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Review Article

Physiology Section

Serum Urokinase Plasminogen Activator as a Novel Biological Marker for COPD- A Review

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD), a progressive disease of the airways is associated with chronic inflammation of respiratory passages that leads to irreversible lung dysfunction and distinct morphological changes. The progressive increase in airflow limitation that is seen in COPD is associated with systemic inflammation with the development of extra-pulmonary complications like muscle atrophy, cachexia and osteoporosis. Several biomarkers like C-Reactive Protein (CRP), fibrinogen and Interleukin have been used as an adjunct tool to diagnose COPD. Soluble Urokinase Plasminogen Activator Receptor (suPAR) has been used as a diagnostic marker for congestive heart failure, sepsis, adult respiratory distress syndrome and acute exacerbation COPD. The present narrative review gives a brief overview on clinical significance of suPAR in the diagnosis and prognosis of COPD. The articles quoted in this review were taken from search engines like PubMed Central, Crossref, Web of Science and Google Scholar for articles published from 1991 to 2016, by using domain words like “COPD”, “suPAR”, “inflammation” and “prognosis”. The relevant references cited in these articles were also reviewed.

Keywords: Airflow, Complication, Irreversible, Inflammation, Progressive

INTRODUCTION

COPD is an irreversible disease which is characterised by progressive airflow obstruction due to inflammatory response of the lung and respiratory passage on exposure to noxious particles [1]. COPD is a common non-communicable disease that contributes to morbidity and mortality among respiratory disease all over the world. According to the study done on Global Burden of Disease, it was estimated that COPD will be the third leading cause of death among non-communicable disease by 2020 [2,3].

Conventionally, the tool used to diagnose stable COPD is the forced expiratory volume in the first second of expiration (FEV1). Owing to lack of available diagnostic laboratory tests, Acute Exacerbation-COPD (AE-COPD) are often diagnosed based on clinical symptoms, which is subjective and is prone to inter-observer variations.

Therefore, there is a need for a better tool for the diagnosis of COPD and to monitor its prognosis. Various biomarkers like CRP, suPAR have been used for COPD diagnosis.

The assessment of suPAR level is being used clinically not only to diagnose COPD but also to diagnose other clinical conditions like Congestive Heart Failure (CHF), Systemic Inflammatory Response Syndrome (SIRS) and Adult Respiratory Distress Syndrome (ARDS). The levels of suPAR vary among AE-COPD, stable COPD and normal controls. The prognostic value of suPAR level among COPD patients may aid in the early diagnosis of underlying pulmonary low grade inflammation, thus allowing the physicians to provide targeted therapies and avoiding unnecessary side-effects of prolonged exposure to drugs, and also avoiding incomplete treatment of COPD [4].

In this review, authors discuss the available literature on suPAR in COPD and provide a descriptive overview of diagnostic and prognostic role of suPAR in COPD.

DISCUSSION

Pathophysiology of COPD

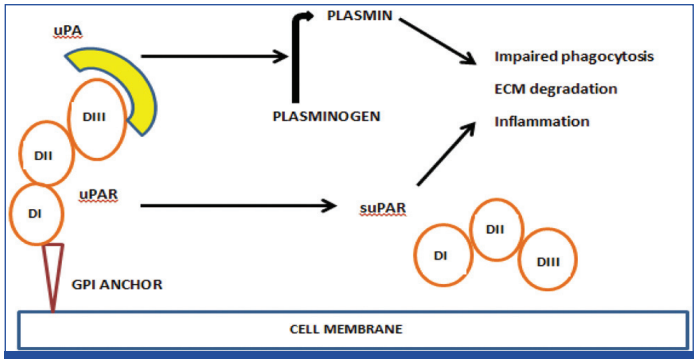
In a normal individual, the damaged respiratory epithelial cells are removed by alveolar macrophages. Inflammatory cytokines like colony stimulating factors and growth factors helps to dampen inflammation, thereby promoting lung repair. However, in COPD patients due to chronic exposure to smoke and dust particles, the inflammatory cells recruitment occur along the respiratory passage and alveoli of the lung. These inflammatory cells release proteinases that damage the extracellular matrix of the lung resulting in inflammation followed by remodelling and scarring of damaged tissue which cause narrowing of the small airways. Moreover, if the exposure to the irritant persists, the bronchial wall becomes inflamed and pus starts to accumulate in the airway lumen [5].

Role of the Immune System in COPD

COPD is most commonly associated with intrinsic immune system disturbances in the lung. Alteration in the number and function of lymphocyte and macrophages has been observed among COPD patients [6]. Due to defect in phagocytic activity of alveolar macrophages the digestion of apoptotic alveolar epithelium gets altered [7]. Moreover, abnormal alteration in polymorphonuclear cells functions and cytokine production with suppression of CD19, CD31, CD44 and CD71 among COPD patients, alters the innate immunity which leads to recurrence of bacterial infection with acute exacerbation [8-10].

Structure and Function of suPAR

The urokinase plasminogen activator/inhibitor system consists of a Plasminogen Activator Inhibitor (PA-I), the receptor for Urokinase Plasminogen Activator (uPAR) and an inactive protease. The uPAR is expressed on the respiratory epithelial cells, neutrophils and macrophages. In 1991, the active form of uPAR called suPAR was identified in serum. uPAR is a G-protein coupled receptor with three domains named Domain I (DI), Domain II (DII) and Domain III (DIII) [Table/Fig-1], information collected from literature [11-13]. Domain-III has chemotactic property for activating the immune system. When uPAR gets activated by a trigger stimulus, the suPAR gets detached from the cell membrane into the blood and other body fluids [14].



[Table/Fig-1]: Structure of suPAR and its role in inflammation [11-13].

suPAR activates plasminogen to plasmin which causes breakdown of proteins in the extracellular matrix during invasion of foreign body or pathogens [15-19]. It also modulates integrin function during chemotaxis, cell adhesion and intracellular signalling. Hence, suPAR contributes to cell proliferation, inflammation, immune system activation, tissue remodelling and signal transduction [20-23].

The level of suPAR in blood, serum and cerebrospinal fluid correlates proportionately with the activation of the immune system. Elevated levels of serum suPAR are associated with adverse prognosis, such as the possibility of developing sepsis in emergency ward patients and in systemic inflammatory response syndrome (SIRS). The level of suPAR measured in the serum, cerebrospinal fluid and urine are constant throughout the day, with limited circadian rhythm compared to the other inflammatory biomarkers like Interleukin and CRP. Hence, suPAR has been used as a marker clinically for the diagnosis of these diseases [17,24-26]. The serum level of suPAR can be measured by routine double sandwich Enzymelinked Immunosorbent Assay (ELISA) technique using commercial kits [13].

Clinical Significance of Serum suPAR

Clinically, suPAR has been used as an independent indicator of mortality among congestive heart failure patients [27]. In Intensive Critical Care (ICU) settings, the distinct advantage of suPAR in addition to APACHE and SOFA score in predicting the outcome of patients with adult respiratory distress has been documented [28,29].

Diagnostic and Prognostic Value of suPAR in COPD

The importance of early prediction of exacerbation among COPD patients cannot be understated as it helps in the ideal management of the disease [30]. Efficient and early intervention in case of exacerbation in patients with COPD are important strategies in the prevention of mortality in these patients. Hence, a "biomarker" is required that could predict the underlying low grade pulmonary inflammation, that can lead to these exacerbations. An ideal biomarker should diagnose the disease severity, exacerbations and predict the mortality [31]. Traditionally, mainly CRP and fibrinogen have been used as biomarkers to determine COPD exacerbation and response. suPAR estimation has been found to have a diagnostic and prognostic role in sepsis and AE-COPD [32]. In a COPD clinic, an ideal biomarker is expected to facilitate the diagnosis of COPD and to predict the prognosis after treatment [33].

suPAR is a novel biomarker of low-grade pulmonary inflammation which is usually associated with the pathogenesis of lung disease. uPA system has a significant role in the development of COPD by activating the low-grade pulmonary inflammation, lung parenchymal destruction and small airway fibrosis that lead to decline in lung function. As a potential biologically stable marker, suPAR is being used clinically to predict the prognosis for sepsis, congestive heart failure and ARDS [34].

A prospective study done by Gumus A et al., on 43 patients with acute exacerbation COPD (AE-COPD) and on 30 healthy controls showed that the median plasma suPAR value was significantly higher among AE-COPD patients than in controls. After treating AE-COPD patients there was a statistically significant decrease in the median value of suPAR ($p<0.001$) [35].

Another prospective study by AboEl MGH and Mabrouk MM, showed that suPAR was high among 45 AE-COPD patients than in the 20 controls. Serum levels of suPAR and fibrinogen were measured among different grades of COPD patients on day 1 and day 14. It was observed that serum biomarkers were more on day 1 than post-treatment. There was a positive correlation ($r=0.715$) between the serum suPAR level and fibrinogen which was statistically significant ($p<0.001$) [36]. Previous studies on diagnostic and prognostic value of suPAR among COPD patients are summarised in [Table/Fig-2] [35-43].

The study done by Kurtipek E et al., showed that the suPAR level was more among AE-COPD than Stable COPD patients. In addition, the post-treatment suPAR levels among AE-COPD patients were lower compared to pre-treatment levels [37].

Author/Year/Reference no.	Study population	Study method	Findings
Xia W et al., 2005 [39]	COPD:74 Asthma:34 Control:44	Cross-sectional	Sputum suPAR level was high among COPD (583±871 pg/mL) compared to asthma (399±103 pg/mL) and control (85±11 pg/mL)
Gumus A et al., 2015 [35]	AE-COPD: 43 Healthy control:30	Prospective	1. Median value of suPAR for control: 2.36±0.89 ng/mL AE-COPD on Day 1: 3.38±1.34 ng/mL AE-COPD on Day 7: 4.84±1.90 2. suPAR plasma levels was found to be negatively correlated with FEV1 post-bronchodilator (p=0.001, r=-0.478
Kurtipek E et al., 2015 [37]	Stable COPD:54 AE-COPD:53 Post treatment COPD:52	Prospective	suPAR level during AE-COPD was 1.28±0.52 ng/mL compared stable COPD 1.21±0.59 ng/mL with p=0.49. The level of suPAR reduced by 1.20±0.41 ng/mL after treatment
Can U et al., 2015 [38]	Stable COPD:46 Control: 41	Cross-sectional	suPAR level was high in stable COPD 4.94±2.79 than control 2.40±2.01 ng/mL
AboEl MGH et al., 2018 [36]	45-AECOPD 20-controls	Prospective	suPAR value was high among AE-COPD patient than controls. The level of suPAR was reduced from day 1 (4678.6±1478.9 pg/mL) on day 1 (3521.3±1382 pg/mL) on day 14 (p<0.001)
Godtfredsen NS., 2018 [41]	AE-COPD patients- 2838	Retrospective	suPAR level was higher among AE-COPD who died within 30 days Vs. than who survived: 5.7 ng/mL (IQR 3.8-8.1) Vs. 3.6 ng/mL (IQr 2.7-5.1) with p<0.0001 and Hazard ratio was 2.0 (95% CI 1.7-2.4)
Bocskei RM., 2019 [42]	COPD patients-24 Control-18	Cross-sectional	Plasma level of suPAR was elevated in COPD patients (2.84±0.67 ng/mL) than controls (2.41±0.57 ng/mL) with p=0.03
Loukeri A., 2016 [43]	Stable COPD patients-9 Control-	Cross-sectional	Level of suPAR was high among COPD Vs. controls (median value 3.3 ng/mL Vs. 2.5 ng/mL) with p<0.001.

[Table/Fig-2]: Summary of the previous studies on the diagnostic and prognostic value of suPAR among COPD patients.

Can U et al., measured suPAR levels among 46 stable COPD patients and reported increased level of suPAR among COPD patients possibly due to underlying pulmonary inflammation [38]. Xiao W et al., has found that suPAR level among COPD patient was significantly higher than asthma and controls. This helps to discriminate COPD with other lung pathology. On the whole, suPAR can be used to diagnose AE-COPD and to monitor treatment response [39].

In a study done on 84 stable COPD patients and 51 healthy subjects, to investigate if PA-I was involved in COPD pathogenesis, the serum level of PA-I was significantly increased among stable COPD patients 125.56±51.74 ng/mL (mean±SD) versus the healthy subjects 102.98±36.62 ng/mL (mean±SD). In addition, the level of PA-I showed statistically significant negative correlation (r=-0.308) with pulmonary function parameters (p<0.001) [40].

The diagnostic and prognostic importance of suPAR among sepsis patients and in AE-COPD patients has been reviewed in this paper. However, the contribution of suPAR to predict ongoing low grade pulmonary inflammation has not been dealt with and can be of use if reviewed.

CONCLUSION

Serum suPAR is a clinically validated biomarker which can help in the diagnosis of Chronic Obstructive Pulmonary Disease (COPD), as well as predict the severity of the disease. Serum suPAR levels are elevated among COPD patients during exacerbation as compared to stable COPD patients: this provides diagnostic and prognostic advantage to the clinician. Soluble Urokinase Plasminogen Activator Receptor (suPAR) can also be used to assess the response to COPD treatment. It is a specific and independent predictor of mortality among COPD patients with comorbid diseases like congestive heart failure and renal failure.

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