Alice G Vassiliou[1], Vlassios Vitsas[2], Matina Kardara[1], Chrysi Keskinidou[1], Pinelopi Michalopoulou[2], Nikoletta Rovina[3], Ioanna Dimopoulou[1], Stylianos E Orfanos[1, 4], Georgios Tsoukalas[2], Antonia Koutsoukou[3], Anastasia Kotanidou[1]

[1]1st Department of Critical Care Medicine & Pulmonary Services, National and Kapodistrian University of Athens, Medical School, Evangelismos Hospital, Athens, Greece
[2]4th Pulmonary Department, Sotiria Chest Disease Hospital, Athens, Greece
[3]Centre for Respiratory Failure and Intensive Care Unit, Sotiria Chest Disease Hospital, Athens, Greece
[4]2nd Department of Critical Care Medicine, National and Kapodistrian University of Athens, Medical School, Attikon Hospital, Athens, Greece

Study of inflammatory biomarkers in COPD and asthma exacerbations

Abstract

Introduction: Exacerbations are critical events in the course of asthma and chronic obstructive pulmonary disease (COPD). These events are potentially life-threatening, and the studies have shown that they have tremendous implications on long-term disease control and the overall prognosis of the patients. The aim of this study was to examine adipokines, cytokines and C-reactive protein (CRP) as potential biomarkers in asthma and COPD.

Material and methods: Prospective cohort study of COPD and asthma patients treated for acute exacerbations. Thirty-nine COPD patients and 15 asthmatic patients were included in the study. Leptin, adiponectin, resistin, interleukin (Il)-6, 8, 18, tumor necrosis factor-α (TNF-α), and CRP were measured at three time points: on admission, at resolution and at the stable phase. Pre- and post-bronchodilation spirometry was additionally performed at resolution and at the stable phase.

Results: In COPD patients, leptin, leptin/adiponectin (L/A) ratio and resistin were elevated on admission compared to the stable phase. In asthmatic patients, leptin levels were raised on admission compared to the stable phase, and adiponectin was elevated at resolution compared to admission. In both diseases, CRP was significantly increased on admission compared to both resolution and stable disease. Finally, TNF-α could distinguish between asthma and COPD stable phase.

Conclusions: Leptin and CRP levels may be useful biomarkers in monitoring COPD and asthma response to treatment during an exacerbation episode. Hypoadiponectinemia was detected in asthma and COPD during all stages of the diseases. TNF-α could distinguish between asthma and COPD stable phase.

Key words: COPD, asthma, biomarkers, adipokines, cytokines

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Introduction

Both bronchial asthma and chronic obstructive pulmonary disease (COPD) are characterized by obstructive ventilator pathophysiology, which in COPD is progressive, varies, however, in bronchial asthma [1, 2]. Intense chronic airway inflammation is a distinctive feature of both diseases, attracting a great deal of research. It is well established that inflammatory cells and their subsequent production of cytokines and chemokines differ between asthma and COPD. Interestingly, in many cases, airway inflammation overlaps between both diseases [2]. Moreover, the inflammatory cascades of the diseases change according to disease severity and depending on whether the patient is in stable condition or at exacerbation [1, 2]. Exacerbation is an important event in the course of these diseases as it alters their inflammatory profiles and negatively affects the patient's outcome. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma

Address for correspondence: Anastasia Kotanidou, 1st Department of Critical Care Medicine & Pulmonary Services, National and Kapodistrian University of Athens, Medical School, Evangelismos Hospital, Athens, Greece; e-mail: akotanid@med.uoa.gr
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(GINA) guidelines define exacerbations strictly on a clinical base [1, 2]. As diagnosis of exacerbation relies exclusively on the clinical presentation of the patient, inflammatory biomarkers that will allow a more precise etiologic diagnosis are urgently needed. In recent years, scientists have devoted much effort to discovering biomarkers which can diagnose these exacerbations at an early stage to prevent their devastating consequences. However, the results of these investigations are inconsistent and occasionally contradictory, possibly due to the precise time point in illness at which they were measured.

Adipokines, including adiponectin, resistin and leptin, are adipocyte-derived cytokines associated with systemic inflammatory activities and nutritional status [3]. These adipokines have been reported to be higher in patients with COPD and asthma [4–8]. Dysregulation of adipokines, hence, could affect the course of patients with COPD and asthma. C-reactive protein (CRP) levels, on the other hand, have been shown to be associated with higher mortality in patients with COPD [9]. Increased levels of pro-inflammatory cytokines, such as TNF-α and Il-6 have been linked to a number of pulmonary inflammatory diseases, including asthma and COPD, since they are central modulators of inflammation and drive many pulmonary pathologies and diseases; Il-8 is a chemokine that induces the migration of neutrophils to the airway, thus enhancing the diseases, while Il-18, a novel pro-inflammatory cytokine, has been shown to be involved in the pathogenesis of COPD by increasing interferon (IFN)-γ release [10].

Since no biomarker other than lung function has been shown to be useful to date for the diagnosis of COPD and asthma, the aim of the present study was to evaluate the levels of selected adipokines and cytokines, and CRP at the resolution of an exacerbation and 6weeks later at the stable phase, as potential diagnostic biomarkers for asthma and COPD exacerbations.

Materials and methods

Ethics

The study was approved by the Sotiria Hospital Research Ethics Committee, and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed written consent was obtained from all patients' next-of-kin prior to any study procedure.

Study subjects

We evaluated all bronchial asthma and COPD patients admitted to our clinic for acute exacerbation. All patients were diagnosed, identified as exacerbating and treated for COPD or asthma according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) guidelines, respectively [1, 2]. Exacerbations were either caused by allergens, air pollution, gastrointestinal reflux or infection. Exclusion criteria included no consent to participate, significant comorbidities, including tuberculosis or other lung disease apart from COPD, congestive cardiac failure, ischemic heart diseases, renal or liver impairment or failure, diabetes mellitus, malignancy at any site, collagen vascular diseases, admission to the intensive care unit (ICU), administration of oral corticosteroids, and other respiratory tract infections, apart from the infection that in some patients was the cause of the exacerbation and subsequent hospitalization, or exacerbation in the past 8 weeks prior to admission. Finally, 39 COPD patients and 15 asthma patients who fulfilled all criteria were included in the study.

Study design

This was a prospective study in which patients were evaluated at three time points: on admission, at resolution and 6 weeks after resolution. On admission, a detailed medical history was recorded and an examination was performed. Medical efforts were exhausted in order to identify the cause of exacerbation, evaluate comorbidities and obtain detailed records of treatment regimens, including long-term oxygen therapy (LTOT). Blood samples were drawn for leptin, adiponectin, resistin, CRP, Il-6, Il-8, Il-18 and TNF-α measurements prior to initiation of treatment. At resolution and 6 weeks following resolution, blood samples were drawn for measurements of the above mentioned molecules. Additionally, pre- and post-bronchodilation spirometry was performed.

Definitions of clinical status at the three time points

Exacerbation was defined as stated in the GOLD [1] and GINA [2] guidelines for COPD and bronchial asthma, respectively. Resolution of exacerbation was defined as completion of treatment with corticosteroids and antibiotics, return of symptoms to baseline and no requirement of increased doses of bronchodilation. The stable phase was considered as no requirements for

increase in treatment and no significant changes in symptoms 6 weeks after resolution.

Pulmonary function tests

All tests were performed in the Pulmonary Function Laboratory of the 4th Respiratory Department of Medicine. A single investigator was responsible for all tests done during the study. Pre- and post-bronchodilation spirometry (Vicatest, Model VEP2, Mijnhardt, Rotterdam, Holland) was performed to determine the forced expiratory volume in one second (FEV_1) %, the forced vital capacity (FVC) and the FEV_1/FVC ratio.

Blood collection

Three millilitres (3 mL) of venous blood were collected within the first 24 hours post- admission, at resolution and 6 weeks after resolution. Serum and plasma were obtained, dispensed in 0.5 mL aliquots and stored at -80°C until used.

Measurement of adipokines and cytokines

All factors were measured in either serum or plasma samples by enzyme-linked immunosorbent assay (ELISA), according to the manufacturers' instructions. The assays use two different polyclonal antibodies against the molecules as catching and tagging antibody. Human leptin, adiponectin, resistin, Il-6 and Il-8 were measured by ELISA assays purchased from R&D Systems (R&D Systems Inc., Minneapolis, MN, USA), while Il-18 and TNF-α assays were purchased from MBL (MBL International, Woburn, MA, USA) and eBioscience (ThermoFisher Scientific, Waltham, MA, USA), respectively.

CRP measurement

CRP was measured in plasma using an immunoturbometric assay (Tina-quart C-reactive protein, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

We estimated mean ± standard deviation (SD) for normally distributed variables and median with interquartile range (IQR) for variables with skewed distribution. Normality of distribution was checked with both the D'Agostino and Pearson omnibus normality test and the Shapiro-Wilk normality test. Two-group comparisons were performed using the paired t-test for normally distributed data, or the non-parametric Wilcoxon matched-pairs signed-rank test for skewed data. Comparisons of biomarkers among the three time points evaluated were performed with Friedman's test for repeated measures, with appropriate *post hoc* multiple comparison tests (Dunn's), for skewed data. Correlations were dicovered by Spearman's correlation coefficient. Statistical analysis was performed using GraphPad Prism 6.01 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Characteristics of the study population

Three hundred and forty-five patients were evaluated after being admitted to the hospital with diagnosed exacerbation of COPD or asthma. Two hundred and fifty-five patients were excluded due to comorbidities (80%) or no consent to participate (20%). Ninety individuals were initially included in the study, but 36 were excluded during follow-up (24 did not follow up, 5 were admitted to the ICU, and 7 were diagnosed with comorbidities during that time). Finally, 54 subjects were included in the study (39 patients with COPD and 15 patients with asthma). Figure 1 diagrammatically illustrates the study enrolment process and Table 1 lists the baseline demographic characteristics of the COPD and asthma patients.

Levels of soluble adipokines

Human leptin, adiponectin and resistin were quantified concurrently in all samples (n = 39 COPD patients and n= 15 asthma patients) using dedicated ELISA assays.

Table 2 and Figure 2 present the time-course of CRP, resistin, leptin, adiponectin and their ratio in COPD patients. As noted, in COPD patients, the levels of leptin on admission remained elevated at resolution, whereas they significantly decreased at stable disease, i.e., six weeks after resolution ($p < 0.01$; Figura 2A; Table 2). Similar results were observed for resistin. Its levels tended to decrease at resolution, without, however, reaching statistical significance, whereas they significantly decreased sixweeks after resolution ($p < 0.001$; Figure 2B; Table 2). On the other hand, no significant differences in adiponectin levels were observed at either time point (Figure 2C; Table 2). The L/A ratio was also elevated on admission compared to the stable phase ($p < 0.05$; Figure 2D; Table 2). A significant decrease was noted when comparing CRP levels on admission to resolution levels, and a further decrease was observed at stable disease ($p < 0.0001$; Figure 2E; Table 2). With regards to the physiological parameter FEV_1, it increased significantly at stable disease (56.35 ±

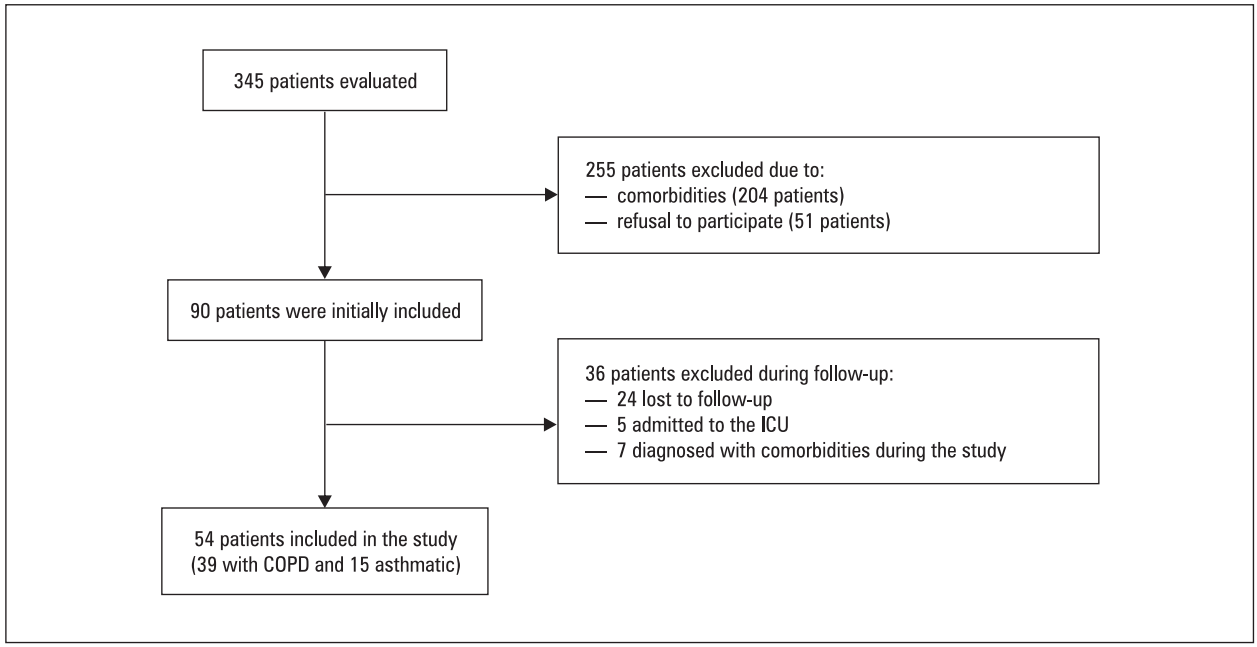

Figure 1. Study enrolment flow chart. COPD — COPD — chronic obstructive pulmonary disease; ICU — intensive care unit

Table 1. Demographics characteristics of COPD and asthma patients on admission

Characteristic	COPD patients N = 39	Asthma patients N = 15
Age	67 ± 8	52 ± 15
Sex (male/female)	31/8	6/9
Smokers/ /ex-smokers	28/11	5/10
Pack years	64.47 ± 34.79	10.20 ± 11.74
Days	6.56 ± 2.07	6.57 ± 2.45
BMI	28.96 ± 6.25	30.81 ± 6.70
MRC breathlessness scale	2.53 ± 0.93	1.06 ± 0.77
FEV_1_0_2_100	48.81 ± 16.20	85.40 ± 14.78
FEV_1_6w100	56.36 ± 18.84	86.09 ± 14.54

Data are shown for 39 COPD patients and 15 asthma patients. Data are expressed as mean ± SD. Ratios of male/female subjects and smokers/ex-smokers are given. Days from exacerbation to resolution are given. BMI — body mass index; FEV_1 — forced expiratory volume in the first second; FEV1_0_2_100 — FEV_1 measured at resolution; FEV1_6w100 — FEV_1 measured 6 weeks after resolution; MRC — Medical Research Council

18%) compared to resolution stage (48.8 ± 16.2%; $p < 0.001$; Figure 2E), a finding that was expected.

Table 3 and Figure 3 present the time-course of CRP, resistin, leptin, adiponectin and their ratio in asthma patients. Leptin response in asthmatic patients was similar to COPD patients; the levels of leptin tended to decrease at resolution, without, however, reaching statistical significance, whereas they significantly decreased 6 weeks after resolution ($p < 0.05$; Figure 3A; Table 3). Resistin in asthmatic patients slightly decreased at resolution and decreased further at the stable phase, nearly reaching statistical significance ($p = 0.058$; Figure 3B; Table 3). Adiponectin showed a different trend in asthmatic patients; adiponectin levels significantly increased at resolution ($p < 0.05$; Figure 3C; Table 3), while its levels returned to admission levels when measured 6 weeks after resolution (Figure 3C; Table 3). The L/A ratio tended to decrease at the stable phase without, however, reaching statistical significance (Figure 3D; Table 3). CRP, however, exhibited a significant decrease; its levels decreased significantly at resolution and the decreased levels persisted in stable disease ($p < 0.01$; Figure 3E, Table 3). Contrary to what was expected, FEV_1 only slightly increased at stable disease (86.09 ± 14.54%) compared to the resolution stage (81.55 ± 14.62%; Figure 3F).

Levels of cytokines

Human Il-6, Il-8, Il-18 and TNF-α were quantified concurrently in all samples (n= 39 COPD patients and n = 15 for asthma patients) using dedicated ELISA assays. All four cytokines were maintained at the same levels from exacerbation of the disease, to resolution and 6 weeks following resolution, in both COPD and asthmatic patients (Tables 2–3). In COPD patients, very high levels of TNF-α were maintained, exhibiting a gradual

Table 2. Levels of leptin, adiponectin, resistin and CRP in 39 COPD patients at three time points: admission, resolution and 6 weeks after resolution

Parameter	Admission	Resolution	6-weeks after resolution
Leptin (ng/mL)	34.06 (16.36–66.11)	34.07 (18.19–39.97)	25.53 (11.79–44.59)**
Resistin (ng/mL)	19.44 (15.20–30.85)	12.36 (7.25–24.70)	9.70 (4.05–16.90)***
Adiponectin (μg/mL)	0.79 (0.61–0.93)	0.74 (0.68–0.97)	0.74 (0.61–0.92)
L/A ratio	0.05 (0.02– 0.08)	0.04 (0.02–0.07)	0.03 (0.02–0.06)*
CRP (mg/dL)	2.40 (0.32–10.40)	0.33 (0.10–0.54)****	0.23 (0.09–0.36)****
Il-6 (pg/mL)	16.46 (13.60–20.11)	16.09 (13.55–18.50)	17.16 (15.73–18.68)
Il-8 (pg/mL)	35.67 (16.29–69.09)	41.64 (16.67–66.36)	38.58 (16.17–66.18)
Il-18 (pg/mL)	350 (224–648)	344 (180–497)	418 (245–579)
TNF-α (pg/mL)	76.20 (36.60–253.40)	86.60 (47.10–175.50)	102.20 (63.60–157.70)

Thirty-nine COPD patients were included in the study. Leptin, adiponectin, resistin and CRP were measured in blood samples drawn at three time points: on admission, at resolution and 6 weeks after resolution. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 compared to value on admission. Results are given as median with interquartile ranges. No significant differences were observed in any of the parameters studied between resolution and 6-weeks. CRP — C-reactive protein; Il — interleukin; L/A ratio — leptin/adiponectin ratio. For differences between more than two groups, the non-parametric Friedman test one-way repeated measures analysis of variance was used for skewed data

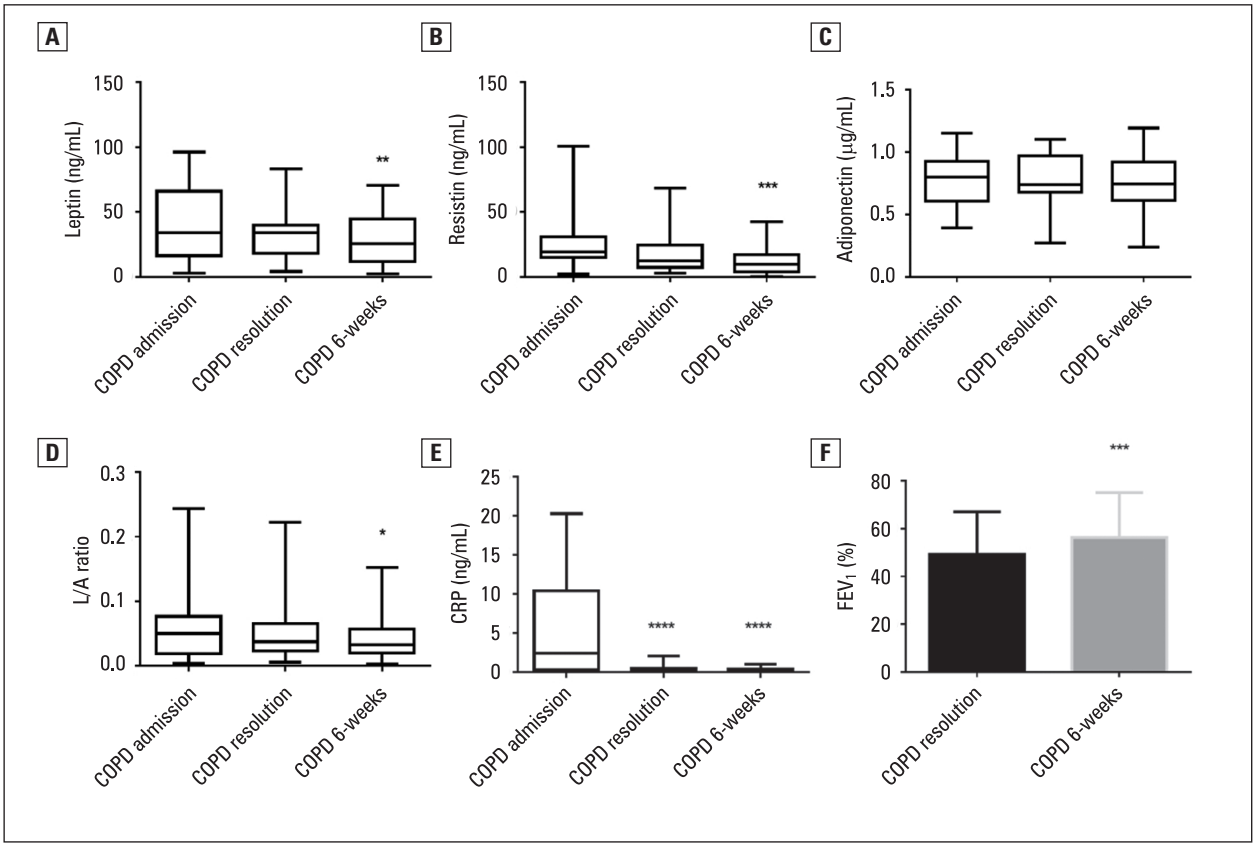

Figure 2. Levels of leptin (**A**), resistin (**B**), adiponectin (**C**), L/A ratio (**D**), CRP (**E**) and FEV_1 percentage (**F**) at the 3 stages of COPD. Thirty-nine COPD patients were included in the study. Leptin, adiponectin, resistin and CRP were measured in blood samples drawn at three time points: on admission, at resolution and 6 weeks after resolution. Pre- and post-bronchodilation spirometry was additionally performed at resolution and 6 weeks from resolution. Two-group comparisons were performed using the paired t-test, and for differences between more than two groups, the non-parametric Friedman test, one-way repeated measures analysis of variance was used for skewed data. Line in the box, median value; box edges, 25th to 75th centiles; whiskers, range of values. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 compared to value on admission. CRP — C-reactive protein; FEV_1 — forced expiratory volume in one second; L/A ratio — leptin/adiponectin ratio

Table 3. Levels of leptin, adiponectin, resistin and CRP in 15 asthmatic patients at three time points: admission, resolution and 6 weeks after resolution

Parameter	Admission	Resolution	6-weeks after resolution
Leptin (ng/mL)	50.41 (38.80–79.34)	44.00 (14.90–75.48)	34.06 (18.61–66.96)*
Resistin (ng/mL)	16.99 (12.32–33.03)	13.23 (5.62–23.25)	7.95 (4.25–15.71)
Adiponectin (μg/mL)	0.79 (0.66–0.86)	0.83 (0.67–1.00)*	0.80 (0.67–0.86)
L/A ratio	0.08 (0.05–0.12)	0.05 (0.02–0.09)	0.04 (0.02–0.09)
CRP (mg/dl)	1.63 (0.72–4.46)	0.17 (0.07–0.20)***	0.36 (0.13–0.54)**
Il–6 (pg/mL)	16.90 (15.13–20.90)	17.18 (14.53–18.51)	18.72 (14.98–22.45)
Il–8 (pg/mL)	22.00 (10.75–78.73)	30.67 (23.09–68.91)	48.04 (13.04–71.82)
Il–18 (pg/mL)	238 (144–547)	221 (184–486)	293 (236–537)
TNF–α (pg/mL)	55.80 (45.20–109.50)	48.20 (42.70–93.80)	62.80 (43.70–104.30)

Fifteen asthmatic patients were included in the study. Leptin, adiponectin, resistin and CRP were measured in blood samples drawn at three time points: on admission, at resolution and 6 weeks after resolution. For differences between more than two groups, the non–parametric Friedman test one–way repeated measures analysis of variance was used for skewed data. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to the value on admission. Results are given as median with interquartile ranges. No significant differences were observed in any of the parameters studied between resolution and 6-weeks. CRP — C–reactive protein; Il — interleukin; L/A ratio — leptin/adiponectin ratio

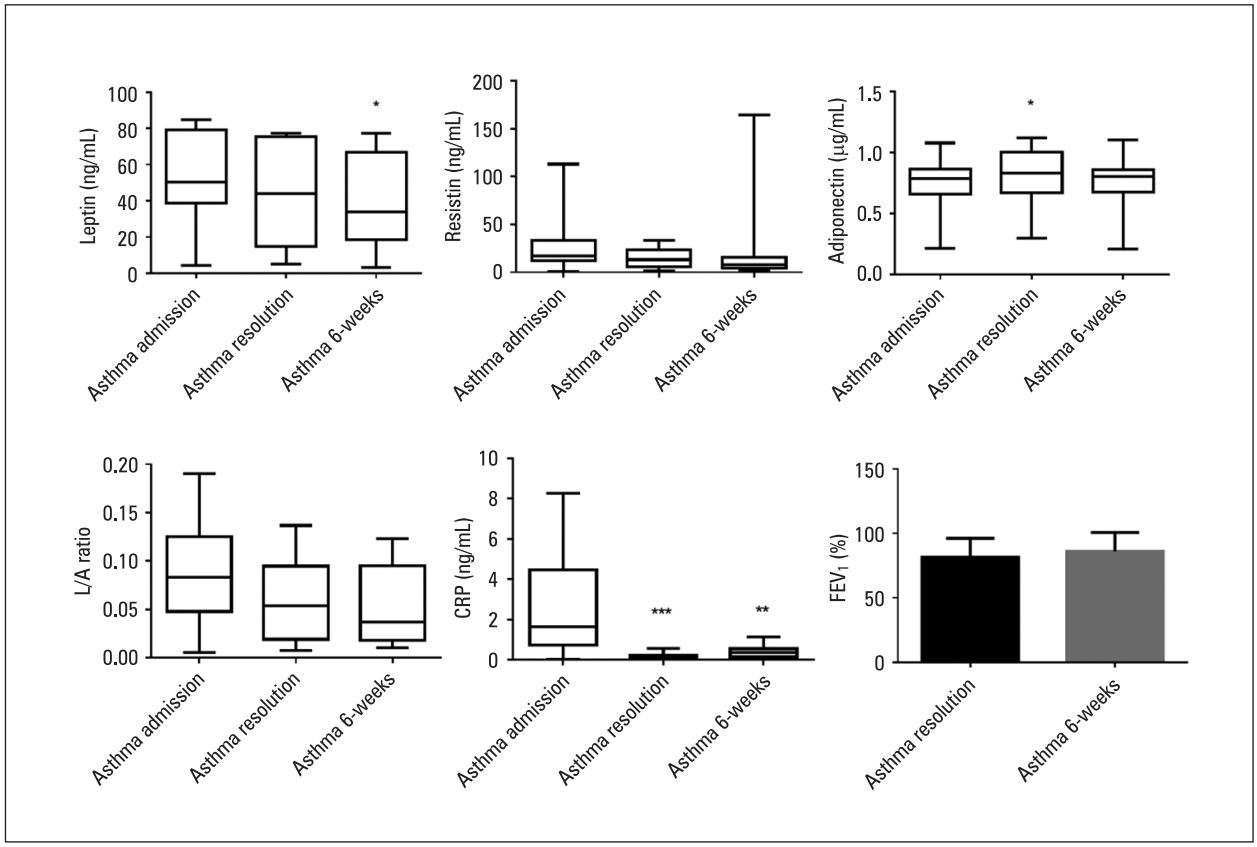

Figure 3. Levels of leptin (**A**), resistin (**B**), adiponectin (**C**), L/A ratio (**D**), CRP (**E**) and FEV_1 percentage (**F**) at the three stages of asthma. Fifteen asthmatic patients were included in the study. Leptin, adiponectin, resistin and CRP were measured in blood samples drawn at three time points: on admission, at resolution and 6 weeks after resolution. Pre- and post-bronchodilation spirometry was additionally performed at resolution and 6 weeks from resolution. Two-group comparisons were performed using the paired t-test, and for differences between more than 2 groups, the non-parametric Friedman test, one-way repeated measures analysis of variance was used for skewed data. Line in the box, median value; box edges, 25th to 75th centiles; whiskers, range of values. *$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$ compared to the value on admission. CRP — C-reactive protein; FEV_1 — forced expiratory volume in one second; L/A ratio — leptin/adiponectin ratio

incline from exacerbation to the stable phase, albeit not statistically significantly.

At the stable phase of COPD, TNF-α levels were much higher than in the stable phase of asthma ($p = 0.03$), providing a possible biomarker to distinguish between the two diseases (Figure 4).

Correlations

As expected, leptin positively correlated with BMI in all three phases of COPD and asthma. Moreover, in asthma and COPD exacerbations, female patients had higher serum leptin levels compared to male subjects ($p = 0.007$ and 0.03, respectively). In COPD exacerbations, Il-18 tended to correlate with sex; male patients had higher Il-18 levels ($p = 0.08$). No differences in the adipokine and cytokine profiles were observed between smokers and non-smokers.

Discussion

In the present study, we aimed to investigate leptin, adiponectin, resistin, Il-6, 8, 18, TNF-α, and CRP as potential diagnostic biomarkers for COPD and asthma exacerbations. According to our data, CRP and leptin levels were increased on admission for exacerbation episodes and reduced at the stable phase, demonstrating that they could represent possible biomarkers for exacerbation of both COPD and asthma. On the other hand, resistin and the L/A ratio might also be useful in identifying exacerbations in COPD patients. Finally, adiponectin is reduced on admission and increased at resolution in asthma patients. TNF-α might be a useful biomarker in distinguishing between the two diseases at the stable phase, since COPD patients exhibit much higher levels compared to asthmatic patients.

Leptin and resistin are hormones produced by the adipose tissue; both are strongly associated with obesity, diabetes, atherosclerosis, coronary heart disease, and inflammatory diseases [11]. On the contrary, adiponectin has an anti-atherogenic cardioprotective and anti-inflammatory function, despite being produced by the adipose tissue [12]. While the primary role of CRP is anti-inflammatory [13], it has a pro-inflammatory action as well [14]. Many cofactors can affect the response of these hormones to inflammation. For instance, leptin can be promoted by glucocorticoids, insulin and glucose levels; on the other hand, fasting, catecholamines and other various inflammatory cytokines inhibit leptin secretion [11]. All of these promoting and inhibiting factors might be potential confounders in patients with asthma and COPD.

Our study showed that leptin exhibited higher levels during COPD and asthma exacerbations. It decreased in both diseases at resolution, without, however, reaching statistical significance, whereas its levels significantly decreased at the stable phase. Two studies have demonstrated similar results [15, 16]; these studies showed significantly elevated leptin levels during acute exacerbations compared to controls. With regards to asthmatic patients, one study reported significantly higher leptin levels in asthmatic patients [17]. Chan *et al.* [4] compared the levels of adiponectin in three different groups (COPD patients, smokers without COPD and non-smokers) and found that the levels of adiponectin in the COPD arm were higher compared to the other groups. Another group reported statistically significant higher levels of adiponectin in the exacerbated COPD patients compared to the stable group [5]. As far as resistin levels are concerned, our study found higher levels than the normal range [18] during exacerbation in both asthma and COPD. Resistin returned to normal levels during resolution and 6 weeks after resolution in COPD patients; in asthma patients, despite its reduction at the time of resolution, it returned to normal levels 6 weeks later without clinically obvious exacerbation. Similar studies comparing resistin levels in COPD at clinical stability and during exacerbation do not exist. However, a study on resistin levels in patients with COPD compared to controls showed that resistin levels were 2-fold higher in the COPD arm [19]. A contradicting study showed that resistin levels were significantly lower in COPD patients compared to healthy subjects [20]. Furthermore, it has been reported that resistin production is highly increased in obese patients with intermittent and severe persistent asthma [21]. These studies, however, did not examine resistin response to asthma exacerbations. The results of our study demonstrate that resistin might be able to identify exacerbation in COPD patients and to monitor response to treatment in our cohort of COPD patients.

As expected, CRP levels in our study significantly decreased from admission to resolution in asthma and COPD patients. The high CRP levels seen in some patients at exacerbation are possible due to the cause of the exacerbation in these patients (infection). Measurement of CRP levels is proven to have diagnostic and prognostic value in COPD [9, 22]. A few clinical studies examining CRP in asthmatic patients have been performed. None of them have compared CRP levels between stable disease and exacerbation in asthmatic patients.

Data from the studies of cytokines in COPD and asthma have been more difficult to interpret. The problems arise from small sample sizes to insufficient replications and limited clinical phenotyping. Associations between cytokines and outcome measures have been found, but their clinical relevance is not conclusive. In our group of patients, we found no difference in Il-6, 8, 18 and TNF-α from exacerbation, to resolution and the stable phase.

The study of cytokines has also been used as a potential tool to distinguish between the two patient groups. High serum Il-8 levels have been shown to discriminate COPD from asthma patients [23], while Il-8, but not TNF-α, has been demonstrated to be significantly higher in the COPD group than in the asthmatic group, concluding that these cytokines may be involved in the inflammation in COPD [24]. In the present study, we were able to demonstrate that in stable disease, TNF-α was much higher in COPD compared to asthmatic patients, supporting the notion that TNF-α constitutes a central modulator of inflammation in COPD.

In our study, COPD patients were older than the asthmatics. More than 2/3 of the COPD patients were male, while asthmatic males constituted just above 1/3 of all asthmatic patients. COPD patients had lower FEV1 and were more dyspnoic than asthmatic individuals. In the asthmatic group, middle-aged obese female subjects were the majority; this observation can be explained by the fact that older obese women with late-onset nonatopic asthma (cluster 3) [25] were identified as a uniquely difficult to control asthma phenotype; likewise, our study recruited patients who were admitted to the hospital through the emergency department due to their poorly controlled asthma.

The main limitation of our study was not adjusting the results for possible confounders that might affect the levels of the biomarkers studied. Such possible confounders include the use of statins, intentional weight reduction, diabetes mellitus and diurnal variation of leptin. We also did not categorize our patients according to the cause of exacerbation, which was either an infection, allergens, air pollution or gastrointestinal reflux. We were, however, able to demonstrate elevated levels of CRP and two adipokines during exacerbation in COPD and asthma, and increased levels of TNF-α in stable COPD. Future studies are needed in order to assess the role of adipokines and cytokines in exacerbation episodes in COPD and asthmatic patients.

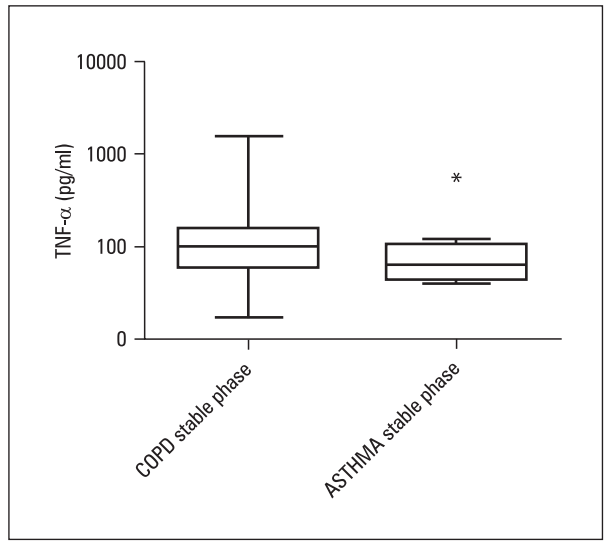

Figure 4. Levels of TNF-α in COPD and asthma at stable disease. Thirty-nine COPD and 15 asthmatic patients were included in the study. TNF-α levels were measured at the stable phase (6 weeks after resolution). Two-group comparisons were performed using the Mann-Whitney test for skewed data. Line in the box, median value; box edges, 25th to 75th centiles; whiskers, range of values. *$p < 0.05$. COPD — chronic obstructive pulmonary disease

Conclusions

Unfortunately, at the moment, an ideal biomarker doesn't exist and the overlap between the biomarkers is a reality. Our results indicate that adipokine levels might be good follow-up biomarkers in COPD and asthma. More specifically, leptin levels might be useful to follow COPD and asthma response to treatment during an exacerbation episode, whereas, resistin levels might be able to detect COPD exacerbations. CRP, on the other hand, is a good biomarker to identify and follow asthma and COPD exacerbations. Finally, TNF-α could distinguish between asthma and COPD stable phase. It should be noted that in our cohort of patients, hypoadiponectinemia was detected in asthma and COPD during all stages of the diseases. Whether or not hypoadiponectinemia contributes to the underlying inflammatory pathogenesis of asthma and COPD is a question to be answered by future research.

Conflict of interest

None declared.

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