Study of Adiponectin and Leptin Levels in Patients of COPD and Its Correlation with Severity and Acute Exacerbation of Disease

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Abstract
Background: COPD is associated with inflammation which leads to acute exacerbation and causes extra pulmonary manifestations of the diseases. Elevated levels of CRP, fibrinogen, leukocyte counts are inflammatory markers associated with COPD. Adiponectin and leptin are biomarkers of inflammation which can be used to assess disease activity and severity in COPD patients.

Aims: To compare the adiponectin and leptin levels during acute exacerbation and remission in patients of COPD & correlate the levels with severity of disease.

Methods: It was a hospital based case control study conducted in VMMC and Safdarjung Hospital, New Delhi. It was conducted on 60 patients of COPD & 30 controls. Adiponectin & leptin levels were measured on admission and 7 days after discharge during remission. Severity of COPD was assessed by GOLD guidelines. Acute exacerbation was defined by Anthonisen criteria. Patients were considered to be in remission if they do not require increased doses of bronchodilator, antibiotics or steroids.

Result: Leptin levels were higher in cases than control on admission 21.12 v/s 4.96. Adiponectin levels were also higher in cases than control on admission 5.91 v/s 3.17. Leptin levels were higher on admission, during acute exacerbation 21.12 than on remission 10.91. Adiponectin levels were higher on remission 7.11 than on admission. L/A ratio was higher on admission 3.71 v/s remission 1.74. Adiponectin levels correlate negatively with FeV₁/FVC with r value of -0.005 but the correlation was not statistically significant. Serum leptin levels also correlates negatively with FeV₁/FVC r value -0.051 but was not significant statistically.

Conclusion: Adiponectin & leptin levels are raised in cases of COPD compared to controls. Leptin levels are higher during acute exacerbation than remission whereas adiponectin levels are higher during remission. Adiponectin & leptin levels correlate negatively with severity of COPD but the correlation is not statistically significant.

Introduction
Chronic Obstructive airway disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airway and lungs to noxious particles or gases. COPD is currently the leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020¹. Patients with COPD are at increased risk of developing heart diseases, lung cancer and stroke².
Exposure to inhaled pollutants, primarily cigarette smoke leads to chronic inflammation via activation of structural and inflammatory cells within the lungs. These in turn release chemotactic mediators which recruit additional inflammatory cells in the lung perpetuating a state of chronic inflammation which is thought to cause structural changes in airway and respiratory symptoms. Recently there has been increasing evidence that COPD is a systemic inflammatory disease in which there is systemic inflammation indicated by raised levels of cytokines, acute phase proteins and inflammatory cells. This systemic inflammation may be implicated in the development of comorbidities in COPD such as cardiovascular diseases, diabetes, lung cancer, pneumonia, pulmonary embolism, osteoporosis and depression.

Leptin and adiponectin are produced by adipose tissue & both play an important role in energy balance. They are established cytokines in energy and fat metabolism. The association of adiponectin and leptin with COPD is becoming increasingly apparent. These cytokines are related to severity of emphysema as well as to the frequency of exacerbation, lower leptin levels have been associated with lower fat mass in emphysematous patients and are thought to be at least partially responsible for pulmonary cachexia. Adiponectin levels have been found to be higher in patients of COPD compared with control patient. It is therefore plausible that dysregulation of these cytokines has an effect on the natural history of COPD. However there are very few Indian studies to study the association of adiponectin and leptin in COPD during phases of exacerbation, remission and further their association with severity of the diseases.

Adiponectin and leptin may be used as biomarkers of inflammation to assess disease activity and severity of disease in cases of COPD. With this in mind we thought to analyse the adiponectin and leptin levels in COPD during exacerbation and remission and their correlation with severity of COPD.

Material and Methods
This hospital based case control study conducted on 60 patients of COPD admitted to the medicine wards of VMMC and Safdarjung Hospital, New Delhi; 30 cases were taken as controls. Each patient was subjected to detailed history and examination of past records with special emphasis on records of any intrinsic Pulmonary disease, cardiovascular diseases and other co-morbid conditions. Patients of metabolic syndrome, hepatic, renal and heart failure, malignancy & collagen vascular disease were excluded. Diagnosis of COPD was based on

- Clinical symptoms of dyspnoea, chronic cough with sputum production.
- History of exposure to risk factors (tobacco, smoke from cooking, occupational dust and chemicals).
- Spirometry (post bronchodilator FeV1/FVC<0.7 confirms the diagnosis.
- Severity of COPD was assessed according to GOLD guidelines.

Acute exacerbation was defined by Anthonisens criteria.

- Increased sputum volume.
- Sputum purulence.
- Increased dyspnoea.

Remission of COPD defined as.

- Asymptomatic patients not requiring increased dose of bronchodilators.
- Doesn’t require antibiotics and steroid.

Adiponectin and leptin levels were done on admission and repeated 7 days after discharge when patients were in remission. Venous blood was drawn in the morning after overnight fast in EDTA containing tubes. Plasma was separated by centrifugation for 10 minutes at 4°C within 1 hour of collection and stored at -70°C until analysis. Plasma adiponectin and leptin were measured by ELISA kit.

Statistical Analysis
Categorical variables were presented in number and percentage and continuous variables were presented as mean ± SD and median. Normality of
data was tested by kolmogorov smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows:
1. Quantitative variables were compared using Independent T test / Mann-Whitney test (when the data sets were not normally distributed) between the two groups.
2. Quantitative variables were correlated using Chi-Square test/ Fisher exact Test.
3. Spearman rank correlation coefficient was used to assess the association of various parameters with each other. A p value of <0.05 was considered statistically significant.

The data was entered in MS Excel Spreadsheet and analysis was done using statistical Package for Social science (SPSS) version 21.0.

Observations & Result
The study was conducted on 60 cases of COPD after fulfilling the inclusion & exclusion criteria. 30 cases were taken as control. The mean age of the cases was 56.78 ± 6.35 years while controls was 52.17± 7.47 years. Majority of cases were in the age group 51-60 years while minimum number were in the age group 61-70 years. Of the 60 cases, 45 were male and 15 were female whereas 25 were male and 5 female among the controls.

Table 1. Comparison of serum leptin, serum adiponectin and L/A ratio in cases V/S controls on admission.

| Variables     | Cases     | Control       | P value |
|---------------|-----------|---------------|---------|
| Serum leptin  | 21.12±5.13| 4.96 ± 1.14  | 0.0001  |
| Serum adiponecin | 5.19 ± 1.36| 3.17 ± 0.71  | 0.0001  |
| L/A ratio     | 3.71 ± 1.11| 1.65 ± 0.58  | 0.0001  |

On admission the mean serum leptin was 21.2 ±5.13, adiponectin was 5.19 ±1.36 and L/A ratio was 3.71 ± 1.1. The values were significantly higher when compared to controls with p value 0.0001.

Table 2: Comparison of serum leptin, Serum adiponectin and L/A ratio during admission and remission in cases

| Variables     | Admission | Remission    | P value |
|---------------|-----------|--------------|---------|
| Serum leptin  | 21.12±5.13| 10.91±3.89  | 0.0001  |
| Serum adiponectin | 5.91 ± 1.36| 7.11 ± 2.95 | 0.0001  |
| L/A ratio     | 3.71 ± 1.11| 1.74 ± 0.76  | 0.0001  |

Figure 1: Comparison of serum leptin, Serum adiponectin and L/A ratio during admission and remission in cases.

It was observed that Serum leptin level were raised on admission & decreased during remission. Serum adiponectin levels were higher during remission (7.11 ± 0.95) compared to those on admission (5.91 ± 1.36). L/A ratio was higher on admission (3.71 ± 1.11) compared to remission (1.74 ± 0.76).

Table 3: Correlation of adiponectin, leptin with FeV1/FVC.

| Variables     | r value | p values |
|---------------|---------|----------|
| Serum Adiponecin | -0.005  | 0.967    |
| Serum Leptin   | -0.051  | 0.699    |
| L/A ratio      | -0.059  | 0.654    |

Figure 2: Correlation of adiponectin, leptin with FeV1/FVC.
Serum adiponectin correlated negatively with FeV1/FVC. 
\( r \) value -0.005, however p value was not significant (0.967).

Serum leptin correlated negatively with FeV1/FVC. r -0.051 with a p value of 0.699 (not significant)

14 cases in the study were in stage I COPD while 46 cases were in stage II while no case was in stage 3 and 4.

**Table 4:** Correlation of Adiponectin, leptin and L/A ratio with severity of COPD

| Variables          | r value | p value |
|--------------------|---------|---------|
| Serum adiponectin  | -0.017  | 0.897   |
| Serum leptin       | -0.196  | 0.133   |
| L/A ratio          | -0.138  | 0.294   |

Adiponectin, leptin and L/A ratio showed a negative correlation with severity of COPD. However the p value in all were not significant.
Adiponectin and leptin on stepwise multiple linear regression analysis. Similar results were seen by K.H Chan et al\textsuperscript{7}, they also assessed relationship between serum adiponectin, IL-6, IL-8 and CRP. They found a positive correlation between serum adiponectin and CRP, IL-6 and negative correlation with IL-8. In our study adiponectin and leptin showed a negative correlation with FeV1/FVC r value of -0.005 and -0.051 respectively. However the p value of all these ventilatory parameters were not significant. Adiponectin and leptin showed negative correlation with severity of COPD (as per GOLD guidelines) though correlation was not stastically significant.

Similar results were seen by Ahmed et al\textsuperscript{11} who saw a significant negative correlation of leptin with FeV1 (r= -0.523, p < 0.005), change in feV1 / FVC (r=-0.541, p< 0.05).

This study showed that leptin correlated inversely with severity of ventilatory function. K.H Chan observed a negative correlation of adiponectin with FeV1, FVC and FeV1 / FVC with r value of –0.370, -0.262 and -0.302 respectively with significant p values. CRP and IL-6 also showed a negative correlation with above ventilatory parameter. They found that serum adiponectin levels increase with disease severity and stage 4 COPD had the highest median levels of adiponectin compared with stage 2 and 3 patients. Jaswal S et al\textsuperscript{12} also found a significant negative correlation of serum adiponectin with FeV1 (r = -0.580, p<0.001) thereby suggesting that adiponectin levels have an association with severity of airway obstruction. Kochi Tomoda et al\textsuperscript{5} observed a positive correlation between residual volume and serum adiponectin but there was no correlation of adiponectin with FeV1. Thereby suggesting that hyperinflation not flow limitation may be leading to adiponectin elevation in COPD.

We thus concluded that serum adiponectin and leptin levels were higher in cases of COPD than in controls. These levels were further raised during acute exacerbation. The levels of leptin and L/A ratio were higher on admission than during remission while the adiponectin levels were higher during remission state. The levels of adiponectin and leptin showed a negative correlation with FeV1/ FVC and severity of COPD (as per GOLD guideline) but this correlation was not statistically significant.

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