

# Effect of exacerbation frequency on body composition and serum ghrelin and adiponectin concentrations in patients with chronic obstructive pulmonary disease

Renata Rubinsztajn, Tadeusz Przybyłowski, Marta Maskey-Warzęchowska, Krzysztof Karwat, Magdalena Paplińska-Goryca, Patrycja Nejman-Gryz, Ryszarda Chazan

Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Warsaw, Poland

## KEY WORDS

adiponectin, body composition, chronic obstructive pulmonary disease, exacerbations, ghrelin

## ABSTRACT

**INTRODUCTION** Exacerbations affect the natural history of chronic obstructive pulmonary disease (COPD). **OBJECTIVES** The aim of the study was to evaluate the effect of exacerbation frequency in COPD on body composition and systemic inflammation assessed by the measurement of serum adiponectin and ghrelin concentrations.

**PATIENTS AND METHODS** The study group included 152 patients with COPD. Body composition was assessed by bioimpedance. Fasting serum adiponectin and ghrelin concentrations were evaluated by enzyme-linked immunosorbent assays.

**RESULTS** Of the 152 patients, 60 did not report any exacerbation in the last 12 months, 53 had 1 exacerbation, and 39 had more than 1 exacerbation. The mean number of exacerbations in the whole group was  $1.04 \pm 1.3$  per patient per year and increased with the increasing degree of airway obstruction. Patients with exacerbations had a lower fat-free mass (FFM) index, lower total body water, and lower resting metabolic rate compared with patients without exacerbations ( $18.3 \pm 2.5$  kg/m<sup>2</sup> vs.  $19.3 \pm 2.7$  kg/m<sup>2</sup>;  $36.9 \pm 8.1$  kg vs.  $40.2 \pm 8.0$  kg; and  $1482.8 \pm 301.1$  kcal vs.  $1616.0 \pm 322.0$  kcal; respectively). The adiponectin concentration was higher in patients with more than 1 exacerbation than in those with 1 or no exacerbations ( $14.5 \pm 8.6$  mg/l vs.  $11.2 \pm 7.6$  mg/l,  $P < 0.05$ ). We observed significant negative correlations between the number of exacerbations and the muscle mass index, FFM index, total body water, resting metabolic rate, and adiponectin concentration in the whole group.

**CONCLUSIONS** Exacerbations affect body composition in patients with COPD. Patients with frequent exacerbations have more enhanced systemic inflammation. Assessment of the body composition and systemic inflammation should be part of the routine management of patients with COPD.

**INTRODUCTION** Exacerbations in chronic obstructive pulmonary disease (COPD) are an important factor affecting the course of the disease. Patients with frequent exacerbations demonstrate a more rapid annual decline in forced expiratory volume in the first second (FEV<sub>1</sub>).<sup>1</sup> An association between the dynamics of lung function decline and morbidity and mortality in COPD has been reported.<sup>2</sup> Moreover, it has been documented that previous exacerbations have the best predictive value for identifying patients at risk for frequent exacerbations.<sup>3</sup> Studies

have shown unequivocally that lung function decline is associated with an increased risk of exacerbation, hospitalization, and death.<sup>4,5</sup> Exacerbations also deteriorate the quality of life in this patient group.<sup>6</sup> According to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations<sup>7</sup> and the Polish Respiratory Society guidelines for the management of COPD,<sup>8</sup> the number of exacerbations should be considered along with FEV<sub>1</sub> in the assessment of the severity of COPD and disease-related prognosis.

Correspondence to:  
Renata Rubinsztajn, MD, PhD, Katedra  
i Klinika Chorób Wewnętrznych,  
Pneumonologii i Alergologii,  
Warszawski Uniwersytet Medyczny,  
ul. Banacha 1a, 02-097 Warszawa,  
phone: +48-22-599-28-51,  
fax: +48-22-599-15-60, e-mail:  
rubinsztajn@wum.edu.pl  
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**TABLE 1** Study group characteristics

age, y	70 (61.5–75)
pack-years	40 (30–50)
BMI, kg/m <sup>2</sup>	27 (24.1–30.7)
prebronchodilator FEV <sub>1</sub> , % predicted	43.8 (36–60.6)
postbronchodilator FEV <sub>1</sub> , % predicted	53.1 (42.1–69.1)
prebronchodilator FVC, % predicted	78.6 ± 17.9
postbronchodilator FVC, % predicted	89.1 (76.3–100.3)
RV/TLC, %	55.8 ± 8.8
RV/TLC, % predicted	134.2 (120.8–149.3)
acyl ghrelin, pg/ml	30.4 (13.6–45.9)
adiponectin, mg/l	9.7 (6.2–16.5)
fat tissue, %	31.1 ± 8.1
fat tissue index, kg/m <sup>2</sup>	8.5 (6.2–11.0)
fat-free mass index, kg/m <sup>2</sup>	18.2 (16.8–20.3)
muscle mass index, kg/m <sup>2</sup>	17.5 (16–19.4)
waist-to-hip ratio	0.96 ± 0.09

Data are presented as mean ± standard deviation or median (interquartile range).

Abbreviations: BMI – body mass index, FEV<sub>1</sub> – forced expiratory volume in the first second, FVC – forced vital capacity, RV/TLC – ratio of residual volume to total lung capacity

Body weight is also one of the most important prognostic factors in COPD.<sup>9</sup> Body mass index (BMI), severity of airway obstruction (FEV<sub>1</sub>), dyspnea, and exercise tolerance (6-minute walk test) are incorporated in the BODE index, one of the most popular prognostic scales in COPD in recent years.<sup>10</sup> Cachexia affects from 20% to 40% of patients with COPD.<sup>10</sup> A lower BMI is more frequently observed in hospitalized patients and is associated with higher mortality,<sup>11</sup> while a higher BMI is an independent positive prognostic factor in COPD.<sup>12</sup> However, BMI does not adequately reflect body composition. A normal BMI does not exclude an altered nutritional status; in COPD, loss of fat-free mass (FFM) and a simultaneous rise in fat mass are observed, and a large proportion of these patients have a normal BMI.

COPD-related cachexia may have numerous underlying causes, including genetic factors such as gene polymorphisms in interleukin (IL) 1β,<sup>13</sup> IL-6, angiotensin-converting enzyme,<sup>14</sup> or tumor necrosis factor α (TNF-α).<sup>13</sup> Patients with COPD have an increased metabolism and resting energy expenditure compared with healthy subjects.<sup>15</sup> Hypoxemia, which stimulates the release of inflammatory cytokines<sup>16</sup> and sympathetic activation,<sup>17</sup> may also contribute to weight loss. Fat tissue-associated hormones such as leptin and resistin also play a role.<sup>18</sup> Some authors have also shown the relationships between COPD exacerbations and serum concentrations of γ-glutamyltransferase<sup>19</sup> and mean platelet volume.<sup>20</sup>

Leptin concentrations have been demonstrated to correlate with BMI, FFM, and the BODE index<sup>21</sup> and to increase during COPD exacerbations.<sup>22</sup> Adiponectin has a positive impact on

glucose and fat metabolism and may influence appetite via receptors located in the hypothalamus.<sup>23</sup> The adiponectin concentration is higher in patients with COPD than in healthy subjects and correlates with the degree of lung hyperinflation. Its elevated serum concentration in underweight patients is associated with a lower risk of cardiovascular complications,<sup>24</sup> which significantly affects the course and prognosis of COPD.

Ghrelin is a hormone associated with the energetic balance and its concentration is affected by the nutritional status; its activity differs depending on the form—acylated (acyl ghrelin) or nonacylated (desacyl ghrelin). Acylated ghrelin enhances appetite and causes weight gain to maintain positive energy balance.<sup>25</sup> Its counterpart, nonacylated ghrelin, is probably responsible for negative energy balance causing weight loss.<sup>25</sup> The ghrelin concentration is increased in a number of conditions leading to cachexia. In patients with COPD with a low BMI, the serum ghrelin concentration was higher than in controls and correlated with lung hyperinflation defined by an increased residual volume (RV) and the ratio of residual volume to total lung capacity (RV/TLC).<sup>26</sup>

Given this rationale, we conducted a study to evaluate the effect of exacerbation frequency on body composition and serum adiponectin and ghrelin concentrations in patients with COPD.

**PATIENTS AND METHODS** The study included 152 consecutive patients with stable COPD (61 women, 91 men; mean age, 68 ± 8 years; smokers, 95%; smoking history, 42 ± 21 pack-years). The analyses were performed in the following groups of patients: with 1 exacerbation in the last 12 months, with more than 1 exacerbation, and without any exacerbation.

Medical history was recorded and physical examination including body weight, height, and waist and hip circumference was conducted. The BMI and waist-to-hip ratio were calculated. The analysis of body composition was performed by bioimpedance (Tanita T5896, TANITA Corporation of America, Inc., Arlington Heights, Illinois, United States). Fat mass, FFM, and muscle mass were expressed as kg/m<sup>2</sup>. Spirometry with bronchial reversibility testing after the administration of salbutamol (400 µg) via a spacer was performed in accordance with the recommendations of the Polish Respiratory Society (Lungtest 1000, MES, Poland).<sup>27</sup> Bodyplethysmography was performed using BodyBox (Medisoftware, Sorinnes, Belgium) and Vmax 6200 Autobox (SensorMedics, Yorba Linda, California, United States). Fasting serum levels of acyl ghrelin and adiponectin were measured by enzyme-linked immunosorbent assays (R&D Systems Quantikine, Minneapolis, Minnesota, United States, and SPIBio Bertin Pharma, Montigny-le Bretonneux, France, respectively).

Statistical analysis was performed by Statistica for Windows (Statsoft Inc. STATISTICA

**TABLE 2** Exacerbation rates in relation to the severity of chronic obstructive pulmonary disease

GOLD stage	Number of patients	Total No. of exacerbations (per patient per year)	No. of exacerbations requiring hospitalization (per patient per year)	P value
I	16	0.97 ± 1.22	0.28 ± 0.36	NS
II	67	0.81 ± 1.04	0.15 ± 0.36	<0.05 <sup>a</sup> <0.001 <sup>b</sup>
III	45	1.03 ± 1.04	0.3 ± 0.36	0.003 <sup>c</sup>
IV	24	1.73 ± 2.05	0.57 ± 0.74	

Data are presented as mean ± standard deviation.

- a** total number of exacerbations, GOLD stage II vs. stage IV  
**b** exacerbations requiring hospitalization, GOLD stage II vs. stage IV  
**c** exacerbations requiring hospitalization, GOLD stage III vs. stage IV

Abbreviations: GOLD – Global Initiative for Chronic Obstructive Lung Disease, NS – nonsignificant

version 10, www.statsoft.com). Data were presented as mean ± standard deviation or median and interquartile range, where appropriate. As the majority of the analyzed variables demonstrated nonnormal distribution, we used the Mann–Whitney test and the Kruskal–Wallis analysis of variance for group comparisons. Correlations were analyzed by the Spearman's rank correlation test. A *P* value of less than 0.05 was considered statistically significant.

**RESULTS** The study group included 16 patients with GOLD stage I COPD, 67 (44.1%) with stage II, 45 (29.6%) with stage III, and 24 (15.8%) with stage IV. The general characteristics of the patients are presented in **TABLE 1**.

Sixty patients (39.5%) did not report any exacerbation in the 12 months preceding the study. In the remaining 92 patients, the exacerbation rates were as follows: 53 patients (34.9%) had only 1 exacerbation and 39 patients (25.7%) had at least 2 exacerbations within the previous year. Thus, the group of patients with less than 2 exacerbations per year consisted of 113 subjects (74.3%): 60 patients without exacerbations and 53 patients with only 1 exacerbation.

The mean number of exacerbations in the group as a whole was 1.04 ± 1.3 per patient per year. The number of exacerbations that required hospitalization was 0.32 ± 0.81 per patient per year. Exacerbation rates in relation to the severity of COPD (GOLD stage) are presented in **TABLE 2**.

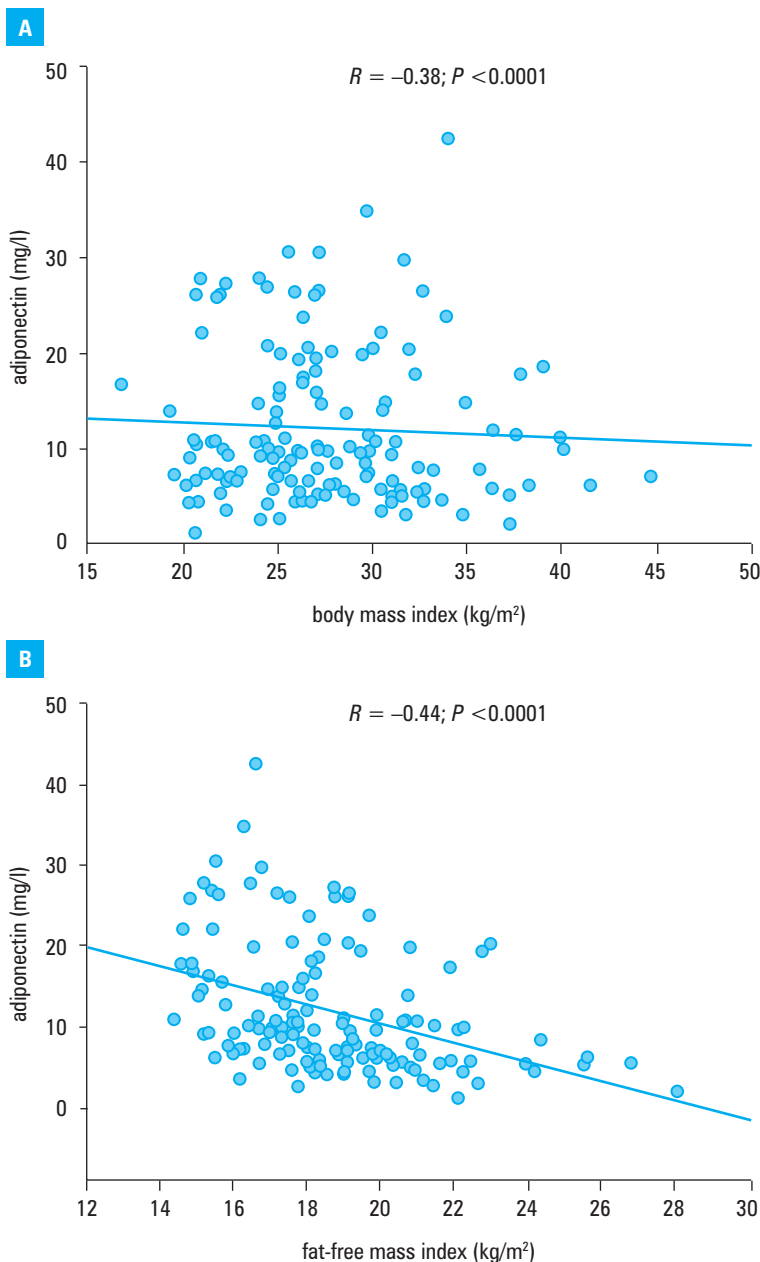
**Comparison of the subgroups with different exacerbation rates** There were no differences in age and BMI between the study subgroups. The sex distribution was similar in the subgroups with 2 exacerbations per year and more and those with fewer than 2 exacerbations per year; however, in general, exacerbations were more common in women than in men with COPD (73.8% vs. 51.6%; *P* = 0.01). Patients with 2 exacerbations and more per year had lower pre- and postbronchodilator FEV<sub>1</sub> than those with a lower exacerbation frequency (prebronchodilator FEV<sub>1</sub>, 41.6 ± 15 % predicted vs. 50.3 ± 16.4 % predicted, *P* = 0.01;

postbronchodilator FEV<sub>1</sub>, 49.3 ± 16.4 % predicted vs. 57.8 ± 18 % predicted, *P* = 0.001). The same trend was noted for forced vital capacity (FVC); however, the difference in the postbronchodilator value was not significant (prebronchodilator FVC, 73.1% ± 20.5% vs. 80.3% ± 16.5%, *P* = 0.003; postbronchodilator FVC, 85.0% ± 18.3% vs. 90.2% ± 17.4%, *P* = nonsignificant [NS]).

Patients with 2 exacerbations and more per year had a higher serum adiponectin concentration than those with a lower exacerbation frequency (14.5 ± 8.6 mg/l vs. 11.2 ± 7.6 mg/l; *P* < 0.05). They also had a higher ghrelin concentration but the difference was not significant (44.0 ± 40.1 pg/ml vs. 32.9 ± 25.9 pg/ml, respectively; *P* = NS). No differences in BMI and body composition between patients with frequent and rare exacerbations were found.

The comparison of the subgroups with any exacerbations and no exacerbations within the last year showed no differences in FEV<sub>1</sub> and FVC; however, patients with any exacerbations had a higher degree of lung hyperinflation (RV/TLC, 139.1 ± 20.8 % predicted vs. 129.9 ± 18.8 % predicted, respectively; *P* = 0.01). Of note, smoking history was less relevant in patients with any exacerbations (38.3 ± 22.2 pack-years vs. 47.9 ± 22.2 pack-years, respectively; *P* < 0.05). Despite a similar BMI, significant differences in body composition between the groups with any and no exacerbations were observed: patients with any exacerbations were characterized by a lower FFM index (18.3 ± 2.5 kg/m<sup>2</sup> vs. 19.3 ± 2.7 kg/m<sup>2</sup>, respectively; *P* < 0.05), lower total body water (36.9 ± 8.1 kg vs. 40.2 ± 8.0 kg, respectively; *P* < 0.05), lower resting metabolic rate (1482.8 ± 301.1 kcal vs. 1616.0 ± 322.5 kcal, respectively; *P* = 0.01), and lower waist-to-hip ratio (0.95 ± 0.1 vs. 0.98 ± 0.01, respectively; *P* < 0.05).

We found some weak but significant correlations between the number of exacerbations and FFM index (*R* = −0.18; *P* < 0.05), muscle mass index (*R* = −0.18; *P* < 0.05), total body water (*R* = −0.18; *P* = 0.03), resting metabolic rate (*R* = −0.17; *P* < 0.05), and serum adiponectin levels (*R* = 0.19; *P* < 0.05) in the whole study group. Adiponectin



**FIGURE 1** Correlation between serum adiponectin levels and body mass index (A) and fat-free mass index (B)

levels significantly correlated with BMI ( $R = -0.38$ ;  $P < 0.001$ ), FFM index ( $R = -0.44$ ;  $P < 0.001$ ) (FIGURE 1A), total body water ( $R = -0.49$ ;  $P < 0.001$ ), muscle mass index ( $R = -0.46$ ;  $P < 0.001$ ), and resting metabolic rate ( $R = -0.51$ ;  $P < 0.001$ ). There were no significant correlations between the ghrelin concentration and body composition.

**DISCUSSION** Frequent exacerbations constitute a specific phenotype of COPD. In the 3-year ECLIPSE study, 23% of the patients did not have any exacerbations, while 12% experienced at least 2 exacerbations of the disease. Among those 12%, more than 60% of the patients had recurrent exacerbations in the subsequent years of follow-up.<sup>3</sup> The rate of exacerbations increased as the severity of COPD increased: from 22% in GOLD stage II to 47% in stage IV. In our study, exacerbations occurred in 25.7% of the patients, and the percentage differed depending on severity: 12.5% of the patients with stage I; 20.9%, with stage II; 26.7%, with stage III; and 45.8%,

with stage IV. Despite a tendency to a higher incidence of exacerbations in more severe stages of the disease, this difference did not reach statistical significance. This may be at least partially explained by the fact that patients do not report all exacerbations.<sup>28-30</sup> The relation between an increased rate of exacerbations and the severity of COPD in our study is supported by the differences in the number of exacerbations between GOLD stages II and IV and the number of exacerbations requiring hospitalizations between stages II and III and stages III and IV. It is noteworthy that an exacerbation frequency of  $0.97 \pm 1.22$  per patient per year in our patients with stage I and  $1.73 \pm 2.05$  per patient per year in those with stage IV was lower than that previously reported.<sup>30,31</sup> Patients with a high exacerbation rate had a significantly lower FEV<sub>1</sub> ( $49.3 \pm 16.4$  % predicted vs.  $57.8 \pm 18.0$  % predicted). Therefore, one would expect them to have altered body composition as well as low BMI and FFM index. The mean BMI in the whole study group of  $27.6 \pm 5.1$  kg/m<sup>2</sup> indicates that the patients were overweight. Patients with a higher exacerbation rate had a lower BMI, FFM index, and muscle mass index but the difference was not significant. Moreover, the comparison of patients without any exacerbations and those with at least 1 exacerbation showed that the latter had lower muscle mass, lower total body water (which might have been connected with higher water loss during breathing), and lower resting metabolic rate. In our opinion, the lower metabolic rate is probably connected to the lower muscle mass. We also observed a negative correlation between the number of exacerbations and FFM index, muscle mass index, total body water, and resting metabolic rate, which seems to confirm the association between exacerbations and body composition in patients with COPD.

Studies in patients hospitalized because of COPD exacerbation reported the incidence of cachexia to be as high as 38%.<sup>32</sup> Patients with a lower BMI had a greater lung function decline, higher degree of hyperinflation, and higher serum C-reactive protein levels.<sup>33</sup> In ambulatory patients with exacerbations, no correlations between BMI and exacerbation severity and between the administered treatment and treatment outcome were noted.<sup>34</sup>

COPD exacerbations are associated with an increase in the levels of inflammatory cytokines including adiponectin. Higher adiponectin levels in patients with COPD compared with healthy controls indicate a potential role of this cytokine in systemic inflammation in COPD. The serum adiponectin concentration increases during exacerbations, and its elevated levels are observed even 8 weeks after treatment.<sup>35</sup> Behnes et al.<sup>36</sup> suggested that adiponectin might play a role in the pathogenesis of systemic inflammatory response during sepsis.<sup>36</sup> An experimental study on cardiomyocytes from neonatal rats showed that hypoxia-reoxygenation-provoked cell death can be attenuated by pretreatment with



adiponectin, and this effect can be partially explained by the inhibition of endoplasmic reticulum stress response.<sup>37</sup> In patients with COPD, the anti-inflammatory effect of adiponectin is more marked in severe and very severe stages as well as during exacerbations.<sup>38,39</sup> In our study, the serum adiponectin concentration was significantly higher in patients with frequent exacerbations, which seems to confirm its role in systemic inflammation. Thus, evaluation of serum adiponectin may be helpful in the identification of patients at higher risk of exacerbation.

In our study, we also analyzed ghrelin. Ghrelin concentrations are the highest in the state of hunger and in diseases leading to cachexia. Other factors, including physical activity and night rest, also have an impact on this hormone. Itoh et al.<sup>26</sup> reported a negative correlation between ghrelin and BMI and FFM and a positive correlation between serum TNF- $\alpha$  and norepinephrine in patients with COPD. Moreover, the ghrelin concentration was significantly higher in patients with GOLD stage IV COPD than in controls.<sup>26</sup> Other authors also demonstrated a higher ghrelin concentration in patients with COPD than in controls; furthermore, there was a significant difference in the ghrelin concentration in patients who were underweight.<sup>40</sup> We might thus speculate that the ghrelin concentration should even be higher in COPD patients with frequent exacerbations who have increased catabolism and continuous decline in lung function. In our study, we found a higher ghrelin concentration in patients with frequent exacerbations, but the difference was not significant. There have been attempts to treat patients with COPD and cachexia with ghrelin,<sup>41,42</sup> and the results seem quite encouraging. The anti-inflammatory effect of ghrelin was also the subject of studies in the experimental model of colitis,<sup>43</sup> hepatic disorders,<sup>44</sup> sepsis,<sup>45</sup> and rheumatoid arthritis.<sup>46</sup>

In conclusion, our study showed that exacerbations affect body composition. There is a negative correlation between the number of exacerbations and FFM, total body water, muscle mass, and resting metabolic rate. In patients with frequent exacerbations, the serum adiponectin concentration was statistically higher in comparison with patients who had fewer than 2 exacerbations per year. This may confirm the role of adiponectin in COPD-related systemic inflammation, which increases its severity during acute exacerbations of the disease. Assessment of the body composition and systemic inflammation should be part of the routine management of patients with COPD.

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# Wpływ częstości zaostrzeń na skład ciała oraz stężenie greliny i adiponektyny u chorych na przewlekłą obturacyjną chorobę płuc

Renata Rubinsztajn, Tadeusz Przybyłowski, Marta Maskey-Warzęchowska, Krzysztof Karwat, Magdalena Paplińska-Goryca, Patrycja Nejman-Gryz, Ryszarda Chazan

Katedra i Klinika Chorób Wewnętrznych, Pneumologii i Alergologii, Warszawski Uniwersytet Medyczny, Warszawa

## SŁOWA KLUCZOWE

adiponektyna, grelina, przewlekła obturacyjna choroba płuc, skład ciała, zaostrzenia

## STRESZCZENIE

**WPROWADZENIE** Zaostrzenia wpływają na przebieg przewlekłej obturacyjnej choroby płuc (POChP).

**CELE** Celem pracy była ocena wpływu częstości zaostrzeń POChP na skład ciała i systemowe zapalenie, oceniane za pomocą pomiaru stężeń adiponektyny i greliny w surowicy.

**PACJENCI I METODY** Grupa badana składała się ze 152 chorych na POChP. Skład ciała oceniany był metodą bioimpedancji. Stężenie adiponektyny i greliny w surowicy oceniano na czczo za pomocą testu ELISA.

**WYNIKI** Spośród 152 badanych pacjentów, 60 osób nie zgłaszało zaostrzeń w czasie poprzedzających 12 miesięcy, 53 miało jedno zaostrzenie, a 39 więcej niż jedno. Średnia liczba zaostrzeń w całej grupie w przeliczeniu na pacjenta/na rok wynosiła  $1,04 \pm 1,3$  i rosła wraz ze stopniem obturacji. Pacjenci, u których występowały zaostrzenia w porównaniu z pacjentami bez zaostrzeń mieli mniejszy wskaźnik beztłuszczowej masy ciała (*fat-free mass* – FFM), mniejszą całkowitą masę wody oraz niższą podstawową przemianę materii (odpowiednio,  $18,3 \pm 2,5$  kg/m<sup>2</sup> vs  $19,3 \pm 2,7$  kg/m<sup>2</sup>;  $36,9 \pm 8,1$  kg vs  $40,2 \pm 8,0$  kg;  $1482,8 \pm 301,1$  kcal vs  $1616,0 \pm 322,0$  kcal). Stężenie adiponektyny było wyższe u chorych z więcej niż jednym zaostrzeniem niż u pacjentów z jednym zaostrzeniem lub bez nich ( $14,5 \pm 8,6$  vs  $11,2 \pm 7,6$  mg/l,  $p < 0,05$ ). W całej grupie obserwowano istotne ujemne korelacje między liczbą zaostrzeń a wskaźnikiem masy mięśniowej, wskaźnikiem FFM, całkowitą masą wody, podstawową przemianą materii i stężeniem adiponektyny.

**WNIOSKI** Zaostrzenia wpływają na skład ciała u chorych na POChP. U pacjentów z częstymi zaostrzeniami stwierdza się bardziej nasilone ogólnoustrojowe zapalenie. Badanie składu ciała i systemowego zapalenia powinno być rutynowym postępowaniem w ocenie chorego na POChP.

Adres do korespondencji:  
dr n. med. Renata Rubinsztajn,  
Katedra i Klinika Chorób  
Wewnętrznych, Pneumologii  
i Alergologii, Warszawski Uniwersytet  
Medyczny, ul. Banacha 1a, 02-097  
Warszawa, tel.: 22-599-25-62,  
fax: 22-599-15-60, e-mail:  
rubinsztajn@wum.edu.pl  
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