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Plasma leptin and adiponectin in COPD exacerbations: Associations with inflammatory biomarkers☆

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Summary
Background: Various systemic inflammatory markers have been evaluated for their value in acute exacerbations of chronic obstructive pulmonary disease (COPD). Leptin and adiponectin have been linked to acute exacerbations and stable COPD.
Objectives: To assess plasma leptin, adiponectin and their ratio in acute exacerbations of COPD and to study possible associations with inflammatory biomarkers.
Methods: Plasma leptin, adiponectin and their ratio (L/A) and serum biomarkers of systemic inflammation C-reactive protein (CRP), Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) were assessed at three time points (admission, resolution and stable phase – 8 weeks after resolution) in a selected cohort of 63 COPD patients hospitalized for acute exacerbations. Subjects with comorbidities related to adipose tissue hormones were meticulously excluded.
Measurements and main results: All systemic inflammatory biomarkers, leptin and L/A ratio were elevated during admission compared to resolution and stable phase (mean L/A ratio 2.6 vs. 1.57 vs. 1.22, respectively; $p < 0.0001$), whereas adiponectin was elevated at resolution compared to admission. Log leptin, adiponectin and L/A ratio were significantly associated with variables of systemic inflammation, after proper adjustments, both on admission and in stable condition. In stepwise multiple linear regression models, IL-6 and TNF-α present the most significant associations with leptin, adiponectin and their ratio.

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Conclusions: Our data suggest that both leptin and adiponectin are associated with the systemic inflammatory process during exacerbations of COPD. The most significant associations seem to be those with IL-6 and TNF-α.

Introduction

Chronic obstructive pulmonary disease (COPD) is considered to be a disease which profoundly affects worldwide mortality and morbidity.[1] Exacerbations of COPD (ECOPD) are associated with worsening of lung function, decreased health-related quality of life, increased systemic inflammation and significant impact on survival.[2]

It is well appreciated that there is an up-regulation of airway and systemic inflammation in ECOPD.[3] Various biomarkers are reported to be higher during ECOPD compared to baseline measurements. Systemic inflammatory parameters like interleukin-6 (IL-6) and C-reactive protein (CRP) correlate with selected airway inflammatory parameters and seem to be higher in the presence of respiratory tract infections.[3] Despite the above evidence, many aspects of the underlying mechanism of increased systemic inflammation in ECOPD remain speculative.

Adipose tissue is a highly active organ and there is evidence that it secretes a large variety of proteins, including cytokines, chemokines, and hormone-like factors such as leptin, adiponectin and resistin.[4] Leptin is a circulating hormone produced by adipose tissue acting both centrally and peripherally to regulate several metabolic and inflammation-related functions.[5] Adiponectin is the adipokine that is mainly involved in the regulation of insulin sensitivity.[4] Adiponectin has also anti-inflammatory properties, by reducing inflammatory cytokines and inducing anti-inflammatory ones.[6,7] Increased levels of leptin were reported in stable COPD as well as in ECOPD.[8,9] However, limited data is available on the role of adiponectin in COPD, with the exception of an increase in its levels in underweight COPD patients and a marginal difference between stable phase and exacerbation.[10,11]

We hypothesized that adipose tissue is an important contributor to the systemic inflammation of COPD particularly to that observed in ECOPD. Given the opposing effect of leptin and adiponectin, we hypothesized that their ratio may be of greater interest in this direction instead of the single adipokines. The aim of the present study was to evaluate the levels of leptin, adiponectin and their (leptin/adiponectin [L/A]) ratio at the onset and the resolution of an ECOPD, as well as at a stable phase 8 weeks later; measurements were performed in a selected cohort of COPD patients without comorbidities in order to eliminate possible bias from diseases where adipose tissue hormones are also implicated. Additionally, associations between leptin, adiponectin and L/A ratio with biomarkers expressing the systemic inflammatory process, such as serum IL-6, CRP and tumor necrosis factor alpha (TNF-α), were additionally studied.

Methods

Study subjects

COPD patients admitted to two University Hospitals for ECOPD were evaluated for the present study. All patients were diagnosed for COPD according to Global initiative for Obstructive Lung Diseases (GOLD) guidelines,[1] and ECOPD were graded as level II—III according to ERS/ATS consensus criteria.[12] All patients fulfilling Anthonisen's criteria for type 1 ECOPD.[13] The management of all patients was in accordance with the ERS/ATS guidelines, including bronchodilators, systemic corticosteroids (30—40 mg prednisolone) for 10 days and antibiotics. Patients with significant comorbidities, including tuberculosis or other lung disease except from COPD, apparent heart failure, coronary artery disease, renal or liver impairment or failure, diabetes mellitus, history of cancer in any site, metabolic syndrome, collagen and vascular disorders were excluded. Patients receiving oral corticosteroids and those with respiratory tract infection or ECOPD in the past 8 weeks prior to admission were also excluded. Study was approved by scientific committees of both hospitals and subjects provided informed consent.

Study design

Patients were evaluated at three time points: on admission, on resolution and on stable state, 8 weeks after resolution. On admission, detailed medical history, clinical examination, identification of the cause of exacerbation, evaluation for comorbidities, as well as treatment regimens, including long term oxygen therapy (LTOT), were obtained and blood samples were drawn prior to the initiation of treatment. On resolution and on stable phase samples were drawn in the morning between 8 and 10 am. Simple spirometry (Vicatest, Model VEP2; Mijnhardt; Rotterdam, Holland) pre- and post-bronchodilation to determine forced expiratory volume in one second (FEV_1)% pred. and FEV_1/forced vital capacity (FVC) ratio was performed on stable phase. Arterial blood gases (Ecosys II, Eschweiler compact BGA, Kiel, Germany) were obtained in the three study phases. FiO_2 was additionally calculated. Hypoxia was determined by arterial oxygen tension (PaO_2)/FiO_2 ratio[14] since some of the patients were already receiving oxygen on admission.

Definitions of clinical status at three time points

Resolution of AECOPD was defined as completion of treatment with corticosteroids and antibiotics, return of symptoms to baseline and no requirement of increased doses of bronchodilation. Stable state was considered as no requirements for increases in treatment and no significant changes in symptoms apart from expected daily variation 8 weeks after the resolution.

Measurement of serum and plasma biomarkers

Blood samples were immediately centrifuged at 4 °C and stored at −80 °C. Plasma leptin and adiponectin, and serum TNF-α and IL-6 were measured by an enzyme-linked immunosorbent assay (R&D systems, Abington, UK). Limits