Physiopathological aspects related to systemic inflammatory syndrome and leptin in obstructive pulmonary diseases

Abstract

Aim. Patients with both bronchiectasis and chronic obstructive pulmonary disease (COPD) experience more frequent and longer exacerbations than patients only with COPD. The aim of the study is to evaluate the role of serum leptin levels and systemic inflammation in order to predict the outcome of patients with COPD and bronchiectasis.

Methods. Body mass index (BMI), forced expired volume in 1 second (FEV1), serum leptin levels, C-reactive protein (CRP) and erythrocytes sedimentation rate (ESR) levels were analysed in two groups of COPD and bronchiectasis patients with an associated obstructive syndrome confirmed via spirometry testing.

Results. The average levels of leptin in bronchiectasis patients were significantly higher than in the case of COPD patients. Systemic inflammation was observed in both groups, with higher levels of CRP and ESR in the bronchiectasis associated with obstructive syndrome patient group. Leptin levels were correlated with the dietary status and acute phase reactants.

Conclusions. Serum leptin levels vary in patients with chronic obstructive pulmonary diseases and systemic inflammatory syndrome. Serum leptin levels, CRP and ESR could be used as predictive factors in patients with chronic obstructive pulmonary diseases.

Keywords: bronchiectasis, inflammation, leptin, COPD

Rezumat

Obiectiv. Pacienții cu bronșieciezii și boltă pulmonară obstructivă cronică (BPOC) prezintă exacerbări mult mai frecvente și mai persistente față de pacienții doar cu BPOC. Scopul studiului este de a evalua rolul nivelului seric al leptinei și al inflamației sistemice în evaluarea prognozaticii pacienților cu BPOC și bronșieciezii.

Metode. S-au analizat indicele de masă corporală (IMC), volumul expirator maxim în prima secundă de expirător (VEMS), nivelul seric al leptinei, proteina C-reactivă (PCR) și viteza de sedimentare a hematocitilor (VSH) în două grupuri de pacienți cu BPOC, respectiv cu bronșieciezii asociate cu sindrom obstructiv confirmat prin spirometrie.


Cuvinte-cheie: bronșieciezii, inflamație, leptină, BPOC

Introduction

From an anatomical point of view, bronchiectasis are defined from an anatomical point of view as irreversible and abnormal dilations of various calibres in the bronchial lumens, being located exclusively in a pulmonary lobe/segment or diffusely.

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

In accordance with the guidelines in force, the clinical diagnosis of stable COPD entails a series of indicators, such as chronic cough with expectoration for a minimum period of 3 months per year, over the course of at least 2 consecutive years, progressive and persistent dyspnea on exertion, patient history of exposure to risk factors.

Bronchiectasis is an underdiagnosed pulmonary disease because of the oftentimes difficult access to a computer tomography (CT) system. The association of a chronic obstructive disease with bronchiectasis may or may not be determined, depending on the radiological appearance and the possibility of performing a CT scan. The presence of chronic inflammatory syndrome associated with COPD is established and sustained by multiple studies. A series of paraclinical modifications may occur when this pathology is associated with bronchiectasis, thus influencing the patient’s long-term outcomes.

Both COPD and bronchiectasis patients can present with modification in terms of their body composition and dietary status due to the chronicity of the primary disease, the infection episodes, the intermittent corticosteroid therapy, and the recurrent hospital admissions with subsequent physical rest period.
High leptin levels are consistent with a series of pulmonary and extrapulmonary pathologies. Leptin influences the cytokines resulting from macrophages and phagocytosis, and may lead to a proinflammatory phenotype, as well as to T-cells activation(9).

The objective of this study is to highlight the correlations between leptin levels, chronic systemic inflammatory syndrome, weight status and respiratory function in patients with chronic obstructive pulmonary disease and bronchiectasis, in comparison with a COPD control group. Thus, there were several objectives, including the differential analysis from a pathology point of view, and the determination of intragroup relationships and intergroup correlations in terms of serum leptin levels, systemic inflammatory syndrome and the respiratory function in patients with bronchiectasis and in the control group. Concurrently, the study also aimed to monitor and identify certain parameters that can define and prevent complications in obstructive pulmonary diseases, whether or not associated with bronchiectasis. The main aim of this study is to establish the role of serum leptin levels in patients with COPD and bronchiectasis, to observe the differences and predict the outcome.

**Methods**

The prospective study included 50 patients with obstructive pulmonary diseases, of which 25 patients with non-cystic fibrosis bronchiectasis and a control group comprising 25 COPD patients registered in the Hospital of Pneumology from Iași, from June to December 2013. The inclusion criteria for the bronchiectasis patients’ group were: the existence of a CT scan confirming the diagnosis, spirometry test, adult age, male gender, and signing the informed consent. The etiology of the bronchiectasis was not studied. The inclusion criteria for the control group were: the existence of a spirometry test supporting the COPD diagnosis, adult patient, male gender, and signing the informed consent, CT scan excluding the existence of bronchiectasis. All the patients included in the study were unaffected by an exacerbated or coexisting extrapulmonary infection and came for the periodical health check-up. Only patients without any comorbidity (which may influence the serum level of leptin and inflammatory syndrome) were included in the study.

The statistical analysis was performed according to the database. Because the number of subjects is relatively low and the groups are medium – especially patients with bronchiectasis, which is limited by the financial inability of the patients/hospital to perform a chest CT scan, the distribution of the studied features is normal.

Data was input and processed using the statistical functions in Microsoft Excel and the SPSS 17 statistical analysis program, a statistical processing variant that allows the use of lots of at least 20 patients (without taking into account errors). The results are expressed as the mean +/- standard deviation. The threshold of statistical significance p<0.05 was considered.

The data were statistically analyzed by computing the following parameters:

- standard error/deviation of mean: the measure of the approximation of the data obtained against the average – i.e., the degree of dispersion of the values in the study;
- 95% confidence interval;

In order to highlight the statistically significant differences between the values of a parameter in the study groups, the t test was used if the variables analyzed were of a numeric type.

The monitored parameters included: serum leptin levels measured in ng/ml (BioVendor products – Leptin Human Elisa, Elisa method), FEV1, markers of systemic inflammatory syndrome (ESR and CRP), patients’ age, weight and BMI. Other related investigations were performed concurrently in order to rule out the existence of any infection or the presence of any decompensated disease. Investigations including patient history, physical exam, chest X-ray, complete blood count, electrocardiogram, as well as peripheral oxygen saturation, blood pressure and body temperature measurements were taken upon inclusion in the study for the purpose of identifying any potential pathology that would preclude the patient from participating in the study.

**Results**

The mean age was 63.7 years old in the COPD patients group and 60.5 years old in the bronchiectasis patients group, respectively. As far as the mean BMIs is concerned, it reached 24.4 kg/m² for the COPD patients group and 25.9 kg/m² in the bronchiectasis patients group.

To facilitate statistical processing works, we divided the patients based on their BMIs into two further subgroups: normoponderal patients, with BMI: 18.5-25 kg/m², and patients with BMI>25 kg/m² (Table 1). The COPD patients group includes 68% normoponderal patients (17 patients) and 32% (8 patients) with various degrees of obesity. The bronchiectasis patients group includes 44% (11 patients) normoponderal patients and 56% (14 patients) with various degrees of obesity. The comparison between the two groups reveal no significant differences, except for the serum level of leptin in COPD patients. The average levels of leptin was 7.5 ng/ml for the COPD group and 12.73 ng/ml for the bronchiectasis patients group.

ESR and CRP levels were determined for the systemic inflammatory syndrome analysis. Thus, the mean ESR level was 26.32 mm/h for the COPD patients group and 32.88 mm/h for the bronchiectasis patients group. In normoponderal COPD patients, this level was 26.47 mm/h and 26 in obese patients, respectively. Mean ESR in the group of bronchiectasis patients was 32.73 mm/h for normoponderal patients and 33 mm/h for obese patients. The average level of CRP was 5.36 mg/dl in the COPD patients group and 11.08 mg/dl in the bronchiectasis patients group. In normoponderal COPD patients, this level was 5.29 mg/dl and 5.5 mg/dl in obese patients, respectively. Mean CRP in the group of bronchiectasis patients was 10.36 mg/dl for normoponderal patients and 11.64 mg/dl for obese patients.
The mean level of FEV1 was 50.39 in the COPD patients group and 62.32 in the bronchiectasis patients group.

The comparative analysis of the main parameters studied in the two groups revealed that the average levels of CRP in patients with bronchiectasis was significantly higher than in the COPD patients (p=0.027, F=5.2), the average of leptin levels in patients with bronchiectasis was significantly higher than in COPD patients (p=0.008, F=7.5), and the average of FEV1 in patients with bronchiectasis was significantly higher than in COPD patients (p=0.024, F=0.12). The comparative analysis of average levels in the parameters studied in the two groups based on their weight revealed that the average levels of leptin in obese COPD patients is significantly higher than in normoponderal COPD patients (U=32, p=0.037).

The correlation analysis in the COPD patients group based on their weight status revealed that leptin levels in normoponderal patients were not significantly correlated with any of the studied parameters. Leptin levels in overweight and obese patients were significantly correlated with ESR and CRP (Figure 1).

Leptin levels in normoponderal COPD patients were not significantly correlated with any of the studied parameters. Leptin levels in overweight and obese COPD patients were significantly correlated with BMI and ESR (Table 1).

Leptin values in normoponderal bronchiectasis patients were significantly correlated with BMI and in overweight and obese bronchiectasis patients were significantly correlated with CRP (Table 3).

High leptin levels were associated with high CRP levels and overweight and obese status in COPD patients (Tables 4 and 5). This was not observed in the group of bronchiectasis patients.

The variance analysis for regression model is indicative of the efficiency of the proposed model (F=4.2, p=0.02) knowing the independent variables, compared with the case in which prediction was to be made randomly.
Correlation analysis in bronchiectasis patients based on their weight status

**Table 3**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Weight status</th>
<th>ESR (mm/h)</th>
<th>CRP (mg/dl)</th>
<th>FEV1 (L)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis patients</td>
<td>Normoponderal patients (BMI 18.5-25 kg/m²) (n=11)</td>
<td>0.583</td>
<td>0.349</td>
<td>0.341</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Overweight and obese patients (BMI &gt;25 kg/m²) (n=14)</td>
<td>0.896</td>
<td>0.043</td>
<td>0.103</td>
<td>0.567</td>
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**Discussions**

The study only included male patients, due to the variability of leptin in women, as this process is connected to hormone fluctuations\(^5,6\). The preferred option for investigating inflammation is currently the use of CRP, as its levels increase precociously in comparison with ESR levels, which require a 24-hour period. Most clinicians use both acute phase reactants for assessment purposes because this boosts sensitivity and specificity in determining the diagnosis or outcomes of a certain pathology.

The results obtained revealed that leptin levels in
patients with bronchiectasis and obstructive pulmonary disease were almost twice as high as compared to the COPD patients group. There is also a relationship between the levels of CRP, ESR, and leptin. The analysis of the two groups revealed a higher level of ESR and CRP in bronchiectasis patients than in obese COPD patients. As such, we can state that chronic inflammatory syndrome associated with obstructive pulmonary disease also carries metabolic modifications. The role of leptin in the pro-inflammatory phenotype is a very important aspect and it can be one of the factors responsible both for the onset and the maintenance of inflammation(7,8,9).

There are suspicions that the systemic inflammatory process plays a major role in the occurrence of fibrosis, proteolysis, emphysema and airway obstruction. The literature comprises data that are indicative of an increasing prevalence of heart disease in these patients presenting with chronic systemic inflammatory syndrome, which confirms the need for further studies in this field.

Recent studies have highlighted the connection between leptin levels and a series of pathologies, such as obesity, sleep apnea syndrome and secondary hypercapnia. The coexistence of COPD and apnea syndrome is an established fact(10-12). Cardiovascular risk factors associated with apnea syndrome (hypertension, hypercholesterolemia, heart rhythm diseases) and increased leptin levels form a complex that influences patient prognosis(13,14).

Literature data indicate that leptin levels are higher during COPD exacerbations than in patients with stable COPD, and that once the infectious episode ends, these levels return to their previous statuses(15,16). Its degree of involvement in patient outcomes and prognosis is insufficiently studied. This study, although includes a small number of patients, supports the relative few data regarding the role of leptine and inflammatory syndrome as markers of prognosis and follow-up for patients with chronic obstructive lung disease.

**Conclusions**

Systemic inflammatory syndrome associated with an obstructive pulmonary pathology plays a major role in the coexistence of various diseases and metabolic changes.

The role of leptin in obstructive chronic pulmonary diseases is not fully understood, thus confirming the need for further studies in the future. Average levels of leptin in bronchiectasis are significantly higher than in COPD, and body composition changes influence these levels. Leptin can be considered an evolution marker for inflammatory syndrome due to the correlations with its parameters.

**Table 4**

<table>
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<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>Change Statistics</th>
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