Role of adiponectin and other inflammatory biomarkers in COPD patients

Nagat Ali Mohamed a,*, M. Amany Fawzy a,1, Reda Elgamry a,2, Doaa Mostafa Gad a,3, Hoda A. Ibraheem b,4

a Chest Department, Faculty of Medicine, Zagazig University, Egypt
b Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt

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Abstract Background: Adiponectin (APN) is a secretory protein synthesized by adipocytes and plays a potential role in regulating the inflammatory response by many of autocrine or paracrine. The mechanism of APN participation in the inflammation of COPD remains unknown. So, we investigated serum and induced sputum adiponectin as a biomarker of systemic inflammatory response and to find its relation with other inflammatory biomarkers like, IL-8, IL-6 and TNF-α. The aim of the work was also to find out its role in the pathogenesis of cachexia in COPD patients.

Patients and methods: The study included 80 subjects including 60 COPD patients (20 stable and 40 exacerbated) and 20 age and sex-matched healthy control subjects. The adiponectin, interleukin-8, interleukin-6 and tumor necrosis factor-alpha levels were measured in serum, induced sputum by enzyme-linked immunosorbent assay. Serum CRP level was measured using the nephelometric method. Body mass index (BMI) was estimated for COPD patients and its relation to the inflammatory biomarkers was studied.

* Corresponding author. Tel.: +20 01096450083.
E-mail addresses: Ak_mego@yahoo.com (N.A. Mohamed), m.ahm84@yahoo.com (M.A. Fawzy), redaelgamry@gmail.com (R. Elgamry), dooaagad@yahoo.com (D.M. Gad), khaledabelaziz_1@hotmail.com (H.A. Ibraheem).

1 Tel.: +20 01062248163.
2 Tel.: +20 01148293330.
3 Tel.: +20 01208595290.
4 Tel.: +20 01001342444.
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Introduction

Chronic obstructive pulmonary disease (COPD) is considered to be a chronic non-specific inflammation, which occurs in the airways, lung parenchyma and pulmonary vessels. This can cause the activation of inflammatory cells and the release of various inflammatory mediators such as IL-8, IL-6 and TNF-α. They can destroy the lung structure and promote the inflammatory response of neutrophils [1]. Adiponectin (APN) is one of the cytokines mainly secreted by adipose tissue [2].

Miller et al. [3] reported that the epithelial cells can also secrete APN which plays a potential role in regulating the inflammatory response by many of autocrine or paracrine.

Other authors like Desruisseaux et al. [4] reported that adiponectin is a secretory protein synthesized by adipocytes and has important anti-inflammatory as well as anti-atherosclerotic and anti-obesity effects.

Also, Lago et al. [5] reported that adiponectin has a wide range of effects in pathologies with immune and inflammatory components such as, cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome and rheumatoid arthritis.

The mechanism of APN participation in the inflammation of COPD is still a point of debate.

Aim of the work

Is to demonstrate the validity of serum APN as a biomarker of systemic inflammatory response in COPD patients and to study the association between serum APN and other inflammatory markers (IL-8, IL-6, TNF-α) in both serum and induced sputum of COPD patients. The aim of the work was also, to study relation of serum level of APN with BMI in COPD patients in a trial to define its role in the pathogenesis of cachexia in those patients.

Patients and methods

Patients

This study included 60 COPD patients (40 exacerbated COPD and 20 stable COPD) and another 20 age and sex matched healthy control personnel. This study is carried out in the period from January 2012 to December 2012 in chest outpatient clinic and inpatient of Chest Department, Zagazig University Hospitals.

Results: Adiponectin levels in COPD patients were significantly higher than those in control subjects (P < 0.001). CRP, APN, IL-8, IL-6, TNF-α were significantly higher in the exacerbated COPD patients compared to the stable group (P < 0.001, P < 0.001, P < 0.001, P < 0.001 and P < 0.001, respectively). The ratio of APN level in serum to induced sputum was (3.1) in AECOPD patients and (2.4) in stable COPD patients while for IL-8, IL-6 & TNF-α the ratios were all < (1).

Conclusion: Adiponectin could play a role as a biomarker of systemic inflammatory response in COPD patients. Also, its rise in the exacerbation period denotes that this may also be a biomarker of the exacerbation phase. While IL-8, IL-6, TNF-α could be used to reflect the airway inflammation in induced sputum. Adiponectin serum level is higher in underweight COPD patients which may reflect its role in the pathogenesis of cachexia in COPD patients.

Methods

All cases were subjected to the following:

1. Complete history taking.
2. General and local chest examination.
3. Chest X-ray PA view.
4. Diagnosis of COPD according to Global Initiative for chronic obstructive lung disease (GOLD) criteria: (NHLBI/WHO (GOLD), update) [6], so, 20 patients had clinically stable COPD for at last 3 months, while 40 patients had clinical signs of COPD exacerbation which are according to GOLD [6] criteria (increased dyspnea, sputum production or sputum, purulence).
5. Dyspnea score was determined according to the Medical Research Council Scale (MRCS). The scale consists of five items, the patients were categorized into the most appropriate grade between 0 and 4 defining their respiratory distress [7].
6. Body weight and height were measured and body mass index (BMI) was calculated as weight/(height)² (kg/m²) in both groups [8].
7. Pulmonary function tests: All patients underwent spirometric PFT with reversibility testing after inhalation of short acting B2-agonist equivalent to 200 μg salbutamol by a metered-dose inhaler. PFT were done using Zan-100 (flow HANDY II) pulmonary function apparatus. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured and were expressed as percentage of predicted normal reference values. The highest value from at least three spirometric maneuvers was used. Patient severity was determined as:
   1. FEV1 < 50% predicted value were considered to have severe/very severe COPD (40 patients).
   2. Those with FEV1 between 50% and 80% as moderate COPD (8 patients).
   3. Those with FEV1 > 80% as mild COPD (12 patients). According to NHLBL/WHO (GOLD) [6].
8. Samples of induced sputum: the samples were collected from the subjects at 8 am after doing PFTs. All the subjects must be confirmed that they rinsed their mouths.
Role of adiponectin and other inflammatory biomarkers in COPD patients

Statistical analysis

Data were expressed as mean ± SD for quantitative variables. Data were checked, entered and analyzed by using SPSS version 19. Statistical analysis was performed when appropriate P < 0.05 was considered statistically significant.

Results

This study was designed to evaluate the role of adiponectin as a biomarker of systemic inflammatory response in COPD patients and also, to study its association with other several inflammatory markers (like, IL-8, IL-6 & TNF-α) in both serum and induced sputum.

Table 1 shows a statistically significant difference in the mean serum level of APN, IL-8, IL-6, TNF-α between COPD and control groups.

Table 2 detects, a significant decrease in the exacerbated group than in the stable group as regards mean FEV1/FVC ratio. Also, dyspnea score was (3.6) in COPD exacerbation and (1.3) in stable COPD (means significant increase of dyspnea score in COPD exacerbation).

Table 3 shows a significant increase in mean serum levels of APN, IL-8, IL-6, TNF-α and CRP in the exacerbated COPD than in the stable COPD, also, in Table 4 there is a significant increase in mean serum levels of the same markers among severe COPD cases than mild and moderate cases.

Table 5 shows a significant increase in mean levels of APN, IL-8, IL-6, TNF-α in the induced sputum of AE COPD than in stable COPD.

Table 6 illustrates that the ratio of APN in serum to induced sputum is highly significant in the exacerbated COPD than stable COPD indicating that, it has a role as a systemic inflammatory biomarker in the exacerbation phase.

Table 7 detects a significant increase in APN, IL-8, IL-6, TNF-α in cases with dyspnea score more than (2). This means that, these biomarkers increase with resp. distress and during exacerbation of COPD.

Table 8 shows that adiponectin and TNF-α were significantly higher in COPD patients who were underweight (BMI < 20). This indicates their sharing in the pathogenesis of cachexia of COPD patients.

There is no difference in BMI or age between the COPD and control groups (both groups are matched regarding age and BMI). There is a significant difference in mean serum levels of APN, IL-6, IL-8 and TNF-α between COPD and control groups being higher in COPD patients.

This table shows a significant decrease in the exacerbated group than in the stable group as regards mean FEV1/FVC. Also, mean dyspnea score was 3.61 in COPD exacerbation but is 1.3 in stable COPD (means significant increase in dyspnea score in COPD exacerbation).

Mean serum level of CRP, adiponectin, IL-8, IL-6 and TNF-α is significantly higher in the exacerbated COPD patients compared to the stable group.

This table shows a statistically high significant difference between mild, moderate and severe COPD patients regarding mean serum levels of APN, IL-8, IL-6 and TNF-α being higher in the moderate and severe groups.

There is a highly significant difference between COPD exacerbation and stable COPD as regards mean values of adiponectin, IL-8, IL-6, TNF-α in induced sputum.

This table illustrates that the ratio of APN in serum to induced sputum is highly increased in exacerbated COPD than stable COPD indicating that, it has a role as a systemic inflammatory biomarker while other biomarkers, their serum/induced sputum ratios are reversed (less than 1).

Table 1: Study of both demographic and mean serum levels of the inflammatory biomarkers in COPD patients and the controls.

| Biomarker         | COPD patients (n = 60) Mean ± SD | Control (n = 20) Mean ± SD | P-value |
|-------------------|---------------------------------|---------------------------|---------|
| Age (years)       | 66.7 ± 6.9                      | 62.72 ± 4.2               | 0.09 NS |
| BMI (kg/m²)       | 25.3 ± 3.0                      | 26.4 ± 4.0                | 0.36 NS |
| Adiponectin (ng/ml)| 14.54 ± 7.6                    | 6.55 ± .3                 | <0.001**|
| IL-8 (pg/ml)      | 44.06 ± 7.8                     | 23.95 ± 13.18             | 0.04*   |
| Interleukin-6 (pg/ml)| 16.5 ± 6.5                     | 9.73 ± 8                  | <0.001**|
| TNF-α (pg/ml)     | 30.58 ± 5.5                     | 16.10 ± 4.5               | <0.001**|

* Significant.
** Highly significant.
### Table 2  Demographic parameters in exacerbated COPD in comparison with stable COPD patients.

| Parameter          | Exacerbated COPD (n = 40) | Stable COPD (n = 20) | P-value |
|--------------------|---------------------------|----------------------|---------|
| Age (years)        | 68.32 ± 6.6               | 64.4 ± 5.6           | 0.08 NS |
| BMI (kg/m²)        | 20.99 ± 5.2               | 24.33 ± 3.7          | 0.068 NS|
| FEV₁%              | 55.28 ± 24                | 71.52 ± 22           | 0.03*  |
| FEV₁/FVC           | 47.13 ± 9.2               | 63.12 ± 13           | 0.015* |
| Dyspnea score      | 3.61 ± 2.2                | 1.3 ± 1.4            | 0.002* |

### Table 3  Serum inflammatory biomarkers in exacerbated and stable COPD groups.

| Biomarker          | Exacerbated COPD (n = 40) | Stable COPD (n = 20) | P-value |
|--------------------|---------------------------|----------------------|---------|
| CRP (mg/dl)        | 28.15 ± 4.5               | 8.35 ± 21            | <0.001**|
| Adiponectin (ng/ml)| 18.33 ± 1.9               | 10.63 ± 3.1          | <0.001**|
| IL-8 (pg/ml)       | 81.52 ± 9.2               | 44.22 ± 4            | <0.001**|
| Interleukin-6 (pg/ml) | 34.42 ± 9.1          | 16.51 ± 6.1          | <0.001**|
| TNF-α (pg/ml)      | 80.41 ± 13                | 32.62 ± 5.3          | <0.001**|

### Table 4  Serum inflammatory biomarkers in different stages of COPD severity.

| Stage            | Mild COPD (n = 12) | Moderate COPD (n = 8) | Severe COPD (n = 40) | P-value |
|------------------|--------------------|-----------------------|----------------------|---------|
| APN (ng/ml)      | 8.51 ± 2.2         | 14.41 ± 3.3           | 19.41 ± 8.4          | <0.001**|
| IL-8 (pg/ml)     | 41.25 ± 6.1        | 61.15 ± 7.4           | 82.11 ± 18.2         | <0.001**|
| IL-6 (pg/ml)     | 15.52 ± 3.1        | 24.31 ± 6.2           | 35.41 ± 7.1          | <0.001**|
| TNF-α (pg/ml)    | 20.59 ± 4.2        | 55.51 ± 8.1           | 80.42 ± 12           | <0.001**|

### Table 5  The concentrations of APN, IL-6, IL-8 and TNF-α in induced sputum of both exacerbated and stable COPD patients.

| Biomarker          | COPD exacerbation (n = 40) | Stable COPD (n = 20) | P-value |
|--------------------|---------------------------|----------------------|---------|
| Adiponectin (ng/ml)| 6.23 ± 1.7                | 3.51 ± 1.2           | <0.001**|
| IL-8 (pg/ml)       | 445.32 ± 160.1            | 170.44 ± 60.71       | <0.001**|
| Interleukin-6 (pg/ml) | 185.43 ± 1.8         | 112.9 ± 9.6          | <0.001**|
| TNF-α (pg/ml)      | 135.62 ± 1.4              | 56.48 ± 14.1         | <0.001**|

### Table 6  Ratios of serum to induced sputum values of inflammatory biomarkers in exacerbated and stable COPD patients.

| Biomarker          | AECOPD Mean ± SD | Stable COPD Mean ± SD | P-value |
|--------------------|------------------|-----------------------|---------|
| APN                | 3.1 ± 1.1        | 0.0009 ± 0.0001       | <0.001**|
| IL-8               | 0.00 ± 0.001     | 0.19 ± 0.01           | 0.59 ± 0.02|
| IL-6               | 0.24 ± 0.01      | 0.083 ± 0.002         | 0.36 ± 0.01|
| TNF-α              | 0.36 ± 0.01      | <0.001                | <0.01    |

### Table 7  Relation between dyspnea score & mean serum values of the studied inflammatory biomarkers in COPD patients.

| Dysp. score | APN Mean ± SD | IL-8 Mean ± SD | IL-6 Mean ± SD | TNF-α Mean ± SD |
|-------------|---------------|----------------|----------------|-----------------|
| <2          | 9.88 ± 2.1    | 42.2 ± 5.1     | 14.33 ± 6.2    | 30.55 ± 4.4     |
| >2          | 17.51 ± 6.7   | 79.41 ± 17.1   | 31.22 ± 7.3    | 81.42 ± 15      |
| P-value     | <0.001**      | <0.001**       | <0.001**       | <0.001**        |
Adiponectin, IL-8, IL-6, TNF-α are significantly higher in cases with dyspnea score more than 2. This indicates that these biomarkers increase with increasing dyspnea & distress that occur in AECOPD.

Adiponectin and TNF-α are significantly higher in COPD patients who are underweight (BMI < 20). This indicates their sharing in cachexia of COPD patients.

**Discussion**

The inflammation in the airways leads to the main pathological process of COPD [10]. COPD is also a kind of systemic inflammatory disease [11] and is characterized with the abnormal activation of inflammatory cells and the abnormal increase of circulating cytokines including CRP, IL-8, TNF-α and IL-6. Adiponectin is a newly discovered cytokine [12], IL-8, IL-6, TNF-α and APN were highly expressed in bronchoalveolar lavage fluid (BALF) of COPD patients. Among whom the level of APN was the highest? APN in the BALF of COPD patients was 3–5 times than that in healthy control subjects. Because of the unacceptance of fiberoptic bronchoscopy in getting BALF, induced sputum was collected instead in this study. Another study reported that COPD patients had increased APN level in the plasma and the level was related to elevated TNF-α and IL-6 [13].

Also, another study reported that, the adipose tissue is an important contributor to the systemic manifestation of COPD. Indeed, the inflammatory/anti-inflammatory effects of adipokines highlight the fact that adipose tissue is more than an energy storage organ; they also highlighted the importance of body composition in the pathogenesis of COPD [11]. The precise mechanism of malnutrition in COPD has not yet been clarified. Tomada et al. [14] also found that serum levels of the anti-obesity adipokine adiponectin were significantly higher even in COPD patients with normal BMI than levels in healthy subjects indicating that adiponectin levels rise earlier than body weight loss as a component of the systemic inflammatory response and consequently may contribute to the development of malnutrition.

So, this study was designed to elucidate the validity of serum adiponectin as a biomarker of systemic inflammatory response in COPD patients and to study the association between serum adiponectin and other inflammatory markers (TNF-α, IL-8, IL-6, CRP) in both serum and induced sputum. The aim of this study was also to study relation of serum level of adiponectin with BMI in a trial to define its role in the pathogenesis of cachexia in COPD patients.

In Table 1, there is no difference in BMI or age between the COPD and control groups.

In the present study, there is a significant increase in APN, interleukin-6, interleukin-8, TNF-α in COPD compared to that in control group (Table 1). These results agree with Kirdar et al. [12].

Tomada et al. [14] and Kirdar et al. [12], detected, that adiponectin level was approximately 2-fold higher in normal weight, stable COPD patients than in control. This result can be explained by the increase in respiratory effort that correlates with the overload of respiratory muscles and excess respiratory exercise [14]. Previous studies have revealed that chronic exercise increases plasma adiponectin levels and enhances expression of adiponectin receptor-1 in skeletal muscles [15]. Adiponectin receptor-1 promotes glucose uptake and lipid oxidation in the muscle [16]. The persistent excess respiratory exercise caused by hyperinflation elevates plasma adiponectin levels before body weight loss [14]. Also in the same table there is a significant increase of IL-8, IL-6 and TNF-α due to abnormal activation of inflammatory cells and the abnormal increase of circulating cytokines.

In Table 2 there is a significant decrease in FEV₁ and FEV₁/FVC in exacerbated COPD patients than stable COPD patients, also, there is an increase in dyspnea score in exacerbated COPD patients than stable COPD patients.

These results are in line with Kirdar et al. [12] who illustrated that this is an indicator of respiratory muscle distress and match with the definition of AE-COPD introduced by GOLD [17].

In Tables 3 and 4, there is a significant increase in the serum level of CRP, adiponectin, IL-8, IL-6 and TNF-α in COPD exacerbated patients than stable COPD patients. These inflammatory biomarkers are also significantly elevated in the serum of severe COPD than mild and moderate COPD. Xie et al. [13] reported that the concentration of APN in the serum or induced sputum in AECOPD patients were significantly higher than those in stable COPD patients (P < 0.01). Also, APN was positively correlated with IL-8 and TNF-α in the serum and induced sputum (P < 0.05). APN was also, positively correlated with IL-8 and TNF-α in the serum and induced sputum (r = 0.751, 0.659, 0.707 and 0.867 respectively, P < 0.05).

Ehling et al. [15] explained that, the main cytokines involved in the inflammation of COPD are IL-8, TNF-α and IL-6. Among them, IL-8 is the most important which can activate neutrophils and cause degranulation. Otero et al. [18] and Wert [19] illustrated that, various inflammatory mediators are released in the degranulation, promoting inflammatory reaction. Epithelial cells in the airways will stimulate the expression of IL-8 under APN control, suggesting a potential pro-inflammatory role of APN. TNF-α is an important inflammatory mediator produced by several kinds of cells, playing a role in activating the neutrophils and stimulating the release of IL-8. Its over-expression can lead to the chronicity of inflammatory response and the aggravation of lung injury [11].

In our study, there is elevated concentration of APN, IL-8, IL-6 and TNF-α in the serum and induced sputum of COPD patients especially exacerbated COPD (Tables 3 and 5), indicating that APN and inflammatory mediators were inter-regulated. It suggests that APN could be a new marker of COPD inflammation.

In Table 5, there is a significant increase in induced sputum APN, IL-8, IL-6 and TNF-α in COPD exacerbation than in stable COPD. This result is concomitant with Krommidas

### Table 8: Relation of body mass index to mean serum values of the studied inflammatory biomarkers in COPD patients.

| BMI | APN | IL-8 | IL-6 | TNF-α |
|-----|-----|------|------|-------|
|     | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| < 20| 15.23 ± 4.7 | 42.2 ± 8.3 | 14.37 ± 1.8 | 33.8 ± 1.1 |
| 20–24.9| 13.1 ± 3.9 | 41.5 ± 7.2 | 14.35 ± 2.2 | 31.9 ± 3.1 |
| 25–29.9| 9.81 ± 2.8 | 41.3 ± 6.9 | 14.32 ± 3.1 | 30.7 ± 1.7 |
| ≥ 30| 9.21 ± 4.6 | 40.9 ± 7.2 | 13.9 ± 3.6 | 28.6 ± 2.1 |

P-value 0.01 0.9 0.98 0.008*
et al. [20] who reported that, adiponectin is associated with the systemic inflammatory process during exacerbation of COPD. They also reported that the most significant associations seem to be with IL-6 and TNF-α.

Also, Xie [13] reported that IL-8, IL-6, TNF-α are mainly secreted in the airways by the inflammatory cells. However, APN is mainly secreted by fat cells and released into blood and its secretion by airway epithelial cells plays a less important role [21].

Table 6 revealed that the ratios of APN level in serum to induced sputum was (3.1) in AE COPD patients and (3.4) in stable COPD patients while for IL-8, IL-6, TNF-α the ratios were all < (1).

This result is in line with Xie [13] who reported that the ratios of APN level in serum to induced sputum 2.85 in AE COPD and 3.03 in stable COPD patients while for IL-8, TNF-α and IL-6 the ratios were all less than (1), all these results indicate that the concentration of APN in blood could better reflect the systemic inflammation of COPD while concentration IL-8, TNF-α & IL-6 in induced sputum could better reflect airway inflammation.

Table 7 shows a significant increase of APN, IL-8, IL-6, TNF-α in cases with dyspnea score more than 2, this indicated that APN, IL-8, IL-6 & TNF-α can be used as inflammatory biomarkers to indicate respiratory distress especially in AE COPD patients. This result is concomitant with Kirdar et al. [12].

Table 8 shows that adiponectin and TNF-α were significantly high in COPD patients with underweight (BMI < 20). This result can be explained by Wouter et al. [11] who stated that adiponectin levels rise earlier than body weight loss as a component of the systemic inflammatory response and consequently may contribute to the development of malnutrition.

Conclusion

APN could play a role as a new biomarker of systemic inflammation among COPD patients especially in serum. While IL-8, IL-6, TNF-α could better reflect the airway inflammation in induced sputum. Also adiponectin serum level is higher in underweight COPD patients which may reflect its role in the pathogenesis of cachexia in COPD patients.

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