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Systemic inflammation up-regulates serum hepcidin in exacerbations and stabile chronic obstructive pulmonary disease

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ABSTRACT

Objectives: Hepcidin is the main regulator of systemic iron homeostasis and its expression is modulated by iron status, hypoxia, erythroid factors and inflammation. The aim of our study was to examine a relationship between level of hepcidin and iron status, erythropoietic activity, hypoxia and inflammation in exacerbations and stable COPD patients. We hypothesized that hepcidin concentration is changed in COPD patients and is substantially influenced by inflammation and/or hypoxia.

Design and methods: The study included 40 COPD patients and 30 healthy subjects. We measured haemoglobin, serum level of hepcidin and parameters indicative for inflammation: interleukin-6 (IL-6) and C reactive protein (CRP); hypoxia: partial oxygen pressure and haemoglobin oxygen saturation; iron status: iron, total iron binding capacity (TIBC), transferring saturation and ferritin; and erythropoietic activity: soluble transferrin receptors, reticulocytes, and erythropoietin.

Results: Hepcidin was elevated in exacerbations and in a stable phase compared to the control group and we found positive correlations of hepcidin with inflammatory markers IL-6 and CRP. Hepcidin also correlated positively with ferritin and inversely with TIBC. However, in COPD patients reticulocyte count was significantly reduced and negative correlation with hepcidin was established in exacerbation. No correlations were observed with iron, or indices of hypoxia. In the control group, positive associations were observed only with indices of iron status, positive with ferritin and negative one with TIBC.

Conclusion: Systemic inflammation and elevated values of IL-6 present in exacerbations and stabile COPD might be responsible for the observed increased hepcidin level.

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1. Introduction

In the last decade a number of new molecules involved in iron metabolism have been characterised. Recently, a liver hormone hepcidin has been proposed as the molecule that plays pivotal role in the regulation of iron metabolism and development of anaemia of chronic disease (ACD) [1–3]. Hepcidin regulates intestinal iron absorption and its mobilisation from the stores in order to meet erythropoietic demands. Hepcidin synthesis is modulated by various stimuli, iron loading, inflammation, hypoxia/anaemia, and erythroid factors [2,4]. The influence is exerted mainly at the transcriptional level. The data on regulation of hepcidin in COPD are rather scarce. Chronic inflammatory diseases are most often accompanied by raised hepcidin synthesis provoked by inflammatory stimuli. However, the regulation of hepcidin synthesis in COPD is probably more complex since hepcidin production could be modulated by stimulatory effect of inflammation and suppressive effect of hypoxia [3,5,6].

COPD is often associated with anaemia rather than previously described polycythemia [7,8]. Although anaemia in COPD has some characteristics of ACD, underlying mechanism is not fully understood. Schneckenpointner et al. showed that 67.6% of anemic patients with a

Abbreviations: ACD, anaemia of chronic disease; AECPOD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Epo, erythropoietin; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IL-6, interleukin-6; PAH, pulmonary arterial hypertension; PaO_2, partial oxygen pressure; post-B/D, post-bronchodilatation; Rtc, reticulocytes; SaO_2, haemoglobin oxygen saturation; sTfR, soluble transferrin receptors; TIBC, total iron binding capacity; TSat, transferrin saturation; WBC, white blood cells.

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chronic respiratory failure had disturbances of iron homeostasis [9]. Moreover, iron deficiency present in 40% of COPD patients without anaemia was associated with poorer aerobic capacity [11]. Anaemia in COPD patients impairs oxygen delivery, further reduces functional capacity and is associated with a poor outcome and early mortality [10]. Recent studies established that iron availability affects vascular responses to hypoxia and could be involved in development of pulmonary arterial hypertension (PAH) which is common complication of COPD [12,13]. Iron deficiency present in patients with idiopathic PAH was also related to the inappropriately raised hepcidin level in this study group [14].

Acute exacerbations of COPD (AECOPD) are occurring in the natural course of the disease and are characterised by change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations [15]. Systemic inflammation and hypoxia are strongly reinforced in the phase of exacerbation, and these stimuli are important factors in regulation of hepcidin level. Therefore, we used AECOPD as a model for examining the influence of intensified signals of inflammation and hypoxia on hepcidin regulation.

The aim of our study was to explore a relationship between concentration of serum hepcidin and level of inflammation, degree of erythropoietic activity and hypoxia during AECOPD and in a stable phase of the disease. We intend to assess how these signals, in particular inflammation, influence hepcidin regulation and consequently iron homeostasis and haematological parameters.

2. Materials and methods

2.1. Study subjects

The study included 40 patients with an established history of COPD, admitted to the University Hospital Center Split because of exacerbation, between September 2012 and December 2013. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. AECOPD was established based on symptoms (increased cough, dyspnea, sputum production, and/or purulence), sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations [15]. Patients were treated according to the American Thoracic Society/European Respiratory Society guidelines, with bronchodilators, systemic corticosteroids, oxygen in case of hypoxemia and antibiotics in case of purulent sputum and/or evidence of microbial growth in sputum [16]. The study was approved by the local ethics committee, and all subjects provided informed consent.

In order to avoid non-COPD related interfering factors we strictly complied with the exclusion criteria: respiratory disorders other than COPD, malignancy within the last 5 years, chronic autoimmune disorders, anaemia other than normocytic/normochromic, sepsis, history of exacerbation in the last 3 months, treatment with oral or parenteral corticosteroids, iron, B_{12} or folates in the last 3 months, surgery or transfusion in the same period. Since hepcidin is synthesized in the liver and partially eliminated by the kidney we also excluded patients with established liver disease or eGFR < 60 ml/min.

The control group consisted of 30 healthy subjects, matched for age and sex with COPD patients, who showed no signs of acute or chronic conditions and showed normal pulmonary function assessed by spirometry.

2.2. Study design

This investigation is designed as a prospective observational study. Parameters were longitudinally monitored at three time points: on admission, on resolution and in stable state. The resolution of AECOPD was defined as completed treatment with corticosteroids and antibiotics, return of symptoms to the level before exacerbation without need for an increased dose of bronchodilator. The stable state was defined as the absence of significant changes of symptoms greater than the expected daily variation, without need for enhanced treatment at least 12 weeks after resolution [17]. Medical history and clinical examination were done on admission to hospital. Demographic data, smoking history of patients and controls were recorded and body mass indexes were calculated. We determined concentration of hepcidin and complete blood count; parameters of iron status: iron concentration, unsaturated iron binding capacity (UIBC), ferritin and calculated transferrin saturation (TSat). Soluble transferrin receptors (sTfR), reticulocyte number (Rtc), and regulatory hormone erythropoietin (Epo) were measured as indicators of erythropoietic activity. Systemic inflammation was assessed by determination of CRP, interleukin 6 (IL-6), white blood cells (WBC) and neutrophil number. In all patients partial oxygen pressure (pO_2) and haemoglobin oxygen saturation (SaO_2) were determined. Parameters of hypoxia were not measured in the control group.

2.3. Methods

2.3.1. Biochemical and haematological analysis

Serum concentration of iron, UIBC, ferritin, CRP and creatinine was determined by standard laboratory methods. Glomerular filtration rate was estimated by MDRD equation. Concentration of sTfR was measured nephelometricaly (Siemens, ProSpec, Erlangen, Germany). The following parameters were determined using commercially available enzyme-linked immunosorbent assay kits: hepcidin (DRG International; Marburg, Germany), hsIL-6 and erythropoietin (eBioscience, San Diego, CA, USA), and measurements performed according to the manufacturers' instructions. Complete blood count and Rtc number were obtained with the haematology analyser (Advia 120, Siemens, Erlangen, Germany). Arterial blood gases were determined on the blood gas analyser (Gem 3000, Instrumentation Laboratory, Lexington, MA, USA).

2.3.2. Blood sampling

On admission, blood samples were drawn prior to initiation of treatment. On follow-up time points, samples were taken in the morning between 7 and 10 am. Serum and plasma samples were separated from cells and stored at −70 °C until analysis. Arterial blood gases were determined in the samples obtained by puncture of the radial artery.

2.3.3. Pulmonary function

Pulmonary function in COPD group was assessed in the stable phase of disease. Classification of COPD patients in relation to severity of airflow limitation was done according post-bronchodilatation (post-B/D) forced expiratory volume in one second (FEV1) [15].

2.4. Statistical analysis

Collected data were presented as mean ± standard deviation or median and interquartile range (IR) depending on distribution of data. The Kolmogorov–Smirnov test was used to test normality of distribution. Comparison of data obtained in the related measurements was performed by Friedman tests, non-parametric test or parametric ANOVA (repeated measures analysis of variance) in case of normal distribution. Differences between variables in COPD and the control group were examined by parametric independent t-test or nonparametric Mann–Whitney test for independent samples. Correlations between variables were investigated by Spearman's correlation. Distribution of categorical variables between two groups was tested by chi-square test, and between three related measurements by Cochran Q test. P values <0.05 were considered statistically significant.

The study had a power of 0.80 for detecting the difference of 30% in normally distributed variables and 0.80 for detecting correlations between variables with r exceeding 0.5.

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