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Research Article

Elevated levels of serum sialic acid and C-reactive protein: markers of systemic inflammation in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a systemic chronic inflammatory disease with pulmonary and extra-pulmonary manifestations involving lungs causing airways dysfunction. C-reactive protein (C-RP) is a positive acute phase reactant and albumin a negative phase reactant during inflammation in COPD patients. Sialic acid (SA) prevalent in mucus rich tissues is gaining importance as biochemical marker in inflammatory immune response. Purpose of present study was to measure serum C-reactive protein (C-RP), total sialic acid and albumin levels in COPD patients and establish there association in COPD and compare with healthy controls.
Methods: Seventy five clinically confirmed COPD patients, both male and female between the age group of 38-70 years were selected for the study and age/ sex matched healthy volunteers as controls were selected for comparison. Serum samples were analyzed for C-RP (mg/dl) by nephalometry and TSA (mmol/L) by periodate resorcinol method and albumin by dye binding method by spectrophotometer.
Results: The mean value of serum C-RP in cases was 3.26±2.0 (mg/dl) and in controls 0.57±0.34 (mg/dl) with $p<0.001$. TSA in cases was 3.53±1.41 (mmol/L) compared to controls 1.81±0.53 (mmol/L), $p<0.001$. There was a statistically significant positive correlation between C-RP and TSA ($r=0.755$, $p<0.001$). The mean value of Albumin in cases decreased (2.54±0.87) as compared to control (4.07±0.66) ($p<0.001$) showed negative correlation with C-RP ($r= -0.418$, $p<0.01$) and TSA ($r= -0.728$, $p<0.001$). There was a significant decrease in BMI among cases 19.95±3.17 compared to control 21.17±1.78 $p<0.001$.
Conclusions: C- reactive protein in association with TSA has increased in COPD as a marker of systemic inflammation. Albumin and BMI decreased as a result of nutritional depletion. Patients with low BMI and low serum albumin level have greater risk of having exacerbation, acute respiratory failure than patients with normal BMI.

Keywords: COPD, C- reactive protein, Total sialic acid, Albumin

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in countries of high, middle, and low income worldwide representing the largest fraction of mortality form respiratory diseases.[1] By 2020, the World Health Organization predicts that COPD will become the leading cause of death and the fifth leading cause of disability worldwide.[2] COPD includes chronic obstructive bronchitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways. The obstruction of peripheral airways due to inflammatory cell infiltration and fibrosis, together with inflammatory exudates in the lumen, correlate best with the severity of airflow obstruction, indicating the importance of chronic inflammation in COPD.

Classification of severity of airflow limitation in COPD

In pulmonary function testing, a post-bronchodilator FEV1/FVC ratio of <70% and an FEV1 of <80% is commonly considered diagnostic for COPD. The global initiative for chronic obstructive lung disease (GOLD) system categorises airflow limitation into stages:

- Stage I - Mild: FEV1/FVC <70% and FEV1 ≥80% of predicted value, with or without symptoms
- Stage II- Moderate: FEV1/FVC <70% and FEV1 50% to 80% of predicted value, with or without symptoms
- Stage III- Severe: FEV1/FVC <70% and FEV1 30% to 50% of predicted value, with or without symptoms
- Stage IV- Very severe: FEV1/FVC <70% and FEV1 <30% of predicted value or FEV1 <50%, with chronic respiratory failure.

COPD is considered as a multi-component, complex disease associated with chronic low grade systemic inflammatory response. Systemic inflammation in COPD is associated with, systemic complications such as coronary artery disease, stroke and skeletal muscle dysfunction.[4] The clinical course of the disease is an accelerated decline in lung function, usually caused by cigarette smoking, resulting in increasing symptoms and disability, punctuated by exacerbations of the disease which leads to morbidity and mortality, and significant reductions in the quality of life.[5]

CRP is acute-phase reactants, member of the pentraxin family of proteins which binds to damaged membranes and nuclear auto antigens. CRP has an ability to recognize pathogens and to mediate their elimination by recruiting the complement system and phagocytic cells, synthesized by liver and its levels rise dramatically during inflammatory processes occurring in the body.[6] C-reactive protein is evaluated in chronic obstructive airway disease patients, in order to establish a possible association with basal systemic inflammation in stable period, cardiovascular risk events, disease prognosis and identification of infectious exacerbations. When considering the stable state, CRP levels tend to be independent of smoking, lung function, strongly associated with arterial oxygen tension and 6- minute walk distance.[7] It is therefore possible that serum CRP as a systemic marker of on-going lung inflammation could be used as a predictor of future COPD outcomes. It reflects the total systemic burden of inflammation of individuals and has been shown to be increased in COPD in stable condition and during exacerbations.[8] Finally, elevated levels of C-RP seem to predict cardiovascular risk in patients with COPD.[9]

Serum sialic acid is N-acetyl Neuraminic acid. Although over 50 natural sialic acids have been identified, 2 two forms are commonly determined in glycoprotein products: N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc). Sialic acid (composed of alkylated derivatives of the neuramic acid) is a carbohydrate moiety on membrane glycoprotein, characterizes the cohesive, adhesive and antigenic properties by its effect on cell to cell contacts. Clinically, neuraminic acid may be considered as an aldol condensation product of pyruvic acid with either D-glucosamine or D-mannosamine. The sialic acid is distributed in biological fluid as components of mucoprotein and mucolipids.[10]

The sialic acid levels may be influenced by inflammation, neoplastic or inborn genetic disorder.[11] It is found that Sialic acid can be used as a measurement of the acute phase response because many proteins of the immune response are actually glycoproteins, and these glycoproteins have sialic acid as the terminal sugar on their oligosaccharide chain. Serum sialic acid is a marker of the acute-phase response being produced by the liver, stimulated by proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α.

An increase in their levels is reflected as release of cytokines from macrophages that trigger the hepatic production of SA rich glycoproteins in order to provide a substrate for resialylation of the endothelium. In the last few years different workers have demonstrated that the concentration of sialic acid in human serum is abnormally high in tissue destruction, tissue proliferation, depolymerization or inflammation.[12] COPD exacerbation, or episodic worsening of symptoms, often results in hospitalization and increased mortality rates. Airway infections by new bacterial strains, such as non-typeable haemophilusinfluenzae (NTHi), are a major cause of COPD exacerbation. NTHi express lipo-oligosaccharides that contain sialic acids, and may interact with Siglec-14, a sialic acid recognition protein on myeloid cells that serves as an activating.[13] Mucus hypersecreation in COPD has characteristics features, patients can produce at about 100ml/day. The increased mucus is associated with goblet cell hyperplasia; sub mucosal gland hypertrophy which is mainly due to increased level of sialic acid due to altered glycosylation.[14]

Serum albumin is the major negative acute phase protein. During the acute phase response the demand for amino acids for synthesis of the positive acute phase proteins is markedly increased, which necessitates reprioritisation of hepatic protein synthesis. Thus, albumin synthesis is down-regulated and amino acids are shunted into synthesis of positive acute phase proteins. It has been reported that during the acute phase response 30-40% of hepatic protein anabolic capacity is used for the production of positive acute phase proteins; thus, the production of other proteins needs to be curtailed.[15]

Low serum albumin level is one of the poor prognostic indicators in COPD patients. Over the past few years several studies have indicated that nutritional state is impaired in a high proportion of patients with chronic

obstructive lung disease.[16] Weight loss is common with severe disease.[17] Malnutrition is a leading cause of impaired respiratory muscle contractility, affecting both strength and endurance.[18] In patients with severe malnutrition significant changes in respiratory and limb muscle contraction and relaxation characteristics and fatigability properties have been described with decompensation in lung function. Studies indicate that people with low BMI are at a higher risk of developing COPD. [19] Body weight and body mass index (BMI) are independent risk factors for mortality in chronic obstructive pulmonary disease (COPD) patients.[20,21] The role of low BMI as a determinant of poor survival in these patients could have been due to several factors, such as respiratory muscle weakness, impaired gas exchange, and impaired immune response, all of which have been related to malnutrition in COPD patients.[22]

Hence serum levels of CRP and albumin together as acute phase reactant could provide a direct measure of systemic inflammation in COPD, TSA which will be useful in detecting early complications, management and prognostic value in COPD along with BMI. In a case control study, we tested the hypothesis that increased concentrations of serum CRP/TSA and hypoalbumineamia can be used as a predictor of systemic inflammation in individuals with airway obstruction.

METHODS

This study was the duration based case control study for a period of one year conducted on 75 patients with clinically confirmed chronic obstructive pulmonary disease visiting departments of Medicine, Chest and TB at Vydehi Institute of Medical Sciences & Research Centre, Bengaluru and 75 age/sex matched healthy male/female as a controls visiting the hospital for routine health check-up and also hospital staff members included, with approval of Institutional Ethical Committee. Informed consent was taken both from cases and control. Demographic histories such as age, sex and smoking so on were recorded. Cases had FEV1/FVC <70% and FEV1<80% predicted in their spirometry and asthma was ruled out in them by assessing their clinical history and response to bronchodilators (less than 12% increasein FEV1 after inhaling slabutamol 400>g). After detailed clinical history blood was collected from both cases and controls. Patients suffering from alcoholic, autoimmune, liver, kidney, malignant disorders, bronchial asthma, bronchiectasis, cardiovascular diseases, diabetes mellitus, pleural effusion, pulmonary tuberculosis, osteoarthritis, Patients on medications like steroids and antioxidants are excluded. 5 ml of blood from each of the mentioned subjects was collected from median cubital vein by venipuncture avoiding hemolysis into an evacuated vacuum tube. The samples were aliquoted and kept at -20° C until analysis was done. C-RP was measured by Nephalometrically using (IMMAGE 800) (Serum <0.75mg/dL) and TSA spectrophotometrically by periodate resorcinol (Men: 1.57-2.63 mmol/L, Women: 1.69-2.64 mmol/L).[23,24] Serum albumin levels are measured by Dye binding method using bromocresol green using spectrophotometrically.[25] Serum albumin levels is measured by and classified as low i.e., <3.5g/dl and Normal 3.5-5.5g/dl and classified as low i.e., <3.5g/dl and normal 3.5-5.5g/dl. Body mass index is calculated weight in kg divided by square of height in meters.[26] They were further classified as per Indian Council for Medical Research classification. Underweight <18, normal 18-23, overweight 23-25, obese >25. The data were expressed as mean±SD. Student t test (two tailed, independent) has been used to find the significant mean difference of study parameters between control and COPD patients. Results were analysed statistically by One-way ANOVA (Analysis Of Variance) using standard statistical software package of social science (SPSS) version 20. The difference was considered significant if p <0.05. Pearson's correlation has been used to find the strength of relationship between the proportion of study features and the associated parameters. Receiving operating characteristics (ROC) has been used to find the diagnostic accuracy of CRP and TSA among patients.

RESULTS

The mean age in controls was 48.03±11.30 and in cases it is 53.43±9.64, the difference in age is not statistically significant (p<0.127). There were 70% of males and 30% of females in controls and in cases 82.5% of them are males, 17.5% of them are females with p=0.189. In our study the C-RP values are significantly higher in COPD patients (3.26±2.0 mg/dL) compared to controls (0.57±0.34 mg/dl).The mean TSA concentration in COPD subjects was (3.53±1.41 mmol/L) higher when compared to controls (1.81±0.53 mmol/L) (p<0.001). In our study the albumin values are significantly lower in COPD patients (2.54±0.87 g/dL) compared to controls (4.07±0.66g/dL). BMI also found low in COPD patients (19.95±3.17 kg/m^2) than controls (21.17±1.78 kg/m^2) (Table 1).

Table 1: Mean levels of study parameters among controls and Cases in COPD patients.

Parameters	Controls Mean±SD	Cases Mean±SD	p Value
Age (years)	48.03±11.30	53.43±9.64	p<0.127
Gender Male/Female	54/21	49/26	P=0.189
BMI kg/m2	21.17±1.78	19.95±3.17	<0.001**
C-reactive protein(mg/dL)	0.57±0.34	3.26±2.0	<0.001**
Albumin(g/dl)	4.07±0.66	2.54±0.87	<0.001**
Total sialic acid (mmol/L)	1.81±0.53	3.53±1.41	<0.001**

** p < 0.001 Statistically highly significant.

In patients with COPD, CRP was significantly positively correlated with TSA (r = 0.755, p<0.001), and negative

correlation was observed between C-RP and Albumin (r= -0.418, p<0.01) and C-RP and BMI (r= -0.028, p<0.1). There was significant negative correlation between TSA and Albumin (r= -0.728). TSA and BMI (r= -0.505) with p<0.001 (Table 2).

Table 2: Pearson correlation between study parameters in controls and COPD patients.

Parameters	Controls		Cases	
	r value	p value	r value	p value
Serum CRP/Albumin	-0.0142	0.93	-0.418	<0.01
Serum CRP v/s BMI	-0.2962	0.06	-0.28	<0.10
Serum CRP v/s TSA	0.1218	0.46	0.755	<0.001**
Serum TSA v/s Albumin	-0.1894	0.26	-0.728	<0.001**
Serum TSA v/s BMI	-0.0159	0.95	-0.505	<0.001**

** p < 0.001 Statistically Highly Significant

In this study, diagnostic values based on accuracy of total sialic acid seemed to be a good marker in COPD with Area under ROC curve 0.867, 95% CI 0.77-0.93 and 70.0% Sensitivity, 90% specificity makes the test as good test. Also found that area under ROC curve for CRP was 0.789, 95% CI 0.68-0.87 and to be a fair marker in COPD (Table 3 and Figure 1).

Table 3: Area under curve ROC curve of total sialic acid and C - reactive protein for diagnosing COPD.

Study parameters	Area under curve	95% CI	Result
Total sialic acid	0.867	0.77-0.93	Good test
C-reactive protein (mg/dl)	0.789	0.68-0.87	Fair test

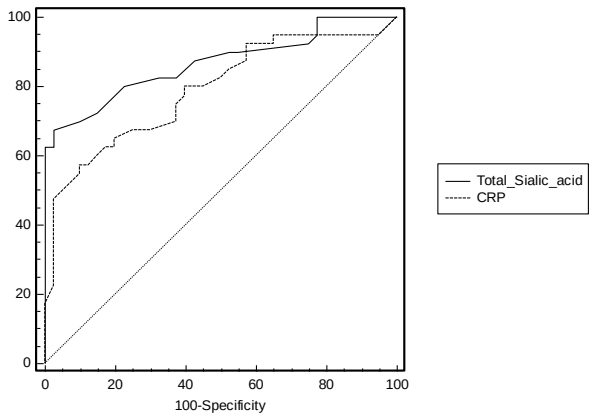

Figure 1: Area under curve ROC curve of total sialic acid and C - reactive protein for diagnosing COPD.

DISCUSSION

The present study showed that there was a significant difference in mean serum C-RP level between COPD patients and healthy subjects, as CRP serum concentration was higher in patients with COPD. Yende, et al reported a higher level of serum C-RP in cases with an obstructive pattern in their spirometry (3.5 mg/L) in comparison to normal population (2.5 mg/L) (p<0.0001).[27]

In the present study 43 among 75 cases had C-RP above normal limits as compared to 14 among 75 controls. This data suggests a strong correlation between high C-RP and COPD. Various studies done across the world have projected similar results. The result obtained in our study is similar to results of R Broekhuizen, et al.[28] The present study confirms the existing data, supporting the fact that C-RP levels increases when lung function worsens, leading to development of COPD. According to De Torres JP, et al there is a large body of work that shows that systemic inflammation exists in stable COPD.[29] Systemic inflammation has been associated with reduced lung function, diminished muscle strength, and 6-minute walking distances. They report that prospective measurements of serum C-RP in both crude and confounder-adjusted analyses were predictive of hospitalization and death from COPD.

Based on various studies, it has been demonstrated that individuals without inflammation usually have CRP levels below 1 mg/dl. Patients with C-RP levels between 1 and 3 mg/dl have intermediate risk and above 3 mg/dl have high risk of CAD. However in patients with CRP levels more than 10 mg/dl other causes of inflammation must be sought for. Thus with this in view, estimation of CRP plays an important role in detection of systemic inflammation and its associated risk factors.

Serum albumin level is found low in our study and inversely correlated with C-RP and TSA serum albumin level has been considered to be part of the acute phase protein response. Low levels of this protein may, therefore, reflect a deterioration of clinical status or increased persistent inflammation during acute exacerbations of COPD. However, low serum albumin level is also a good indicator for long-term health status in chronically ill patients. The incidence of under nutrition in patients with COPD depends on disease severity. Several studies indicate that the prevalence of nutritional abnormalities increases as disease severity increases.[30]

Malnutrition is prevalent in patients with COPD and may act synergistically with the depletion of specific amino acids during COPD exacerbation to play a role in the decline of circulating albumin levels.[31] Schols, et al Serum albumin level decreased with declining in pulmonary function same result is also found in our study.[32]

Katsura, et al found that low serum albumin can be a risk factor for poor outcome in COPD. We found that serum albumin levels correlated better with pulmonary functions than BMI. This finding suggests that systemic catabolic process in COPD affects serum albumin concentration more than BMI.[33]

In our study 80% of patients with COPD had low BMI. Majority (83.3%) of the control group had normal BMI. Studies have shown that low BMI is one of the independent poor prognostic factors in COPD with a clear association between decreased BMI and increased mortality. Skeletal muscle dysfunction is associated with underweight. COPD patients with low BMI have skeletal muscle dysfunction. Several studies have highlighted the association between low BMI and respiratory muscle weakness and impaired gas exchange. Patients with low body weights have greater gas trapping, lower diffusing capacity, and less exercise capacity than do persons with similar respiratory mechanics but normal body weights.[34] Loss of body cell mass is associated with a reduction in the mass of the diaphragm and of the respiratory muscles, resulting in declines in strength and endurance. These effects can contribute to decreased albumin level. Decramer, et al has proposed that the pathogenesis of nutritional depletion in COPD is high energy expenditure and low energy intake. Importantly, low BMI is one of the independent predictors for mortality in patients with COPD.[35] Low BMI could be a consequence of COPD. Basal metabolic rate is increased in moderate to severe COPD.[36]

In addition Lindberg G, et al showed smoking to be a cardiovascular risk factor, in which total sialic acid is increased. Thus raised serum TSA concentration has been proposed to be a strong predictor of cardiovascular mortality in patients with COPD.[37]

The result obtained in our study is similar to the results of Lopezvidriero. Thus elevated levels of Total sialic acid are associated with increased production of mucus and air way obstruction which is very much established in our study. [38] Increased TSA concentrations have been observed in several diseases like tumours, myocardial infarction, diabetes, inflammatory disorders, and alcoholism. The clinical usefulness of serum TSA determination in inherited TSA storage diseases is well established. Serum TSA is also increased during inflammatory processes because of increased concentrations of richly sialylated acute phase glycoproteins. The absolute increase in TSA levels establishes clinical potential of TSA as a marker. Tentatively, TSA markers might serve as adjuncts, when combined with other markers, in disease screening, disease progression follow-up, and in the monitoring of treatment response. To become clinically useful, however, the existing TSA determination assays need to be considerably refined to reduce interferences, to be specific for positive correlation between hs-CRP and serum TSA levels is supported by previous work by Sathiapriya, et al in which elevated levels of these inflammatory markers were shown to interact to increase cardiovascular morbidity and mortality.[39] Browning and co-workers reported that CRP could underestimate inflammation and TSA measurement could be used as an inflammatory marker for chronic diseases.[40]

CONCLUSIONS

C- reactive protein in association with TSA has increased in COPD as a marker of systemic inflammation. Albumin and BMI decreased as a result of nutritional depletion. Patients with low BMI and low serum albumin level have greater risk of having exacerbation, acute respiratory failure than patients with normal BMI. The absolute increase levels establish the clinical potential of TSA as a marker. Nevertheless, when combined with other markers, TSA concentrations are helpful in disease screening, follow- up, as well as, in monitoring of treatment. 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.

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