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Dynamics of body composition in male patients during chronic obstructive pulmonary disease (COPD) development

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Abstract

Introduction: The various distribution of fat mass (FM) and lean mass (LM) during COPD development is not yet researched.

Material and methods: 82 male patients (40–67 years) with acute exacerbation of COPD and 19 comparable healthy males (the control group) were examined by dual-energy X-ray absorptiometry. The patients were divided into 3 groups according to COPD severity: 1st — 19 (GOLD I stage); 2nd — 43 (GOLD II) and 3rd — 20 (GOLD III).

Results: The patients of 3rd group had lower indices of FM, LM, bone mineral component (BMC) vs. the control and 1st, 2nd groups. A significant increase in FM share was noted in android and gynoid regions, trunk, legs and arms in 2nd groups vs. the control with the decline of these parameters in the 3rd group below the control level. A greater proportion of FM in 1st and 2nd groups was distributed in android and trunk regions vs. the control. TNF-α and leptin levels were significantly increased by 12%, 15% 17% and by 18%, 75%, 79% respectively in 1st, 2nd, 3rd groups vs. the control, while free testosterone level was lower in these groups vs. the control (by 28%, 30% and 47% respectively; $p < 0,05$).

Conclusions: Body mass index (BMI) was within the control range in mild-moderate COPD patients in spite of LM, FM and BMC changes. The level of LM and BMC was decreased during COPD progression, while FM was increased in mild-moderate COPD and then it was decreased in severe COPD.

Key words: COPD, body composition, lean mass, fat mass, leptin

Introduction

The picture of systemic manifestations of COPD is not complete without the evaluation of patient's body composition (BC) parameters [1]. Repeated COPD exacerbations are accompanied by an impaired energy balance that has a negative consequence on patient's BC [2]. In turn, BC abnormalities may be a significant contributor to the low-grade systemic inflammation and may indirectly stimulate stimulate COPD progression. Thus, BMI loss (from 10% in mild to 50% in severe COPD) has an unfavorable impact on disease development due to decreased skeletal and respiratory muscle strength (with subsequent lower exercise capacity), resistance to infection as well as the higher frequencies of exacerbations [3–5]. The reasons for progressive loss of tissue mass and BMI include [6, 7]: increased load on the respiratory muscles (enhanced by 15% breathing work and its energy costs at rest and during exercise), a high level of proinflammatory cytokines and basic metabolism (increased by 25% vs. the healthy persons), to a smaller degree — expressed hypoxia and tissue oxygen debt, oxidative stress, the use of long acting β_2-agonists and teophylline, smoking, hypoandrogenism, impaired regulation of hormones that reduces food intake, disorders of gastro-intestinal tract and protein metabolism (with increased protein degeneration).

BMI does not give the complete information about BC changes in COPD patients. Thus, loss of LM is not always accompanied by a loss of BMI and may occur in the case of normal patient's BMI level against the background of FM component excess [8]. Only 17% of the patients with chronic respiratory failure had a BMI < 20 kg/m^2 as well as only 5% of mild COPD patients had a BMI < 18.5 kg/m^2 vs. 30% of patients with severe COPD [9, 10]. Three malnutrition profiles can be identified in advanced COPD [11]: underweight patients with concomitant depletion of body LM (60%) or with a normal LM (20%) and the patients of normal body weight with depletion of LM. A shift in BC structure towards a relative abundance of FM and reduced LM during COPD exacerbation (due to increased: hypoxemia, sympathetic tone, using β_2-agonists and systemic corticoids — sCS) was revealed. LM loss (significant problem in 1/3 of moderate to severe COPD patients) may adversely affect the peripheral skeletal and respiratory muscles (development of their weakness) and respiratory function [5, 12].

The metabolic syndrome is observed in up to 53% of COPD patients in GOLD grade 2 [13] and it was associated with higher levels of the systemic inflammation markers and frequency of exacerbations [14]. Overweight and obesity were often observed (in 1/3 and 1/5 of cases respectively) in COPD patients [15] and they did not worsen the respiratory function and symptoms in many cases of mild-to-moderate COPD as well as they had even a protective effect in relation to mortality [10]. But severe obesity favors the disorders of carbohydrate metabolism, pulmonary dysfunction (reduced compliance of the chest wall, lung volume and impaired airway function) and appearance of cardiovascular pathology [14, 16].

Hormonal changes are also closely linked to disturbed BC. Gradually decreasing levels of circulated androgens in males with age is related to increased levels of total and abdominal body FM [17]. A key role in the relationship between lung pathology and adipose tissue play adipokines (APN) — leptin and adiponektin, for which important source is an abdominal subcutaneous and visceral FM. APN significantly influence the inflammatory process, immune response, lipid metabolism and regulation of energy balance [18]. Pro-inflammatory effects of APN may dominate under the certain conditions. Thus, visceral obesity and visceral FM in overweight COPD patients may be associated with a high level of proinflammatory cytokines (TNF-α) and leptin as well as have a greater inflammatory ef-

fect [19, 20]. It was shown, that sCS and TNF-α induce increased leptin level in normal subjects, besides TNF-α may decrease all the components of BC. The increased levels of TNF-α and leptin in blood circulation favor decreased appetite and food intake in COPD patients, mostly with severe hypoxia, which induces increased leptin expression and intensified fat metabolism in COPD [12, 19]. Leptin resistance is common in overweight COPD patients and results in lung hypoventilation [21]. Systemic leptin concentration may be disproportionately higher in COPD, reflecting a greater airway inflammation and disease severity [22].

The purpose of this study was to evaluate distribution of BC as well as the relationship between the latter and TNF-α, leptin and free testosterone levels in relation to COPD development.

Material and methods

The study was undertaken at the Pulmonology Department of the 10th Minsk Clinical Hospital in the years 2009–2013. All participants gave their written informed consent. The study protocol was approved by the Human Studies Committee on Research Ethics at the Belarusian State Medical University. The inclusion criteria for the study were the following: males aged 40–69 years with different COPD grades and FEV$_1$ increase < 15% in bronchodilator test. Exclusion criteria included substantial uncontrolled co-morbidities that may affect nutritional status (uncontrolled heart failure and diabetes, chronic renal failure, neoplasms). The study group consisted of 82 COPD male patients with acute exacerbation who were divided into three groups according to the severity of disease (mild — COPD$_1$, moderate — COPD$_2$ and severe — COPD$_3$) using post-bronchodilator FEV$_1$ and clinical symptoms. The diagnosis of COPD and its severity was based on the GOLD guidelines published in 2011. The intensity of dyspnea was defined according to a modified MRC questionnaire. The clinical investigation of these patients on admission included: self-reported co-morbidities, smoking status and previous treatment, spirometry (using a portable spirometer "Spirovit SP-10" of "Shiller"), physical examination, day-time pulseoximetry, chest radiography and blood laboratory analyses. The patients (mostly COPD$_{2-3}$) were treated with a combination of inhaled long-acting anticholinergic (or β_2-agonists) plus inhaled and sometimes sCS (5 days of dexametasone intravenously, 4 mg a day) as well as broad spectrum antibiotics if there was clinical evidence of Type 1 or 2 exacerbation according

to Anthonisen criteria. The control group consisted of 19 healthy male persons of comparable age, smoking status, BMI and without history of chronic diseases.

TNF-α, leptin and free testosterone levels were detected by immynoenzyme (ELISA) methods. Distribution of BC parameters was measured using dual-energy X-ray absorptiometry (DXA) ("Prodigy Lunar", General Electric Medical Systems, USA). We calculated: FM index (FMI = FM/height^2), LM index (LMI = LM/height^2) that reflects non-fat and non-bone soft tissue content, skeletal muscle index (SMI = fat-free mass of arms + legs/height^2) and bone mineral component index (BMCI = bone mineral component of body/height^2).

The statistical analysis was performed using Statistica 8.0 software (2007, Statsoft Inc., USA). The preliminary analysis of the variables under consideration was a Shapiro-Wilk test of correspondence to normal distribution. The results of the analysis were shown as median and interquartile range (25–75%) because all the parameters differed from normal distribution. The comparison of non-parametric parameters in two independent groups was carried out using a Mann-Whitney test, while in three or more independent groups it was performed using the Kruskal-Wallis rank sum test. Fisher's exact test was used to detect statistically significant differences between independent groups according to the frequency characteristic of the investigated parameter. Spearman's rank correlation coefficient (rs) was used to describe the relationship between the two quantitative variables that differed from normal distribution. The level of statistical significance was set at $p < 0.05$.

Results

As shown in Table 1, the control group did not differ from COPD$_1$ patients in terms of median age, the percent of patients under 60 years, BMI and intensity of smoking. COPD$_1$ patients had only slightly decreased ventilation parameters compared with the controls. A progressive

Table 1. Baseline characteristics of the control group and COPD patients groups according to different degrees of airflow limitation severity (GOLD spirometry level, 2011) on admission (Me; 25, 75)

Parameters	Control n = 19	COPD$_1$ n = 19	COPD$_2$ n = 43	COPD$_3$ n = 20
Median age (years): < 60/> 60 years (%)	52 (47; 55) 70/30	55 (51; 58) 79/21	57 (53; 60)* 66/34	62 (56; 67)*, **, *** 50/50
Body mass index [kg/m^2]	28.6 (27.5; 29.2)	29.0 (27; 32.5)	30,3* (26.4; 32.2)	22.9*, **, *** (20.7; 27.7)
Present smokers (%)	62	68	77	96*, **
Smoking history, index packs/years	18 (10; 30)	20 (12; 30)	21 (12; 30)	30*, *** (25; 40)
Median duration of COPD (years)	–	3 (1; 6)	9 (4; 12)	13**, *** (10; 19)
FVC (% pred.)	100 (98; 112)	86 (75; 90)*	57 (48; 66)*, **	39 (32; 46)*, **, ***
FEV$_1$ (% pred)	86 (77; 92)	82 (78; 87)*	56 (50; 65)*, **	33 (22; 44)*, **, ***
FEV$_1$/FVC (%)	95 (89; 104)	70 (62; 72)*	67 (57; 75)*, **	51 (39; 58)*, **, ***
SatO$_2$ (%)	97 (96; 97)	97 (96; 97)	96 (95; 98)	93 (90; 95)*, **, ***
C-reactive protein [mg/dL]	0.3 (0.1; 1.8)	0.3 (0.1; 1.3)	4.3*, ** (1.9; 8.3)	3.3*, ** (1.3; 5.3)
Home treatment: corticoids inhaled/intermittently oral (%);	–	–	35/2	43/15***
with inhaled long acting anticholinergic (%);	–	–	22	7
with inhaled long acting β_2-agonists			1	17***

*p < 0.05 vs. the control group; **p < 0.05 vs. COPD$_1$; ***p < 0.05 vs. COPD$_2$ group; Me — median, 25–75% — interquartile range

Table 2. Distribution of COPD patients with different severity according to the degree of BMI and LMI (%)

BMI (kg/m^2)	COPD1		COPD2		COPD3	
	LMI (kg/m^2)					
	< 16.6	> 16.6	< 16.6	> 16.6	< 16.6	> 16.6
Deficiency BMI < 18.5	0	0	0	0	5	0
Normal BMI ≥ 18.5–24.9	0	10	2	17	30***	26
Overweight BMI 25.0–29.9	0	50	3	22**	0	17**
Obesity BMI > 30.0	0	40	0	56	0	22**, ***

The designations are the same as in the Table 1
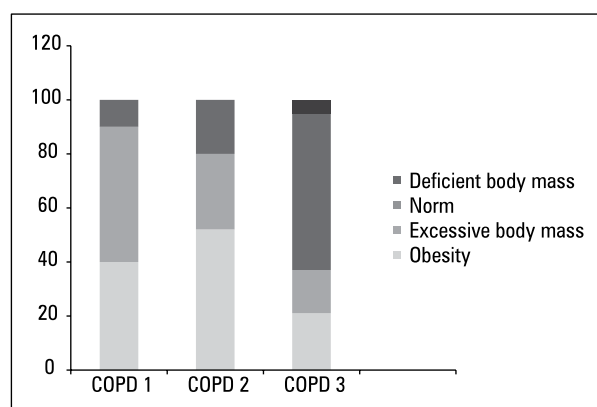
Figure 1. Distribution of COPD patients according to their BMI

decrease in ventilation parameters was noted as the disease became worse: FVC dropped from 86% in COPD$_1$ to 39% in COPD$_3$; FEV$_1$ and blood oxygen saturation dropped from 82% to 33% and from 97% to 93% in COPD$_1$ and COPD$_3$ respectively. A significant increase in the number of exacerbations for the past year was found in COPD$_3$ compared with COPD$_{1,2}$. COPD$_3$ patients had a significantly higher median age, disease duration, MRC breathlessness index and the number of current smokers than the control group and COPD$_{1,2}$ patients, whereas mean BMI of COPD$_3$ group was significantly lower than in the latter.

As seen from Figure 1, the part of BMI within the normal range was increased (from 10% in COPD$_1$ to 58% in COPD$_3$) in the course of COPD development, while overweight and obesity were naturally decreased as COPD became worse. Thus, overweight was detected in 50%, 28% and 16% of COPD$_{1,2,3}$ patients respectively.

We revealed that the number of patients with decreased LMI level was higher among the patients with normal BMI as the disease progressed (Table 2). We did not detect these patients in COPD$_1$ group, whereas 1 and 6 such patients were revealed in COPD$_{2,3}$ groups respectively.

Meanwhile decreasing LMI was detected in 5% of COPD$_3$ patients with low BMI and in 30% of these patients against the background of normal values of BMI. The latter was decreased only in severe COPD, but it was in the normal range (or increased to some extent) in most of the observed patients. LMI, BMCI and SMI did not differ in COPD$_1$ from the control (Table 3), whereas in COPD$_3$ these parameters (including FMI) were significantly decreased compared with the control and COPD$_{1,2}$.

More changes of FM were detected in the trunk and android regions and fewer — in legs and arms. The changes of FM distribution in different body regions had the phased character. There was no difference of FM distribution between COPD$_1$ group and the control. But we revealed significant increase of FM share in arms, legs, trunk, android and gynoid regions in COPD$_2$ group (by 30%, 31%, 24%, 18% and 19% respectively vs. the control). Then, in COPD$_3$ group these parameters were decreased to the control values.

Deposition of FM in definite body regions (particularly in trunk and android zone) in COPD patients may be associated with the certain co-morbidities, such as arterial hypertension (AH). Therefore we additionally assessed the influence of BC distribution upon the presence of AH. Thus, we detected an increased number of COPD patients with concomitant AH: 41%, 81% and 74% in COPD$_{1,2,3}$ groups respectively.

Table 3. Distribution of FMI, LMI, BMCI and SMI levels (kg/^{2}) among males according to COPD severity (Me; 25%,75%)

Parameter	Control n = 19	COPD$_1$ n = 19	COPD$_2$ n = 43	COPD$_3$ n = 20
FMI	7.2 (6.2; 7.7)	8.3* (6.2; 10.1)	9.7* (6.8; 11.0)	4.7*, **, *** (3.1; 9.3)
LMI	20.3 (19.9; 22.0)	20.8 (20.1; 21.4)	20.1** (18.8; 21.2)	17.7*, **, *** (16.5; 18.9)
BMCI	1.06 (0.99; 1.12)	1.04 (0.97; 1.08)	1.01 (0.92; 1.08)	0.89*, **, *** (0.83; 0.94)
SMI	9.34 (8.76; 9.70)	9.41 (8.81; 9.74)	8.92*, ** (8.05; 9.51)	7.61*, **, *** (7.13; 8.38)

The designations are the same as in the previous Table 1

FMI — fat mass index, LMI — lean mass index, BMCI — bone mineral component index, SMI — skeletal muscle index

There were significant differences between COPD$_1$ and COPD$_{2, 3}$ groups according to the share of patients with concomitant AH (χ^2 = 12.52 and χ^2 = 3.68 respectively). COPD isolated group did not differ from COPD plus AH group according to age, disease severity and smoking status, while BMI was higher in the latter (30 vs. 25.3 kg/m^2; p < 0.05). A similar picture was observed concerning the levels of triglycerides (1.59 and 1.16 μmol/L respectively; p < 0.05) and glucose (5.7 and 5.2 μmol/L respectively; p < 0.05). We revealed (Table 4) significant difference of all BC parameters in COPD patients with concomitant AH compared with pure COPD patients. The central type of FM deposition (with excess FM accumulation in android region) prevailed in COPD male patients with concomitant AH.

The leptin and TNF-α level was increased during COPD progression by 18%, 75%, 79% and by 21%, 52% and 64% respectively in COPD$_{1, 2, 3}$ groups compared with the control (p < 0.05 for COPD$_{2, 3}$). The level of free testosterone was variable, depending on the severity of the disease. It was the highest in mild COPD (COPD$_1$) — 7.6 pg/mL and significantly lower in severe COPD (COPD$_3$) — 5.2 pg/mL.

Discussion

BC abnormalities can modulate functional limitation in COPD independent of airflow obstruction degree. We detected median BMI decrease in severe COPD patients against the background of increased patients share with normal BMI during COPD development. Weight loss may involve all tissue compartments, although loss of skeletal muscle may be particularly important in COPD due to wasting of respiratory muscles with following loss of their power and endurance [23].

Table 4. Distribution of body FM in different body regions and their relations in COPD patients with/without concomitant AH (Me; 25%,75%)

Region	COPD isolated n = 26	COPD with AH n = 59
Arms (%)	18.7 (13.9; 24.6)	24.9* (20.0; 29.0)
Legs (%)	21.5 (16.6; 25.9)	26.1* (22.5; 31.0)
Trunk (%)	28.8 (16.9; 35.0)	36.2* (32.1; 39.2)
Android (%)	31.4 (22.3; 40.6)	41.4* (36.2; 45.2)
Gynoid (%)	26.8 (21.1; 31.9)	30.2 (26.8; 34.4)
Total level of FM (%)	25.8 (17.3; 30.7)	31.1* (26.9; 34.5)
Total level of LM (%)	74.2 (69.3; 82.7)	69.3* (65.5; 72.5)
Android/gynoid regions	1.12 (1.04; 1.27)	1.28* (1.18; 1.42)
Trunk/total FM	0.56 (0.54; 0.60)	0.61* (0.58; 0.65)
Legs/total FM	0.30 (0.26; 0.33)	0.26* (0.24; 0.29)
Arms+legs/trunk	0.71 (0.60; 0.80)	0.59* (0.51; 0.67)

The designations are the same as in the previous Table 1

* p < 0,05 between these groups;

BMI did not give the complete information about BC changes in our patients because BMI remained within the normal range (or slightly increased) in most of them. Probably, overweight can reduce the cost of breathing in COPD with better mechanical efficiency of respiratory muscle. Also advanced COPD may accelerate the impact of BC structural changes that occur with normal ageing [24].

The level of FMI was increased in $COPD_{1,2}$ (could mask the loss of muscular and bone tissues) and then decreased in $COPD_3$ group. This depletion of FMI, LMI, BMCI and SMI in severe COPD was largely related to the increased level of tissue hypoxia, pulmonary systemic inflammation (through inflammatory cytokines), intensive smoking and catabolic metabolism. Thus, the "frequent exacerbators" (mostly patients with severe COPD) had lower levels of these BC parameters. This relationship was strengthen by the finding of increased circulating levels of CRP and TNF-α in severe COPD patients who might have a longer exposure to inflammation before entering the study. Probably, faster decline in FM, LM, BMCI and SMI in severe COPD patients with low BMI were significantly related to older age and lower FEV_1. We can suppose that decrease of BMI, FMI, LMI and SMI in severe COPD patients is an adaptation to deficient intake of energy and substrates as well as it has reduces airflow limitation by improving peripheral airway function, because a smaller airways are constrained to a greater extent by visceral fat than larger airways. Our results suggest that disorders of BC distribution occur before being underweight. Thus, asymptomatic loss of skeletal muscle may occur in up to 25% of COPD patients with normal BMI [25].

Depletion of muscle mass (which may be roughtly estimated by LMI level) can significantly affect peak oxygen consumption and ventilatory response in severe COPD patients. LM or SMI (as surrogate markers) are still more suitable in detecting muscular wasting than BMI due to an unapparent and asymptomatic loss of skeletal mass [26]. Probably, in COPD the impairment first develops in the respiratory muscles strength (that is affected more, than peripheral muscle force) preceding the obvious changes of pulmonary function.

We cannot detect characteristic changes of LMI, SMI and BMCI in mild-to-moderate COPD. Probably, DXA method assessed not entirely LM or SMI but included smaller and highly metabolically active ectopic FM within and around the skeletal muscle and viscera. Therefore, our findings in respect to BC distribution in overweight COPD men could be to a certain extent explained by the excess of ectopic FM. The loss of muscle mass was aggravated by infiltration of muscles by fat that leads to decreased muscle strength and their inadequate functioning. It was shown, that intramuscular fat infiltration was more pronounced in moderate-to severe COPD male patients [27]. There was a positive correlation between LMI and SMI ($\rho = 0.87$, p < 0.05) in entire COPD group, showing that they are interrelated and reflected the decrease in skeletal muscles component.

The short courses treatment with sCS was used only in one moderate COPD patient and in three severe COPD patients. Therefore, we do not think that our findings can be partially explained by the effect of sCS on the repartition of FM and LM.

Segmental BC assessment more often detected central types of obesity (increase of FM ratio in the trunk region to total FM and decreased level of legs FM to total FM) than peripheral type in our COPD patients. A various distributions of FM may have varying mechanical and inflammatory properties as well as consequent COPD-related effects. Thus, trunk FM (collection of fat compartments with varying metabolic activity) may have a greater mechanical impact on diaphragmatic movement, chest wall recoil and FVC than FM of arms or legs [28].

The absence of significant differences between the control and mild COPD according to the distribution of FM in arms, legs and trunk as well as the presence of these differences in moderate COPD could be due to the fact that skeletal muscle in different body regions may have different metabolic and inflammatory effects in advanced stage of disease. Probably, the location of smaller ectopic fat deposits become more important in advanced COPD (due to higher inflammatory status) than larger size of fat deposits [29].

We detected a direct effect of disturbed BC on lung function. There were a significant correlations between LMI, BMCI and FEV_1, FVC ($\rho = 0.34, 0.39$ and $\rho = 0.34, 0.32$ respectively) as well as dyspnea severity ($\rho = -0.44$ and -0.38 respectively). These correlations indicate that decreased muscular and bone tissue components of COPD patient's BC were combined with the disorders of lung function and lowered tolerance to physical activity. BMCI had a significant correlation with SpO_2 and MRC score ($\rho = 0.46$ and $\rho = -0.36$ respectively). These data emphasize a negative influence of severe hypoxia on muscular and bone tissue components of BC in COPD patients. Our study revealed increased concentrations of leptin and TNF-α against the background of free testosterone level decrease during COPD development. Similar changes of leptin and TNF-α levels in general COPD group were noted ($\rho = 0.32$, p < 0.05, n = 82). They may be due to the production of these factors by fat tissue. Additionally, we detected a significant correlation

between free testosterone, leptin level and FMI ($\rho = -0.38$, 0.33 respectively), indicating that low free testosterone level was associated with increased body FM in mild-to-moderate COPD male patients [17, 30]. The presence of positive correlation between FMI and leptin level could be explained by the association of intramuscular fat with high leptin concentrations and increased expression of TNF-α.

Conclusions

BMI was within the normal range (or was even increased) in many of mild-to moderate COPD male patients and did not give a complete information about BC changes. The levels of FMI, LMI, BMCI and SMI were decreased only in severe COPD group, while FMI was increased in mild-to-moderate COPD. Severe COPD was associated with decreased share of FM in the arms, legs, trunk as well as in android and gynoid regions.

Our findings suggest a likely multifactorial basis for BC abnormalities in male COPD patients. Initially (mild-to-moderate COPD) BMI and BC parameters were within the normal range. Later, as COPD progresses, significant changes in BC were noted. These findings showed that the assessment of BC may be useful clinically for evaluation of COPD patients.

Conflict of interest

The authors declare no conflict of interest.

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