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Relationship between serum sialic acid levels and prolidase activity with airflow obstruction in patients with COPD

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Abstract

Our aim in this study was to evaluate the prognostic significance of sialic acid (SA) and prolidase activity and to evaluate the association between airflow obstruction severity and these parameters in chronic obstructive pulmonary disease (COPD) patients.

Ninety-four patients (84 M, 10 F) and 34 healthy subjects (19 M, 15 F) were included into the study. COPD staging was performed to COPD patients according to new global initiative for chronic obstructive lung disease criteria which includes pulmonary function tests, symptoms and hospitalization; COPD patients were divided into 4 subgroups as group A (n = 25), group B (n = 19), group C (n = 20), and group D (n = 28).

SA and C-reactive protein levels were significantly higher than the control group in all COPD groups. SA levels were significantly higher in group B patients than the control and group A. Prolidase activity was significantly lower than control group in total COPD groups ($P < .05$). There was a weak negative correlation between SA and forced vital capacity ($r = –0.217$, $P = .038$) and forced expiratory volume in 1 second (FEV1) ($r = –0.210$, $P = .045$), whereas weak positive correlation was present between SA and C-reactive protein ($r = 0.247$, $P = .018$) in all patient groups. There was weak positive correlation between prolidase and FEV1 ($r = 0.222$, $P = .033$) and FEV1/forced vital capacity ($r = 0.230$, $P = .027$).

Our study shows that systemic inflammation, prolidase activity, and SA levels in stable COPD patients are associated with airflow obstruction severity. In addition to the prolidase activity; SA levels might be associated with inflammation.

Abbreviations: COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = global initiative for chronic obstructive lung disease, mMRC = modified Medical Research Council, NA = neurominadase, PFT = pulmonary function tests, SA = sialic acid, TSA = total SA.

Keywords: chronic obstructive pulmonary disease, C-reactive protein, prolidase activity, sialic acid

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease characterized by airflow obstruction. COPD causes serious morbidity and mortality in affected patients and disease prevalence is high; therefore, it is counted as an important health problem all over the world.[1] The global initiative for chronic obstructive lung disease (GOLD) established a consensus report on COPD patients and introduced a classification for the disease according to pulmonary function of patients and it is being revised in every year.[2]

Sialic acid (SA) is a generic term for a family of acetylated derivative of neuraminic acid (N-acetyl neuraminic acid, NANA).[3] It is a negatively charged complex carbohydrate and is present in the terminal saccharide of glycoproteins and glycolipids on cell membrane.[4] SA is proposed to play a role in several cellular functions, including stabilization of molecules

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and membranes, modulating cellular interactions, protection of cells from enzymatic activity including proteases and glycosidases, and regulating affinity of receptors. SA is also important for the prevention of aggregation and protection of membrane integrity due to the negative charge they provide to cell membranes.[5]

Total SA (TSA) levels were shown to be elevated during inflammation, probably due to the increase of acute phase glycoproteins containing SA, such as α-1-acid glycoprotein, α-2-macroglobulin, and haptoglobin.[4,5] Protein sialisation is also increased early in the course of inflammation. In COPD patients, who have extensive pulmonary inflammation, TSA levels also increase as a marker of systemic inflammation.[6] Therefore, serum SA levels can be used as an indicator of acute phase response in COPD patients. Several studies have reported serum SA levels[7] and serum prolidase enzyme activity[8,9] in various inflammatory conditions.

Prolidase, or proline dipeptidase, is an enzyme responsible for the hydrolysis of iminodipeptides containing proline and hydroxyproline in collagen metabolism.[10] In the absence of proline and hydroxyproline, urinary excretion increases, and collagen synthesis is impaired. Therefore, clinical signs related to impaired collagen synthesis, including skin ulcers due to improper wound healing, hematological problems, hepatosplenomegaly, dysmorphic facial appearance, and chronic infections are observed.[11] Enzyme activity has been shown in patients with COPD, bronchial asthma, cardiomyopathy, and pancreatitis.[10–12]

2. Objective

The aim of this study was to determine the serum SA levels and prolidase activity together with the systemic inflammatory parameter C-reactive protein levels in COPD patients and to evaluate whether they play a role in the severity of airflow obstruction or chronic inflammatory process in COPD.

3. Materials and methods

The prospective study has been approved by the ethical committee of the Acibadem Mehmet Ali Aydınlar Medical Faculty and written informed consent was obtained from each subject. We included patients with COPD who were diagnosed at least for 1 year and who had stable disease for 3 months without any change in the medication. Exclusion criteria were the presence of either of the following conditions: respiratory disorders other than COPD, pulmonary embolism, left ventricular systolic or diastolic dysfunction, comorbidities such as diabetes, chronic renal insufficiency, thyroid dysfunction, hepatic dysfunction, metabolic syndrome, and lower respiratory tract infection. Detailed anamnesis was taken from all participants and physical examination was performed. COPD disease severity and related comorbidities of all patients were recorded and transthoracic echocardiography was performed to all patients. The management of all patients was in accordance with the ERS/ATS guidelines, including bronchodilators, systemic corticosteroids (30–40 mg prednisone) for 10 to 14 days and antibiotics.

The severity of COPD was recorded according to 2020 GOLD report.[2] COPD groups were graded as group A–D according to symptoms which were tested by modified Medical Research Council and COAH Assessment tests and also by pulmonary function tests (PFT), exacerbation of disease, and hospitalization.[2]

PFT were done in accordance with the criteria recommended by ERS using a computer-assisted spirometry (Vmax22D, Sensor Medics, CA). Pulmonary function parameters including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio were performed on stable phase. These patients had a stable airflow limitation with FEV1 $<80\%$ of the predicted value in combination with a FEV1/FVC $<70\%$ predicted with a reversibility of $<12\%$ predicted post-bronchodilator. COPD groups were classified as group A, B, C, and D according to new GOLD classification.

Blood samples were collected in EDTA containing tubes and anticoagulant-free tubes. After centrifugation at 5000 rpm for 15 minutes, the plasma and serum were divided into 4 aliquots. Samples were stored at $-80\,^{\circ}C$ until biochemical analysis.

Total protein, albumin, and uric acid levels were measured using the spectrophotometric method by the autoanalyzer (Hitachi Modular System, Roche Diagnostic, Corporation, Hague Road, Indianapolis, IN). CRP values were measured with the turbidimetric method by auto analyzer (ADVIA 1800 Auto Analyzer, Siemens medical Sol., Deerfield, IL).

3.1. Measurement of serum prolidase activity

Prolidase activity was assessed according to the method of Myara et al[13] based on colorimetric determination of proline by Chinard reagent.[14] The within-day precision, expressed as CV (n = 20), was 4.3% at 960 μmol prolin/L/min (400–1600 μmol prolin/L/min) of prolidase activity. The day-to-day precision, expressed as CV (n = 20), was 5.1% at 940 μmol prolin/L/min (350–1680 μmol prolin/L/min) of prolidase activity.

3.2. Measurement of SA concentrations

SA concentrations were determined by combined modification of the thiobarbituric acid (TBA) method by SkozoMohos and dimethylsulfoxide method by Aminoff, namely Tram method.[15] The within-day precision, expressed as CV (n = 20), was 4.1% at 77 mg/dL (25–120 mg/dL) of SA. The day-to-day precision, expressed as CV (n = 20), was 4.9% at 79 mg/dL (20–130 mg/dL) of SA.

3.3. Statistical analysis

Statistical analyses were performed using the SPSS 20.0 for Windows (SPSS Inc., Chicago, IL). All data were expressed as means ± standard deviation (SD). Descriptive statistics were obtained and data were tested for normality using the Levene test for Gaussian distribution. For comparison of parameters with normal distribution parametric tests and comparison of parameters with abnormal distribution non-parametric tests were used. For this purpose, One-Way Analysis of Variance, unpaired *t* test, Kruskal–Wallis, and Mann–Whitney *U* tests were used. Tukey (for parametric analysis) and Dunn tests (for non-parametric analysis) were used as post-hoc tests. Relationships between variables were evaluated with Pearson or Spearman correlation coefficient. A P value $\leq .05$ was considered statistically significant.

4. Results

Ninety-four patients (84 M, 10 F) and 34 healthy subjects (19 M, 15 F) were included into the study. No statistically significant

Table 1

Demographic, clinical, and laboratory findings of the groups.

	Control (n:34)	Mild (Group I) (n:25)	Moderate (Group II) (n:19)	Severe (Group III) (n:20)	Very severe (Group IV) (n:28)
Age, yr	55.07 ± 5.15	55.44 ± 9.80	58.26 ± 7.06	59.95 ± 6.30	60.86 ± 9.06
Gender (F/M)	15/19	11/14	9/10	10/10	13/15
FVC (% pred)	91 ± 10 c***,d***,e***	92 ± 11 c***,d***,e***	74 ± 8 a***,b***,d***,e***	56 ± 12 a***,b***,c***,e***	38 ± 9 a***,b***,c***,d***
FEV1 (% pred)	99 ± 9 b**,c***,d***,e***	92 ± 10 a**,c***,d***,e***	65 ± 8 a***,b***,d**,e***	41 ± 6 a***,b***,c***,e***	25 ± 4 a***,b***,c***,d***
FEV1/FVC ratio	104 ± 8 b**,d***,e***	93 ± 4 a**,c***,d***,e***	88 ± 12 b***,d***,e***	74 ± 12 a***,b***,c***	71 ± 15 a***,b***,c***
T.Protein, g/dL	7.49 ± 0.39	7.42 ± 0.42	7.32 ± 0.63	7.29 ± 0.62	7.58 ± 0.55
Albumin, g/dL	4.54 ± 0.23	4.37 ± 0.25	4.22 ± 0.37	4.02 ± 0.30	4.50 ± 0.27
Uric acid, mg/dL	3.57 ± 0.76 b***,c***,d***,e***	5.16 ± 1.36 a***	6.07 ± 1.01 a***	5.08 ± 0.95 a***	5.50 ± 1.57 a***

F = female, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, M = male, T. Protein = total protein.

[a] vs Control.

[b] vs mild COPD.

[c] vs moderate COPD.

[d] vs severe COPD.

[e] vs very severe COPD.

*** $P < .001$.

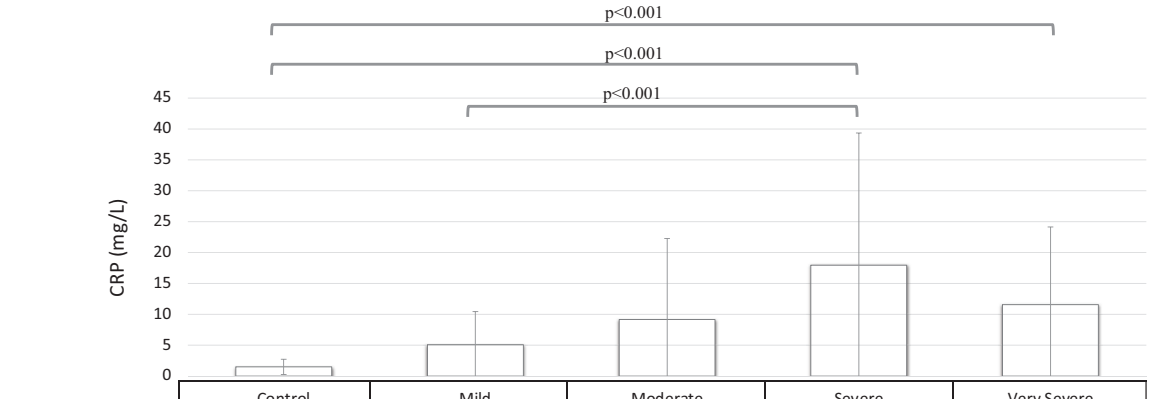
** $P < .01$.

* $P < .05$.

difference was found between the study groups and the control group regarding the social and demographic data (age, gender, education level) ($P > .05$) (Table 1). Clinical and laboratory findings including FEV1 (% predicted), and FEV1/FVC (%) values of the patients are given in Table 1.

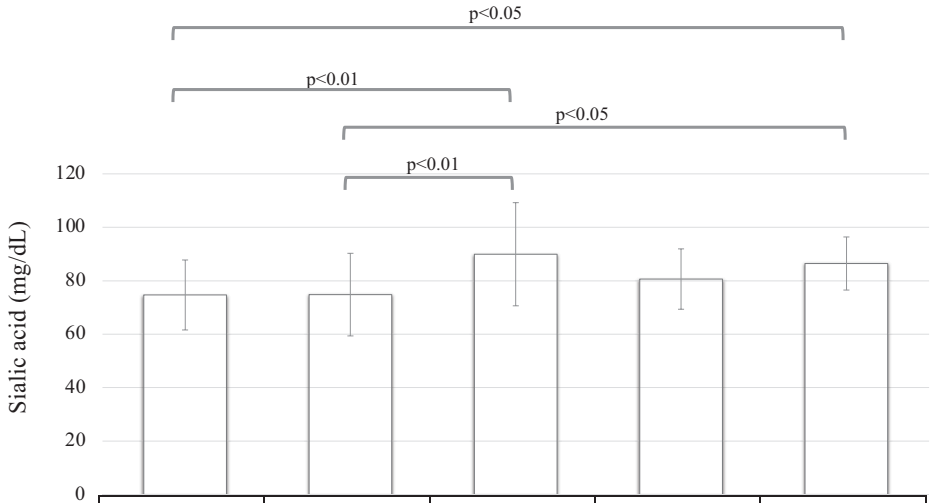
As shown in Table 1, total protein and albumin levels were not significantly different between the groups ($P > .05$). Serum uric acid concentrations were especially significantly decreased in patients in moderate group when compared with control ($P < .001$) (Table 1). C-reactive protein levels of control group were significantly lower than patients with group C and D (for both, $P < .001$) (Fig. 1). There were significant differences between patients with COPD and healthy controls with respect to SA (Fig. 2) and prolidase activity (Fig. 3).

When correlation analysis was performed in all patients with stable COPD, SA levels were found to show weak negative correlation with FVC ($r = -0.217$, $P = .038$) as well as with FEV1 ($r = -0.210$, $P = .045$). Also, SA levels were found to have weak positive correlation with CRP ($r = 0.247$, $P = .018$). Prolidase activity showed weak positive correlation with FEV1 ($r = 0.222$, $P = .033$) and FEV1/FVC ($r = 0.230$, $P = .027$) in all patients with stable COPD.



	Control (n:34)	Mild (Group I) (n:25)	Moderate (Group II) (n:19)	Severe (Group III) (n:20)	Very Severe (Group IV) (n:28)
CRP (mg/L) Mean ± S.D.	1.50 ± 1.23	5.09 ± 5.36	9.16 ± 13.11	17.95 ± 21.39	11.56 ± 12.58
(95% CI of mean)	(1.07 – 1.93)	(2.88 – 7.30)	(2.84 – 15.48)	(7.94 – 27.96)	(6.68- 16.44)

Figure 1. CRP levels in all groups. CRP = C-reactive protein.

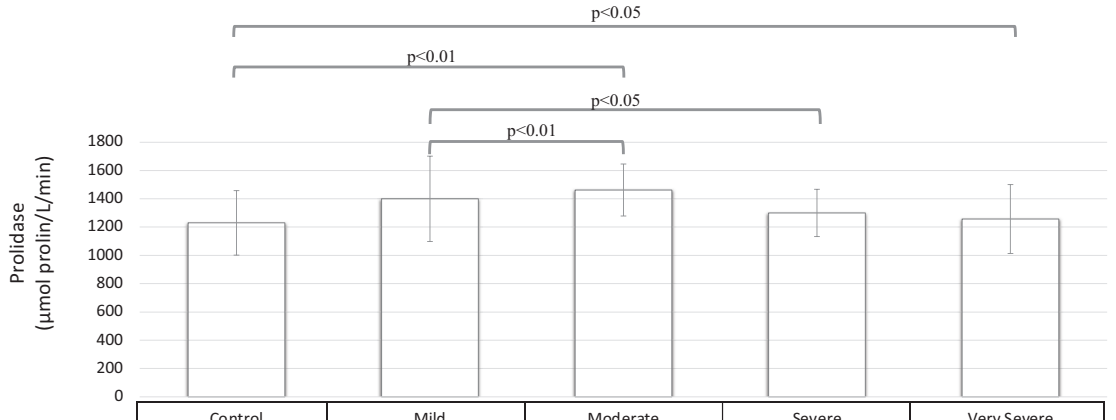


	Control (n:34)	Mild (Group I) (n:25)	Moderate (Group II) (n:19)	Severe (Group III) (n:20)	Very Severe (Group IV) (n:28)
Sialic acid (mg/dL) Mean ± S.D.	74.68 ± 13.09	74.79 ± 15.45	89.91 ± 19.32	80.61 ± 11.3	86.45 ± 9.95
(95% CI of mean)	(70.11 – 79.25)	(68.42 – 81.17)	(80.60 – 99.22)	(75.33 – 85.90)	(82.59 - 90.31)

Figure 2. Sialic acid levels in all groups.

5. Discussion

Increased airway and systemic inflammation in patients with COPD are associated with a decline in lung function. FEV1 is used as airflow limitation severity biomarker in COPD patients, but several other markers, such as CRP, fibrinogen, white blood cell count, neutrophil count, and cytokines are used for detection of disease severity both in stable disease and in its exacerbations. Despite the fact that COPD is a very common chronic inflammatory disease and its mortality is high, there are only few studies about inflammation markers that can be used as acute phase reactants in the literature. CRP is synthesized by the hepatocytes and released into the blood to stimulate the production of biologically active substances, such as endothelin-1, and some cytokines, also to enhance the inflammatory reaction. Therefore, CRP levels are elevated in patients with inflammatory diseases including COPD and significantly altered with aggravation of lung function damage.[16] This study showed that in COPD patients, SA was elevated and prolidase activity



	Control (n:34)	Mild (Group I) (n:25)	Moderate (Group II) (n:19)	Severe (Group III) (n:20)	Very Severe (Group IV) (n:28)
Prolidase (µmol/prolin/min) Mean ± S.D.	1230 ± 227.9	1400 ± 301.5	1462 ± 183.5	1300 ± 167.1	1257 ± 243.4
(95% CI of mean)	(1151 – 1310)	(1276 – 1525)	(1373 – 1550)	(1222 – 1379)	(1163- 1352)

Figure 3. Prolidase levels in all groups.

was decreased compared with controls. Therefore, in addition to PFT and CRP, both prolidase activity and SA levels is associated with systemic inflammation in stable COPD.

Different values of serum SA and serum prolidase enzyme activities were recorded in various inflammatory conditions previously. In the current study, SA levels in all COPD patients were significantly higher than the control group. SA levels were also significantly higher in group C and D patients than groups A and B. There was only a weak negative correlation between SA levels and both FVC and FEV1; whereas there was a weak positive correlation between SA and CRP levels. These results suggest that SA can be used as an inflammatory marker in COPD.

Studies with SA in COPD patients are limited. Recently, similar to our findings, Qaisar et al[17] reported that TSA have positive associations with FEV1% in COPD. TSA were also strong predictors of FEV1% in men and women participants with COPD; serum TSA levels were elevated among participants with GOLD groups C and D but not groups A and B when compared with non-COPD control group. Rathod et al[18] evaluated and compared periodontal health status and salivary SA levels in patients with COPD and chronic periodontitis. They showed that salivary SA levels were highest in the COPD group, followed by the periodontitis group, and the lowest in the healthy group. Sirsikar et al[6] suggested that CRP in association with TSA is increased as a marker of systemic inflammation in COPD. Hence measurement of CRP and TSA simultaneously can be regarded as a marker of systemic inflammation and are helpful for the monitoring and management of COPD. Further studies are required to establish the efficacy of serum TSA in COPD.

SA level is accepted as an indication of acute phase response and there are studies in the literature showing increased SA levels in various rheumatologic inflammatory diseases, including rheumatoid arthritis and ankylosing spondylitis.[7,8,19,20] This has been explained by the fact that SA is bound to serum α and β globulin fractions, which are known to increase during the inflammatory process. Tajiri et al[21] showed that serum SA levels were higher in the acute phase of subacute granulomatous thyroiditis compared with control group and serum SA levels decreased after the treatment. They suggested that the monitoring of SA levels can be a useful tool in diagnosis and follow-up of subacute granulomatous thyroiditis.

Previous studies have investigated prolidase activity under different clinical conditions, such as choroid plexus calcification, non-alcoholic fatty liver disease, *Helicobacter pylori* infection, osteoporosis, and asthma.[8–12,22] Serum prolidase activity may reflect the degree of fibrosis and inflammation. In the current study, prolidase activity in total COPD patients group was significantly lower than control group, especially in the moderate group. Moreover, prolidase activity weak positively correlated with FEV1 and FEV1/FVC in all patients with stable COPD.

Viral neurominadase (NA) is an enzyme that catalyzes the removal of terminal sialic acids. NA breaks down sialic acid, facilitates the release of newly formed virions from the cell, and the spread of viruses. NA also plays an important role in viral infection and hemagglutinin-mediated membrane fusion by binding to SA receptors. Anti-viral treatment such as neuraminidase inhibitors may reduce the severity of disease.[23] Thus, treatment to prevent influenza has been recommended for COPD patients.[24] Because NA associated with some viruses breaks down SA, measuring this particular biomarker in the context of exacerbations can be useful in distinguish between bacterial and viral causes.

Prolidase activity has already been shown to be lower in patients with bronchial asthma,[8] COPD,[9,25] dilated cardiomyopathy, pancreatitis, and pancreatic cancer. Prolidase activity was reported to be different in each chronic illness: while prolidase activity was reported to be decreased in chronic uremic type 2 diabetes mellitus patients,[26] it is increased in chronic liver diseases.[27] Gencer et al[9] found decreased prolidase activity and total antioxidant capacity, whereas increased plasma lipid peroxidation in COPD patients. They have suggested that COPD caused oxidative stress in the lung and oxidative–anti-oxidative balance and collagen transformation were altered in lungs of COPD patients, therefore altered prolidase activity in COPD patients may be due to collagen metabolism disturbances in COPD patients. Ekin et al[25] also evaluated prolidase activity with oxidative and antioxidative parameters in patients with COPD and found lower prolidase levels in those patients. In our current study, we also found lower prolidase activity in COPD patients than healthy controls, which was in accordance with the literature. Increased airway and systemic inflammatory markers in patients with COPD and high levels of these markers are associated with a more rapid decline in lung function.

However, this study has some limitations. First, our sample size is relatively small. Second, physical activity and the exercise level of the subjects were not documented. Gold standard angiographic evaluation was not used to establish coronary heart disease. Due to the cross-sectional design of our study, we cannot make any suggestions about the association between the laboratory and clinical parameters of the subjects.

6. Conclusions

To conclude, in stable COPD, prolidase, and SA levels are associated with airflow obstruction severity and might be associated with inflammation. Systemic prolidase activity may reflect disorders of turnover and tissue collagen metabolism in the lung, so it can serve as a marker of the disease, especially for the progression of the fibrotic process in the airways. It was also found that SA and CRP levels were significantly higher in subgroups. In addition to CRP, which is an acute-phase reactant, SA levels and prolidase activity may also contribute to determine of COPD severity. However, further clinical studies are needed to verify these conclusions.

Author contributions

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