODUCTION

Acute exacerbation of COPD (AECOPD) is characterized by deterioration of the respiratory symptoms that is beyond the normal day-to-day variations and leads to a change in medication.[1,2] Although exacerbations are the main determinants of COPD-related morbidity and mortality, their exact incidence remains unknown. Exacerbations have a major impact on the quality of life of COPD patients, resulting in multiple hospitalizations.[3] AECOPD leads to increased airway inflammation, provoking the exaggerated release of numerous inflammatory mediators.[4]

The most commonly used marker of COPD severity is FEV_1. However, FEV_1 does not correlate well with symptoms and other factors that quantify the progression of COPD.[5] It is therefore important to seek other markers of COPD activity.

Urokinase-type plasminogen activator receptor and plasminogen activator inhibitor type 1 are the main urokinase-type plasminogen activators. They are considered important components of the immune system and the inflammatory response.[6,7] Elevated levels of soluble urokinase-type plasminogen activator receptor (suPAR) result from increased stimulation of the immune system by different types of infections or solid tumors. Therefore, serum suPAR levels are believed to indicate the degree of immune activation.[8] There have been many studies reporting elevated suPAR levels in patients with infection, cancer, inflammatory diseases, sepsis, or bacteremia.[9-12]

Determination of the serum level of suPAR is a simple test that is easy to perform and, in comparison with determination of the plasma level of fibrinogen, requires fewer precautions related to sample collection and processing.[13] Determination of the serum level of suPAR and the plasma level of fibrinogen could play an important role in the evaluation of patients with stable COPD.[14] Fibrinogen has come to be a helpful biomarker in COPD and is being considered as a drug development tool for qualification by the U.S. Food and Drug Administration and the European Medicines Agency. Fibrinogen is synthesized in the liver and converted to fibrin by thrombin during blood coagulation; it is considered an acute phase plasma protein.[15]

The objective of this study was to evaluate the value of suPAR as a biomarker in the diagnosis of AECOPD and as a tool for monitoring the treatment response. We also analyzed the relationship between suPAR and fibrinogen in patients with AECOPD.

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METHODS

We enrolled 45 patients with AECOPD and 20 healthy control subjects. The patients were recruited from among those under treatment at the outpatient clinics or in the inpatient wards of the Chest Department of the Tanta University Hospitals, in the city of Tanta, Egypt, between August 2015 and January 2016. The study was performed in accordance with the ethical standards of the Tanta University Hospitals and was approved by the Research Ethics Committee of the Tanta University Faculty of Medicine. All of the participants gave written informed consent.

The diagnosis of COPD was made in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[16] on the basis of smoking history, clinical manifestations, and pulmonary function test results showing airflow obstruction, with a post-bronchodilator FEV_1/FVC ratio < 0.7. AECOPD was defined as prolonged (≥ 48 h) worsening of dyspnea, coughing, or the production of mucoid or purulent sputum, leading to increased use of rescue and maintenance medications.[17]

Patients who had conditions that could alter their serum level of suPAR[18]—such as bronchial asthma, bronchiectasis, requiring mechanical ventilation, malignancies, liver failure, renal failure, heart failure, and uncontrolled diabetes mellitus—were excluded. Pneumonia was ruled out if a chest X-ray revealed no pulmonary infiltrate.

The patients were admitted and managed with supplemental oxygen at an optimum saturation of 90-92%. Bronchodilators (short-acting β_2 agonists), with or without short-acting anticholinergic agents, were used for the treatment of exacerbations. Prednisolone (40 mg/day for 5 days) was prescribed. Antibiotics were given if there were clinical signs of a bacterial infection, such as purulent sputum.[19] Medical histories were taken, and all patients underwent the following: thorough clinical examination; chest X-rays, in posteroanterior and lateral views, at enrolment (on day 1, when treatment for AECOPD was initiated) and on day 14 (after the end of that treatment); laboratory tests, including a complete blood count, renal function tests, liver function tests, and determination of fasting blood glucose levels; arterial blood gas analysis (arterial blood samples were collected, with sterile, disposable plastic syringes containing heparin, on day 1); pulmonary function tests to determine FEV_1 and the FEV_1/FVC ratio, with a spirometer (CHESTGRAPH HI-101; Chest M.I., Inc., Tokyo, Japan); and determination of the levels of fibrinogen and suPAR in plasma and serum, respectively, peripheral blood samples having been collected on day 1 and on day 14.

Plasma and serum were obtained from peripheral blood samples by centrifugation for 15 min at 1,500 *g*. Plasma and serum samples were stored at ≤ −20°C until analysis. Plasma fibrinogen was measured with a commercial kit (Fibrinogen Human ELISA Kit, ab108842; Abcam/KEMET Medical, Cairo, Egypt), with a typical sensitivity of approximately 0.10 μg/mL, the intra- and inter-assay coefficients of variation being 4.0% and 9.7%, respectively. Serum suPAR was also measured with a commercial kit (Quantikine Human uPAR Immunoassay Kit, DUP00; R&D Systems Europe, Oxon, United Kingdom), with a sensitivity < 33 pg/mL, the intra- and inter-assay coefficients of variation being 4.1% and 5.1%, respectively.

Statistical analysis

We calculated means and standard deviations, to which we applied unpaired Student's t-tests, paired t-tests, and chi-square tests, as well as determining linear correlation coefficients and constructing ROC curves. Data were analyzed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

We included 45 patients diagnosed with AECOPD and 20 healthy, age- and gender-matched control subjects. Patients with AECOPD were treated for 14 days and re-evaluated at the end of treatment. The characteristics of the patients and control subjects are presented in Table 1. The AECOPD patients were stratified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of airflow limitation: stage I, in 7 patients (15.5%); stage II, in 16 (35.6%); stage III, in 13 (28.9%); and stage 4, in 9 (20.0%).

The serum levels of suPAR were significantly higher in the AECOPD patients than in the control subjects, on day 1 and day 14 ($p < 0.001$ for both). In the AECOPD group, there was a significant post-treatment decrease in the mean serum suPAR level—from 4,676.8 ± 1,478.9 pg/mL to 3,521.3 ± 1,382.9 pg /mL ($p < 0.001$)—as shown in Figure 1.

The plasma levels of fibrinogen were significantly higher in the AECOPD patients than in the control subjects, on day 1 and day 14 ($p < 0.001$ for both). In the AECOPD group, there was a significant post-treatment decrease in the mean plasma fibrinogen level—from 567.3 ± 216.6 mg/dL to 445.1 ± 190.8 mg/dL ($p < 0.001$)—as shown in Figure 2.

Serum levels of suPAR and plasma levels of fibrinogen increased in proportion to increases in the severity of COPD, being significantly higher in patients with GOLD stage III or IV than in those with GOLD stage I. Table 2 shows the comparison between suPAR and fibrinogen levels, by GOLD stage. The serum suPAR level was found to correlate negatively with FEV_1 (% of predicted), the FEV_1/FVC ratio (% of predicted), PaO_2, and SpO_2, whereas it correlated positively with the GOLD stage, both correlations being significant. Likewise, the plasma fibrinogen level correlated negatively with FEV_1, the FEV_1/FVC ratio, and SpO_2, whereas it correlated positively with the GOLD stage, both correlations also being significant ($p < 0.001$).

There was a significant positive correlation between the serum suPAR level and the plasma fibrinogen level ($r = 0.715$; $p < 0.001$).

The suPAR and fibrinogen cut-off values for the diagnosis of AECOPD were obtained by calculating the maximum sum of sensitivity and specificity. The ROC curves for suPAR and fibrinogen are shown in Figures 3 and 4, respectively. For the diagnosis of AECOPD, the sensitivity, specificity, and accuracy of suPAR were 95.6%, 80.0%, and 93.0%, respectively, compared with 77.8%, 85.0%, and 89.5%, respectively, for fibrinogen.

Of the 45 COPD patients, 9 (20.0%) did not recover from the exacerbation: 1 patient in GOLD stage II; 4 patients in GOLD stage III; and 4 patients in GOLD stage IV. Analyzing those 9 patients together, in comparison with the 36 patients who recovered, we found that the mean serum suPAR on day 1 had been slightly but significantly higher in the former group (5,551.1 ± 1,483.2 pg/mL vs. 4,462.71 ± 1,411.3 pg/mL; $p = 0.046$), as had the plasma fibrinogen levels on day 1 (685.5 ± 271.1 mg/dL vs. 522.5 ± 190.8 mg/dL; $p = 0.048$).

DISCUSSION

In patients with AECOPD, the deteriorating lung function and pronounced systemic inflammation worsen quality of life and reduce survival.[20] In the present study, suPAR and fibrinogen were evaluated as blood biomarkers of AECOPD. In accordance with our results,

Table 1. Baseline characteristics, pulmonary function parameters, stages of COPD, and arterial blood gas analysis results in patients with acute exacerbations and healthy control subjects.

Variable	AECOPD group (n = 45)	Control group (n = 20)	p
Age (years), mean ± SD	56.65 ± 6.48	57.711 ± 5.723	0.510
Male gender, n (%)	13 (65.0)	31 (68.9)	0.758
Current smoker, n (%)	14 (70.0)	32 (71.1)	0.928
Smoking history (pack-years), mean ± SD	31.00 ± 6.15	39.62 ± 9.56	0.003
FEV_1 (% of predicted), mean ± SD	87 ± 4.078	50.44 ± 19.83	< 0.001
FEV_1/FVC ratio (% of predicted), mean ± SD	88.2 ± 8.16	54.53 ± 10.43	< 0.001
pH, mean ± SD	7.38 ± 0.016	7.332 ± 0.043	< 0.001
PaO_2 (mmHg), mean ± SD	75.75 ± 5.18	58.77 ± 4.96	< 0.001
$PaCO_2$ (mmHg), mean ± SD	41.8 ± 3.17	55.40 ± 6.62	< 0.001
SpO_2, mean ± SD	95.75 ± 1.65	88.02 ± 4.25	< 0.001
GOLD stage of COPD, n (%)			
I	7 (15.5)		
II	16 (35.6)		
III	13 (28.9)		
IV	9 (20.0)		

AECOPD: acute exacerbation of COPD; and GOLD: Global Initiative for Chronic Obstructive Lung Disease.

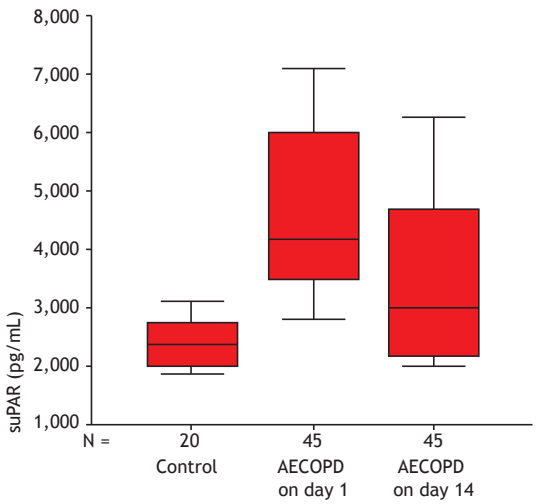

Figure 1. Serum levels of soluble urokinase-type plasminogen activator receptor (suPAR) in the control group, as well as in the acute exacerbation of COPD (AECOPD) group on day 1 and after 14 days of treatment.

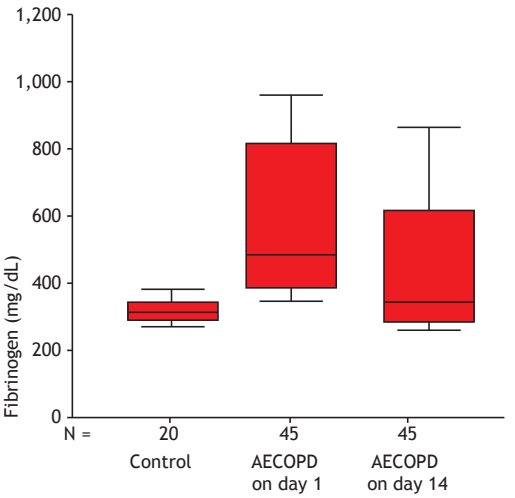

Figure 2. Plasma fibrinogen levels in the control group, as well as in the acute exacerbation of COPD (AECOPD) group on day 1 and after 14 days of treatment.

Table 2. Comparison between serum levels of soluble urokinase-type plasminogen activator receptor and plasma levels of fibrinogen, by GOLD stage, in patients with acute exacerbation of COPD.

Marker	GOLD stage			ANOVA	
	I or II	III	IV		
	Mean ± SD	Mean ± SD	Mean ± SD	F	p
suPAR (pg/mL)					
Day 1	3,504.34 ± 542.53	5,309.23 ± 994.52	6,760.0 ± 502.81	78.232	< 0.001
Day 14	2,558.69 ± 607.38	4,084.61 ± 1,201.23	5,167.77 ± 1,054.14		
Fibrinogen (mg/dL)					
Day 1	443.47 ± 107.98	595.38 ± 229.98	843.33 ± 125.0	21.669	< 0.001
Day 14	337.82 ± 101.88	473.84 ± 201.31	677.77 ± 125.07		

GOLD: Global Initiative for Chronic Obstructive Lung Disease; and suPAR: soluble urokinase-type plasminogen activator receptor.

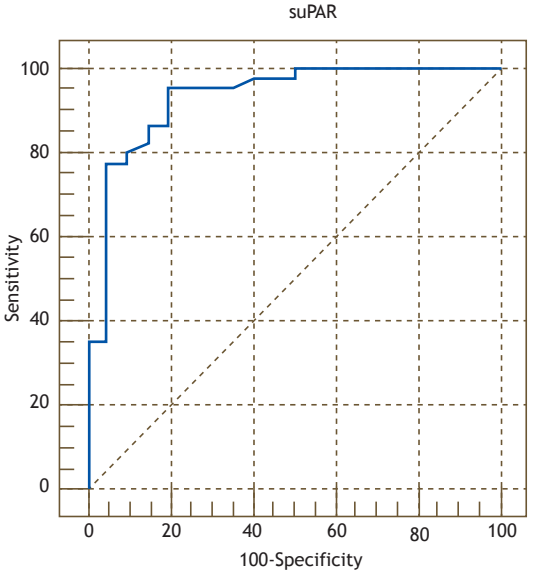

Figure 3. ROC curve of the accuracy of soluble urokinase-type plasminogen activator receptor (suPAR) in identifying acute exacerbation of COPD, with an area under the curve of 0.93 (p <0.001). The curve was constructed by calculating the sensitivity versus the specificity for the different possible suPAR cut-off points.

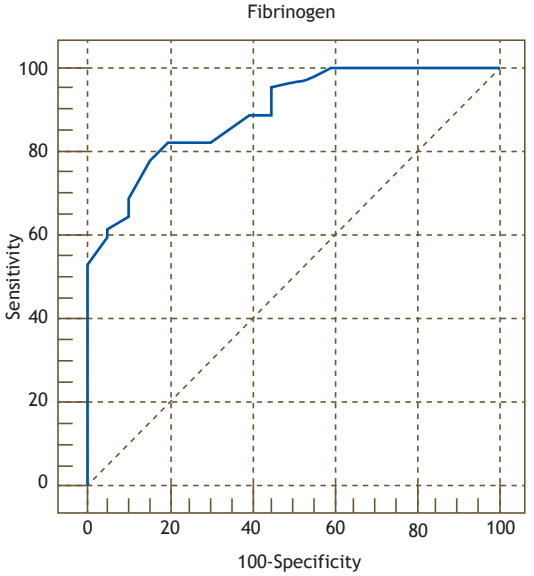

Figure 4. ROC curve of the accuracy of fibrinogen in identifying acute exacerbation of COPD, with an area under the curve of 0.89 (p < 0.005). The curve was constructed by calculating the sensitivity versus the specificity for the different possible fibrinogen cut-off points.

other studies have reported fibrinogen levels to be significantly higher in COPD patients than in control subjects.[21-23] Similarly, Portelli et al.[23] found that levels of serum suPAR were higher in patients with asthma or COPD than in control subjects. In another recent study,[14] fibrinogen was found to be higher in AECOPD patients than in healthy subjects. Therefore, determining the serum levels of suPAR and fibrinogen could be helpful in the evaluation of patients with stable COPD.[24]

The presence of C-reactive protein and fibrinogen indicates systemic inflammation, and the levels of both of those markers increase during AECOPD.[25] In contrast, suPAR has been shown to be an independent marker of inflammation, because it is very stable and its serum concentration is unaffected by circadian changes.[26]

In our study, serum suPAR levels were higher in the AECOPD patients than in the control subjects, and the difference was statistically significant. Our finding that serum suPAR levels were significantly higher before treatment than after is in agreement with the findings of another recent study[27] in which the suPAR levels of patients with stable COPD were compared with those of control subjects and were found to be significantly higher in the former, suggesting that there are inflammatory processes in stable COPD.

One recent study of patients with stable COPD[14] reported that serum suPAR levels were significantly higher on day 7 of treatment than on the day before treatment, and that levels of suPAR were higher in COPD patients than in healthy control subjects. Despite the fact that we measured serum suPAR after 14 days of treatment for AECOPD, that is in agreement with our results. Assessment of serum suPAR levels could play an important role in the evaluation of the inflammatory process in COPD. An increase in the serum suPAR level

has been associated with GOLD stages III and IV,[18] which is also in agreement with our results.

Many studies have reported that fibrinogen levels are higher in COPD patients than in healthy control subjects.[28-32] As in our study, Gumus et al.[24] found a significant positive correlation between serum suPAR and fibrinogen. Those authors concluded that suPAR should be considered a marker of acute inflammation.

In the present study, a significant negative correlation was found between serum suPAR levels and FEV_1 (% of predicted), which indicates the degree of airflow obstruction. That is in accordance with the findings of previous studies evaluating the relationship between inflammatory markers and lung function.[16,33,34] On the basis of these findings, suPAR can be considered an inflammatory marker in AECOPD.

Plasma fibrinogen appears to be an important blood biomarker of systemic inflammation. In COPD exacerbations, steroids might alter plasma fibrinogen through an effect on the inflammatory response, an effect not seen in patients with stable COPD.[15]

Our study also showed a decrease in plasma fibrinogen and serum suPAR levels after 14 days of treatment for AECOPD. Analysis of the area under the ROC curve showed that suPAR was superior to fibrinogen in identifying patients with AECOPD on day 1 and day 14, which is in agreement with the findings of Gumus et al.,[24] despite the fact that those authors evaluated their patients at 7 days of treatment.

We conclude that the determination of serum suPAR levels can be helpful in the follow-up of AECOPD and in the monitoring of the treatment response, potentially making suPAR a valuable biomarker in the prognosis of AECOPD. Because serum suPAR levels correlated with plasma fibrinogen levels, both markers have the potential to predict AECOPD. There is a need for further clinical studies including more patients in order to evaluate the diagnostic value of serum suPAR in comparison with that of other known markers of AECOPD.

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