Nutrition disorder and systemic inflammation in patients with chronic obstructive pulmonary disease

Zorica Ćirić, Ivana Stanković, Tatjana Pejčić, Lidija Ristić, Milan Rančić, Milan Radović, Desa Nastasijević-Borovec

University of Niš, School of Medicine, Clinic for Lung Diseases “Knez Selo”, Clinical Centre of Niš, Niš, Serbia

ABSTRACT

Aim To detect nutrition disorders (underweight and obesity) in patients with chronic obstructive disease (COPD) and presence of systemic inflammation by determination of inflammatory mediators serum values C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α) and leptin.

Methods The examination involved 85 patients with COPD. Nutrition categories were defined by body mass index (BMI). Fat free mass (FFM) was evaluated by mid upper-arm circumference (MUAC) and fat mass (FM) by tricipital skin-fold thickness (TFS). Values of TNF-α and leptin were measured by standardized ELISA kits and, CRP by latex turbidimetry.

Results There were 14 (16.5%) underweight patients, 28 (32.9%) normal, 28 (32.9%) pre-obese and 15 (17.6%) obese. Values of MUAC and TSF were significantly different among the nutrition categories (p=0.000). The lowest MUAC and TSF values were in the underweight, and the highest in the obese. There was no significant difference of CRP and TNF-α among nutrition categories. Leptin of the underweight and normal nutrition was significantly different from leptin of the pre-obese and obese (p=0.000). The highest CRP and the lowest TNF-α and leptin were in the underweight patients. The obese had the lowest CRP (although increased as compared to normal values) and the highest leptin, while the pre-obese had the highest TNF-α.

Conclusion Two basic nutrition disorders (underweight and obesity) were manifested in COPD patients. The inflammatory profile differs between underweight COPD patients and obese. Probably that happens due to systemic inflammation, and in part due to dysfunction of adipose tissue.

Key words: chronic airflow obstruction, nutrition assessment, C-reactive protein, tumor necrosis factor-alpha, leptin
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has significant extra pulmonary effects which influence the course and prognosis of the disease (1). Systemic inflammation is considered to be the cause for occurrence of extra pulmonary manifestations of COPD (2). There many hypotheses about the origin and mechanisms of systemic inflammation occurrence, but so far there have been no definite evidence about which mechanism has the key significance (3). A large number of inflammatory mediators are involved in the occurrence and maintenance of the inflammatory reaction in COPD. Mediators that are most commonly associated with the systemic inflammation in COPD are C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and leptin (4).

Nutrition disorder is a common extra pulmonary effect in COPD (5). It is manifested clinically through the weight loss (underweight) (5), or the weight gain (obesity) (6).

Cachexia is the term that is used for describing the state of underweight in COPD (7). It is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism (8). Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (9).

A few potential occurrence mechanisms of underweight in COPD are mentioned: systemic inflammation, energetic imbalance hypoxia, and hormone insufficiency (5). An important mechanism in obesity occurrence is lowered tolerance of physical exertion of a COPD patient, and inactivity developed due to it (6). Still, it is considered that systemic inflammation and the increase in inflammatory mediators in systemic circulation due to it, is one of the key occurrence mechanisms for underweight (2). On the other hand, obesity related hypoxia results in local inflammatory response within adipose tissue per se, and many contribute to elevations in circulatory inflammatory mediators by spillover form adipose tissue to the systemic circulation (10).

The body composition depends on the quantity of fat in the organism (fat mass – FM) and the fat free mass (FFM) (11). The decline in FFM points to the decline of muscle mass and protein deficit (11). Thus, the decline in FFM is now very often used for defining underweight, along with the Body Mass Index (BMI) (12). Mid upper-arm circumference (MUAC) indicates the development of the muscle mass and reflects the reserve of muscle proteins (12), thus, it is used as a simple and cheap method of FFM evaluation (13). By measuring tricipital skin-fold thickness (TFS) the estimation of total fat content in the organism (FM) is done (11).

Systemic inflammation has been suggested to be the cause of extra pulmonary effects in COPD (14,15). The aim of the paper was to detect nutrition disorders in COPD and presence of systemic inflammation in COPD patients with nutrition disorders by determination of inflammatory mediators values (CRP, TNF-α, leptin).

PATIENTS AND METHODS

The examination was done in the Clinic for Pulmonary Diseases “Knez Selo”, Clinical Center of Niš, Serbia, in the Center for Biochemical Medicine, and in the Polyclinic for Laboratory Diagnostic - Neolab in Niš. The examination involved 85 patients. All patients had a clinical diagnosis of COPD and were in a stable phase of the disease. Spirometry, body mass index (BMI), mid-upper arm circumference, tricipital skin-fold thickness, serum levels of CRP, TNF-α and CRP were measured in all participants.

Spirometry was performed before and 15 minute after 400μg salbutamol inhalation using a spirometer Master Lab (Erich Jaegar Germany). Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio were measured. Post-bronchodilator FEV₁/FVC ≤ 70% confirmed the presence of airway obstruction that is not fully reversible (1).

Body weight was assessed with a beam scale to the nearest 0.1 kg with subjects standing barefoot and in light clothing. Height was measured by a clinical stadimeter in bare or stocking feet. Body mass index was calculated as the weight in kilograms divided by square of the height in meters (kg/m²). Considering the fact that BMI<20kg/m² is widely accepted as underweight, particularly in well-developed countries (13), as recommend...
by Nikolic M. et al. (11), value for defining was BMI<20 kg/m². The other nutrition categories were defined by BMI values as recommended by the World Health Organization (16): normal BMI=20-24.9 kg/m²; pre-obesity BMI=25-29.9 kg/m² and obesity BMI≥30 kg/m². For FFM estimation MUAC was measured to the nearest 0.1 cm midway between olecranon and acromion using a non-stretch tape and also nutrition category was determined based on the measured values (11). Tricipital skin-fold thickness measurement served for the estimation of fat content (FM) in the organism and it was measured to the nearest 0.5 mm using the Skinfold Caliper Harpenden. Since females and males differ in body composition (rate FFM/FM), MUAC and TSF were calculated for females and males separately.

Blood samples were taken between 8:00 and 9:00 AM from patients who had been fasting since 8:00 PM the previous night. Both serum and plasma were separated from blood cells by centrifugation at 1000 x g for 5 minutes. All samples for leptin and TNF-α were stored at -70 °C until analyzed, and the samples for CRP were analyzed immediately. Serum leptin levels were measured with enzyme immunoassay DRG Leptin (Sandwich) ELISA EIA 2395 kit (DRG Instruments GmbH, Germany). Serum TNF-α levels were measured with enzyme immunoassay DRG TNF-α ELISA EIA-4641 kit (DRG Instruments GmbH, Germany). Serum CRP levels were measured with latex turbidimetric immunoassay on SYNCHRON CX4 / CX5 Clinical Systems Beckman Coulter.

By using descriptive statistical analysis arithmetic mean, standard deviation and variation interval (min-max) and structure index (%) were shown. Comparisons of the markers mean values among the groups were performed by analysis of variance (ANOVA), followed by Dunnett’s post hoc test. Level of statistical significance was determined at p<0.05. The results of statistical analysis have been shown in the tables.

Ethical Committee of the School of Medicine, University of Niš, approved this investigation. All patients received written information prior to participation, and all patients signed informed consent.

RESULTS

The distribution of the patients in each nutrition category based on BMI and on mid upper-arm circumference is shown in Table 1 and Table 2. If the underweight and borderline underweight were considered as a single group and the pre-obese and obese as well, the number of the underweight and obese patients was larger when defined by mid upper-arm circumference (17 vs. 14 and 48 vs. 43).

Table 1. Number of patients and nutrition categories by body mass index

<table>
<thead>
<tr>
<th>Category of nutrition*</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) of patients</td>
<td>14</td>
<td>28</td>
<td>28</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

*A, underweight; B, normal nutrition; C, pre-obesity; D, obesity; E, overall

Table 2. Number of patients and nutrition categories by mid upper-arm circumference

<table>
<thead>
<tr>
<th>Category of nutrition*</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) of patients</td>
<td>6</td>
<td>11</td>
<td>11</td>
<td>48</td>
<td>85</td>
</tr>
</tbody>
</table>

*A, underweight; B, borderline; C, optimal; D, above optimal; E, overall

The mean values of mid upper-arm circumference and tricipital skin-fold thickness were significantly different among the nutrition categories (defined by BMI) in all patients (p=0.000 and p=0.000, respectively). Both MUAC and TSF values were increased with the increase in nutrition category. The lowest MUAC and TSF values were in the underweight, and the highest in the obese (Table 3).

Table 3. Mid upper-arm circumference and tricipital skin-fold thickness among nutrition category

<table>
<thead>
<tr>
<th>Anthropometric parameters</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUAC (cm)</td>
<td>16.86±3.03</td>
<td>24.36±3.19</td>
<td>31.25±3.68</td>
<td>36.6±3.52</td>
<td>0.000</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>14.14±5.26</td>
<td>19.45±5.94</td>
<td>29.29±8.06</td>
<td>33.8±8.82</td>
<td>0.000</td>
</tr>
<tr>
<td>(5-19)</td>
<td>(10-35)</td>
<td>(12-44)</td>
<td>(15-49)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are presented as mean ± SD and variation interval (min-max).

*A, underweight; B, normal nutrition; C, pre-obesity; D, obesity; MUAC, mid upper-arm circumference; TSF, tricipital skin-fold thickness;

The mean values of CRP and TNF-α among nutrition categories (based on BMI) varied in the range that was not statistically significant (p=0.334 and p=0.987, respectively). The mean leptin values of the underweight and those with normal nutrition were mutually similar, as well as the values of the pre-obese and obese. However, the mean leptin values of the underweight and normal nutrition were significantly different from the mean leptin values of the pre-obese and obese.
The highest mean CRP values, and the lowest TNF-α values and leptin were in the nutrition category of the underweight patients. The obese had the lowest mean CRP values and the highest mean leptin values, while the pre-obese had the highest mean TNF-α values (Table 4).

DISCUSSION

The results of our study showed that the examined COPD patients had nutrition disorders, such as underweight and obesity. We found a larger number of underweight and obese patients when nutrition categories were defined by FFM (estimated by MUAC) than when they were defined by BMI. Furthermore, we determined that the weight loss was followed by the decrease in FFM and FM values (estimated by TSF), along with the simultaneous decrease in TNF-α and leptin values, and the increase in CRP.

It is estimated that the weight loss prevalence in COPD is between 20 to 40% (17). Obesity found in COPD patients ranges from 18% to 54% (18). Similar results regarding underweight (defined by MUAC) were found in our patients, while the results regarding obesity were also similarly defined whether by MUAC or BMI. Body mass index is an inaccurate estimate of FM and FFM constituents of body weight (17). Recent studies have shown FFM depletion prevalence to be higher than presence of lower BMI values in COPD patients (19-21). We also found a larger number of underweight and obese (and pre-obese) patients when nutrition was estimated by FFM than when it was estimated by BMI (20% vs. 16.5% and 56.5% vs. 50.5%). Therefore, FFM was a more sensitive tool for detecting nutrition disorders in COPD patients, especially since similar findings have been shown by some other studies as well (22).

Underweight COPD patients experiencing body weight loss suffer from both loss of FFM in association with the loss of FM (23). In our study, it was found that underweight patients had, at the same time, the lowest FFM values (estimated by MUAC) and the lowest FM values (estimated by TSF) in relation to other nutrition categories. That indicated that the weight loss of our COPD patients occurred due to the decrease in FFM, with the simultaneous decrease in FM.

Our underweight patients had the highest CRP values in relation to other nutrition categories. Considering the fact that the increased CRP values in COPD indicated the existence of systemic inflammation (24) and were associated with loss of FFM (17) our finding confirmed the existence of systemic inflammation in underweight COPD patients and pointed out one of weight loss occurrence mechanisms. At the same time, in this study it was found that obese patients had the lowest CRP values, although they were higher than referential values. That was indicative of existence of low degree chronic inflammation in fat tissue of our obese patients, as suggested by available studies (18, 25).

The results of this study have shown lowest leptin values in underweight patients, and those findings have been shown by other studies as well (17, 26). Lower leptin values of our underweight patients were not followed by appetite increase, suggesting that leptin may have acted as inflammatory cytokines, and not as an appetite regulator, as demonstrated in studies (27, 28). However, this study did not find that the underweight had higher TNF-α values, as it is most often suggested in other studies (17, 29). An explanation for our finding may be a possibility that underweight in COPD did not occur due to inflammation conditioned by TNF-α increase, but that FM was a predictor of increase of TNF-α and leptin, which has been put forward as a hypothesis by recent studies (30-33). The studies have suggested that the expression of adipokines and cytokines from adipocytes in-

<table>
<thead>
<tr>
<th>Inflammatory mediator</th>
<th>Category of nutrition*</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>19.31±23.59</td>
<td>18.87±24.36</td>
<td>13.13±19.81</td>
<td>7.92±12.16</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>(1-80)</td>
<td>(1-89)</td>
<td>(1-92)</td>
<td>(1-97)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>8.09±5.380</td>
<td>8.65±10.412</td>
<td>8.986±6.733</td>
<td>8.876±4.494</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>(0.327-22.942)</td>
<td>(3.535-56.604)</td>
<td>(1.327-31.111)</td>
<td>(3.969-22.159)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>3.09±3.827</td>
<td>6.25±10.57</td>
<td>18.579±20.164</td>
<td>33.616±35.543</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>(0.036-11.503)</td>
<td>(0.181-51.972)</td>
<td>(0.477-71.61)</td>
<td>(1.091-150.812)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Results are presented as mean ± SD and variation interval (min-max); p<0.001, underweight and normal vs. pre-obesity and obesity. *A, underweight; B, normal nutrition; C, pre-obesity; D, obesity; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; NS, not statistically significant;
creases with the increase in fat tissue and number of adipocytes (18,28). Indeed, our underweight patients had the lowest FM values estimated by TSF, while the pre-obese and obese had the highest FM values and the highest TNF-α and leptin values. Another possible explanation could be that in underweight COPD patients the level of inflammation was increased before occurrence of underweight, and when it was established a decrease in its intensity and inflammation mediators values occurred, which has also been suggested by Eagen et al. in his study (33).

In conclusion, our study supports the theory that in underweight and obese patients there is a systemic inflammation mediated by CRP, but it does not support the hypothesis that underweight is mediated through an increase in TNF-α related systemic inflammation. Rather, our results allow the hypothesis that in COPD patients there is a dysfunction of adipose tissue and that high fat mass may be a predictor of high plasma levels of TNF-α and leptin.

FUNDING
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TRANSPARENCY DECLARATIONS
Competing interests: none to declare.

REFERENCES
Nutritivni poremećaji i sistemská inflamacija kod bolesnika s hroničnom opstruktnom bolešću pluća
Zorica Ćirić, Ivana Stanković, Tatjana Pejić, Lidija Ristić Milan Rančić, Milan Radović, Desa Nastasijević-Borovec
Univerzitet u Nišu, Medicinski fakultet, Klinika za plućne bolesti Knez Selo, Klinički centar Niš, Niš, Srbija

SAŽETAK
Cilj Utvrđiti postojanje poremećaja uhranjenosti (pothranjenosti i gojaznosti) kod pacijenata s hroničnom opstruktnom bolešću pluća (HOBP) i prisustvo sistemské inflamacije određivanjem serumskih vrednosti C-reaktivnog proteina (CRP), faktora nekroze tumora alfa (TNF-á) i leptina.
Metode Ispitivano je 85 pacijenata, a kategorije uhranjenosti određivane su vrednostima body mass indexa (BMI). Obim sredine nadlakta (mid upper-arm circumference – MUAC) korišćen je za procenu ne-masne mase tela (fat free mass – FFM), a debljina kožnog nabora (tricipital skin-fold thickness – TSF) za procenu ukupnih masti (fat mass – FM). Vrednosti TNF-á i leptina određivane su standardnim ELISA-kit testovima, a CRP latex turbidimetrijskom metodom.
Rezultati Zabeleženo je 14 (16,5%) pothranjenih, 28 (32,9%) normalno uhranjenih, 28 (32,9%) pregojaznih i 15 (17,6%) gojaznih pacijenata. Vrednosti MUAC-a i TSF-a značajno su se razlikovale između kategorija uhranjenosti (p=0,000). Najmanje vrednosti MUAC-a i TSF-a bile su kod pothranjenih, a najveće kod gojaznih. Nije bilo značajne razlike vrednosti CRP-a i TNF-á između kategorija uhranjenosti. Vrednosti leptina pothranjenih i normalno uhranjenih značajno su se razlikovale od vrednosti leptina pregojaznih i gojaznih (p=0,000). Najveće vrednosti CRP-a, a najmanje TNF-á i leptina, bile su u kategoriji pothranjenih. Gojazni su imali najmanje vrednosti CRP-a (mada povišene u poređenju s normalnim vrednostima) i najveće vrednosti leptina, dok su predgojazni imali najveće vrednosti TNF-á.
Zaključak Dva osnovna poremećaja uhranjenosti (pothranjenost i gojaznost) mogu se naći kod pacijenata s HOBP-om. Profil prisutne inflamacije razlikuje se između pothranjenih i gojaznih pacijenata s HOBP-om, verovatno kao posledica sistemské inflamacije, ali delom i usled disfunkcije adipoznog tkiva.
Ključne reči: hronična opstrukcija disajnih puteva, procena uhranjenosti, C-reaktivni protein, faktor nekroze tumora alfa, leptin.