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Metabolic syndrome in patients with COPD: Causes and pathophysiological consequences

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ABSTRACT

Background: Decreased physical activity significantly increases the probability of prevalent metabolic syndrome (MetS) with substantial impact on the expected course of COPD. *Objective:* Our research aims to assess the metabolic consequences of chronic obstructive pulmonary disease (COPD) and evaluate the prevalence of MetS and its interrelations with age, sex, comorbidities, drug intake, degree of decreased lung function, nutritional status, physical activity and quality of life. *Methods:* A cross-sectional study was performed on a random sample ($n = 401$) at the Department of Pulmonary Rehabilitation of the National Koranyi Institute of Pulmonology from March 1, 2019 to March 1, 2020 in Budapest, Hungary. Anthropometric and respiratory function tests and laboratory parameters of all patients were registered. *Results:* MetS occurred in 59.1% of COPD patients with significant gender difference (male: 49.7% female: 67.6%). Concerning BMI, the prevalence of MetS was higher with BMI≥25 kg m^{-2} ($P < 0.0001$). Patients with this syndrome had significantly worse FEV_1%pred (43 (30–56) vs. 47 (36–61); $P = 0.028$), lower quality of life (CAT: 26 (21–32) vs. 24.5 (19–29); $P = 0.049$) and significantly more frequent exacerbations (2 (1–3) vs.1

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(0–2); $P < 0.05$), than patients without MetS. The prevalence of comorbidities were higher in overweight/obese patients (BMI> 25 kg m^{-2}). *Conclusions:* In COPD patients MetS negatively affect respiratory function and quality of life and promotes exacerbations of the disease. MetS is related to nutritional status and the level of systemic inflammation in COPD patients.

KEYWORDS

chronic obstructive pulmonary disease, metabolic syndrome, prevalence, inflammation, exacerbations, quality of life

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that causes obstructed airflow limitation from the lungs. COPD is currently the third leading cause of death worldwide [1]. In Hungary, about one fifth of smokers suffer from COPD, which is approximately 500,000 people, but most of them seek medical attention late [2]. In Organisation for Economic Co-operation and Development (OECD) countries, this chronic lung disease affects over 5–8% of the population, and its prevalence is unfortunately increasing rapidly year by year [1, 2]. In Hungary, 5–6,000 new cases are registered every year, one third of whom suffer from chronic respiratory failure [2].

The underlying cause of COPD is the inflammatory response to inhaled particles (eg. cigarette smoke, air pollution) which have a wide range of destructive consequences [3]. In that regard it is important that 31% of males and 23% of females in Hungary smoke regularly [4]. COPD is also a systemic disease, which has important manifestations beyond the lungs, including skeletal muscle atrophy and dysfunction, an increased risk of developing cardiovascular diseases, osteoporosis, anxiety and depression, anemia other chronic diseases [3]. The systemic effects of COPD are mediated by low-grade, chronic systemic inflammation [1–4].

The metabolic syndrome (MetS) is a cluster of cardiometabolic conditions frequently found among COPD patients (Table 1) [5–10]. Metabolic syndrome is closely linked to overweight or obesity, physical inactivity and insulin resistance. Recent observations indicate that obese COPD patients show higher prevalence of MetS compared to the healthy group of similar age and BMI [10, 11]. In affected patients MetS exacerbates progression of COPD by promoting inflammation [11]. Obesity rates have continued to surge in Hungary in the past decade, and recent data findicate that approximately 64 percent of the total adult population is overweight or obese [12]. However, the prevalence of MetS in COPD patients in Hungary and its effect of their general health and quality of life has not been documented.

The aim of our study was to assess the prevalence of MetS in Hungarian COPD patients and its interrelationship with age, sex, comorbidities, drug intake, degree of decreased lung function, nutritional status, physical activity, exacerbation of the disease in the previous year and quality of life. As direct indices of insulin resistance in routine clinical practice are usually cannot be readily measured, various simplified diagnostic criteria for MetS have been developed over the past 2 decades. In our study, we used the diagnostic criteria for MetS developed by the International Diabetes Federation (IDF) [13].

METHODS

Study design and target population

Data collection was performed with volunteer participants, anonymously, using self-completed paper-based questionnaires between 1st March, 2019 and 1st March, 2020 among patients in the Department of Pulmonary Rehabilitation of the National Korányi Institute for Pulmonology, Budapest, Hungary. The study involved 401 COPD patients over 40 years of age in a pulmonary rehabilitation ward. No one refused to take part in the study. Participant recruitment was prematurely discontinued due to the COVID-19 pandemic, which resulted in strict lockdown measures in Hungary [14, 15]. Prior to completing the questionnaire, patients received detailed information about the purpose and time of the survey, anonymous and aggregated data processing, and the essence of the research. The inclusion criteria were: age ≥40 years and diagnosis of COPD (post-bronchodilation of $FEV_1/FVC<70\%$) [16]. Exclusion criteria included acute exacerbation, chronic oxygen therapy (resting oxygen saturation less than 89%), history of asthma, lung surgery or severe comorbidities such as severe heart failure or severe liver or kidney failure; acute coronary syndrome or acute cerebrovascular event. The study was approved by the Regional Institutional Scientific Research Ethics Committee of Semmelweis University (licence number: TUKEB 44402-2/2018/EKU) and complies with the Declaration of Helsinki. Participants in the research did not receive any financial, any remuneration or any other allowances.

Assessment of physiological parameters and measurements

We measured the post-bronchodilator FEV_1 (forced expiratory volume in the first second) in each patient and registered all estimated data in percentage. Patients were classified in GOLD A-D stages according to the current and future risk parameters, like spirometric values, relevant symptoms and exacerbation rate [16]. COPD exacerbation was defined as a significant change of the patient's initial symptoms (dyspnea, cough, sputum production), which is an acute event at a level exceeding the daily variability of symptoms, leading to a change in therapy [16].

Quality of life examination

We used the COPD Assessment Test (CAT test) to assess quality of life [17]. The patients responded to eight questions, scoring the symptoms from 0 to 5, where 0 indicates healthy condition, while 5 points indicate severe symptoms. Cough, the amount of sputum, hyperinflation, the load-bearing capacity when climbing stairs, and the level of energy were evaluated subjectively, as well as whether the patients dare to leave home, or whether their illness affects their sleep. Questionnaires were completed by the participants under the coordinators' supervision in the Institute. Additional data were collected using a self-designed questionnaire assessing patients' education, smoking and eating habits, and usage of inhaled medications to treat COPD. During the 6-minute walking test participants were asked to walk for six minutes indoors, while their walking distance was measured [18].

Assessment of nutritional status

To assess the nutritional status of the patients their weight and height were measured. To calculate the body mass index (BMI; kg m^{-2}), the patients' weight (kg) was divided by the square

of their height (m). Patients were divided into three groups based on their BMI: normal weight (21–25 kg m^{-2}), overweight/obese (BMI>25 kg m^{-2}), and underweight (BMI<21 kg m^{-2}). This classification is based on the NHLBI classification [19], because patients with COPD are at increased risk of death if the BMI<21 kg m^{-2}, which is in line with the BMI used in the BODE index of COPD severity [20]. In COPD patients with a body weight of BMI<21 kg m^{-2} the initiation of nutritional therapy is indicated. Abdominal circumference and arm circumference were measured with a centimetric tape in all patients.

Blood tests

A fasting blood test was conducted in the central laboratory of National Koranyi Institute of Pulmonology. Serum CRP was measured with a high sensitivity (hs) immunoassay method and the lipid profile (total cholesterine, triglyceride, LDL and HDL) was obtained. Patients were in clinically stable condition, without fever and respiratory infection throughout the measurements.

Diagnostic criteria for metabolic syndrome

The diagnosis of MetS was made on the basis of a set of diagnostic criteria as defined by the International Diabetes Federation [13].

- Central obesity: Waist circumference ≥94 cm in males, and ≥80 cm in females;

Plus at least two of the following:

- Increased fasting plasma glucose: ≥ 5.6 mmol L^{-1}, or previously diagnosed type 2 diabetes;
- Increased serum triglycerides: ≥ 1.7 mmol L^{-1}, or specific treatment for this lipid abnormality;
- Reduced HDL cholesterol: <1.29 mmol L^{-1} (women), and <1.03 mmol L^{-1} (men), or specific treatment for this lipid abnormality;
- Increased blood pressure: systolic values ≥130 Hgmm and/or diastolic values ≥85 Hgmm, or treatment of previously diagnosed hypertension [13].

Statistical analysis

Since most of the continuous data did not follow the normal distribution (verified by Sapphiro-Wilk test), non-parametric statistical methods were used. Continuous variables were interpreted and represented by medians and interquartile ranges. Categorical data were presented with case numbers and proportions. Mann-Whitney tests were used to detect the differences of continuous variables between the two groups; in case of more than two groups Kruskal-Wallis tests were conducted. Frequencies differences of categorical variables were examined by Fisher's exact test. Spearman's correlation was used to test the relationship between continuous variables, which were interpreted by Spearman's rho and its P-values. All statistical analyses were conducted with STATA SE-10.0 (StataCorp, College Station, TX).

RESULTS

The present study involved 401 stable COPD patients. The median age of the study participants was 67 (61–73) years. 47.6% of study participants were men and 52.4% were women.

Table 1. Basic and partially disputed components of metabolic syndrome and further factors in its development

Basic components	Additional components	Other factors
insulin resistance	hyperuricemia	Smoking
hyperinsulinaemia	increased CRP	oxidative stress
glucose intolerance	hyperhomocysteinaemia	increased resistin
hypertension	PCOS	increased TNF-α, IL-6
dyslipidaemia	hyperfibrinogenemia	endothelial dysfunction
diabetes mellitus	microalbuminuria	decreased adiponectin
obesity (cental type)	sleep apnoea syndrome	increased leptin

CRP: C-reactive protein; PCOS: Polycystic ovary syndrome; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6.

Demographic characteristics and data on tobacco smoking (Table 2) show that 5.2% of the patients have never smoked, 51.4% quit the habit and 43.4% were current smokers. The GOLD standardization indicated the following proportions: GOLD A: 7.5% GOLD B: 29.9% GOLD C: 45.4% and GOLD D: 17.2%.

Concerning BMI, we assessed the risk groups and found that 22.2% had a BMI less than 21 kg m^{-2}, 27.4% had values between 21 and 25 kg m^{-2} and more than half of the sample (50.4%) fell into the overweight/obese category (>25 kg m^{-2}). These values showed a significant correlation with smoking status ($P = 0.006$), blood pressure (136.1/80.6 vs. 146.8/86.6; $P < 0.001$), respiratory function (FEV_1 (%pred) 36.0 (28–48) vs. 49.0 (39–63); $P < 0.0001$), metabolic status (LDL, HDL cholesterin and tryglicerides) ($P < 0.0001$), quality of life ($P = 0.046$), and with comorbidities as hypertension ($P < 0.0001$), diabetes mellitus ($P=0.003$) and ischemic heart disease ($P = 0.014$). The MetS prevalence ($P < 0.0001$) and the rate of administered drugs (SABA, LAMA, LABA, ICS, Theophylline, LTRA) was higher among the overweight/obese (BMI > 25 kg m^{-2}) patients (Table 2). Overweight/obese patients had higher LDL (mmol L^{-1}) serum levels (2.7 vs. 2.9, $P = 0.547$) and significantly lower HDL (mmol L^{-1}) levels (1.5 vs. 1.3, $P < 0.0001$). Serum trygliceride (mmol L^{-1}) levels also significantly differed between overweight/obese patients (1.1 vs. 1.6, $P < 0.0001$) and the adequately nourished group of patients (Table 2).

The prevalence of MetS in the GOLD staging groups is presented in Table 3. The serum levels of C-reactive protein were elevated in 55.1% of patients and the highest values were measured in GOLD C and GOLD D. The prevalence of MetS in the entire cohort was 59.1%. It was significantly more common in women than in men (67.6% vs. 49.7%; $P < 0.001$). The highest MetS prevalence was measured in groups B (65.0%) and C (60.4%).

The IDF criteria of MetS are shown in Table 4. The most typical indicator of MetS was the greater waist circumference (95.4%). Further indicators were hypertension (89.8%) and hyperglicemia (79.3%), however elevated levels of serum tryglicerides (48.5%) and lower levels of serum HDL (38.8%) were not significantly related (Table 4).

A fraction of MetS patients showed impaired respiratory function, performed shorter 6-minute walking distance (m) (250 (150–330) vs. 277 (162–360); $P = 0.235$). Additionally, they had lower quality of life (CAT (points): 26 (21–32) vs. 24.5 (19–29); $P = 0.049$) and had significantly more exacerbations in the previous years (2 (1–3) vs.1 (0–2); $P < 0.05$) if compared with non-MetS patients (Table 5).

Table 2. Characteristics of the patients by BMI categories

	Underweight BMI<21 kg m^{-2} n = 89	Normal weight BMI 21–25 kg m^{-2} n = 110	Overweight BMI>25 kg m^{-2} n = 202	All patiens n = 401	P-value
Median Age (years) (IQR)	66.0 (60–71)	69.5 (63–74)	67.0 (61–72)	67 (61–73)	0.026
Men (*n*, %)	47 (52.80)	56 (50.91)	88 (43.56)	191 (47.63)	0.232
Women (*n*, %)	42 (47.20)	54 (49.09)	114 (56.44)	210 (52.37)	
Smoking status					
Current smokers (*n*, %)	51 (57.30)	40 (36.36)	83 (41.09)	174 (43.39)	0.006
Former smokers (*n*, %)	36 (40.45)	60 (54.55)	110 (54.46)	206 (51.37)	
Never smokers (*n*, %)	2 (2.25)	10 (9.09)	9 (4.45)	21 (5.24)	
SBP/DBP (mmHg)	136.1/80.6	140.9/81.3	146.8/86.6	144.8/83.8	<0.001
FEV_1 (ref%)	36.0 (28–48)	45.5 (35–58)	49.0 (39–63)	46 (34–58)	<0.001
FVC (%)	68.0 (54–79)	73.5 (60–85)	70.0 (58–83)	70 (58–83)	0.062
FEV_1/FVC (%)	42.0 (38–52)	49.0 (42–62)	56.5 (48–66)	51 (42–63)	<0.001
GOLD stage (*n*, %)					
A	3 (3.37)	12 (10.91)	15 (7.43)	30 (7.48)	<0.001
B	14 (15.73)	28 (25.45)	78 (38.61)	120 (29.92)	
C	47 (52.81)	49 (44.55)	86 (42.57)	182 (45.39)	
D	25 (29.09)	21 (19.09)	23 (11.39)	69 (17.21)	
C-Reactive protein (mg L^{-1})	4 (1–21)	6 (2–16)	7 (2–18)	6 (1.9–18.1)	0.481
Metabolic variables					
Triglycerides (mmol L^{-1})	1.1 (0.9–1.7)	1.3 (1–2)	1.6 (1.2–2.1)	1.5 (1–2)	<0.001
HDL-cholesterol (mmol L^{-1})	1.5 (1.2–1.8)	1.4 (1.2–1.7)	1.3 (1.0–1.6)	1.4 (1.1–1.7)	<0.001
LDL-cholesterol (mmol L^{-1})	2.7 (2.0–3.3)	2.8 (2.3–3.4)	2.9 (2.2–3.5)	2.9 (2.2–3.4)	0.547
Fasting glucose (mmol L^{-1})	5.1 (4–7)	6.0 (5–7)	6.6 (5–8)	6 (5–7.5)	<0.001
HbA1c (mmol mol^{-1})	37.1 (33.1–40.4)	37.4 (34.4–40.3)	39.0 (34.7–45.2)	37.6 (34.1–42)	0.005
Quality of Life					
CAT (points, IQR)	27 (22–33)	25.5 (19–31)	25.0 (18–30)	26 (20–31)	0.046
Comorbidity					
Hypertension (*n*, %)	51 (57.30)	76 (69.09)	166 (82.18)	293 (73.07)	<0.001
Diabetes (*n*, %)	6 (6.75)	16 (14.55)	51 (25.25)	73 (18.20)	0.003

(continued)

Table 2. Continued

	Underweight BMI<21 kg m^{-2} n = 89	Normal weight BMI 21–25 kg m^{-2} n = 110	Overweight BMI>25 kg m^{-2} n = 202	All patiens n = 401	P-value
Metabolic syndrome (n, %)	20 (22.47)	57 (51.81)	161 (79.70)	238 (59.35)	<0.001
Ischemic heart disease (n, %)	43 (48.30)	44 (40.00)	119 (58.91)	206 (51.37)	0.014
Psychiatric history (n, %)	10 (11.24)	11 (10.00)	29 (14.36)	50 (12.47)	0.390
Medication (n)					
SABA	30	41	74	145 (36.16)	<0.001
LAMA	5	5	19	29 (7.23)	0.216
LABA	4	3	5	12 (2.99)	0.397
LABA and LAMA	4	6	13	23 (5.74)	0.604
ICS and LABA	9	19	26	54 (13.47)	0.136
LABA and LAMA and ICS	22	26	50	98 (24.44)	0.837
Supplemented with Theophylline	36	39	61	136 (33.92)	0.178
Supplemented with LTRA	5	7	11	23 (5.74)	0.239
No data available	8	9	9	26 (6.48)	-
Influenza vaccination (n, %)	16 (17.98)	42 (38.18)	56 (27.72)	114 (28.43)	0.002
Pneumococcal vaccination (n, %)	8 (8.99)	22 (20.00)	20 (9.90)	50 (12.47)	0.010

Data are presented as median (IQR) or as frequency and percentage; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CAT: COPD Assessment Test; mMRC: Modified Medical Research Council Dyspnoea Scale; FEV_1: forced expiratory volume in 1 s post-bronchodilator; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; 6MWD: six-minute walking distance; SD: Standard deviation; HDL: high density cholesterol level; LDL: low-density cholesterol level; HbA1c: glycated hemoglobin; SABA: short-acting bronchodilators; LABA: long-acting bronchodilators; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists; P <0.05 means the two indicators were significantly correlated.

Table 3. Patient severity classification and comparison of parameters according to GOLD stages

n (%)	GOLD A *n* = 30 (7.48)	GOLD B *n* = 120 (29.93)	GOLD C *n* = 182 (45.39)	GOLD D *n* = 69 (17.21)	*P*-value
CRP					
Normal (≤5 mg L^{-1})	17 (56.67)	62 (51.67)	79 (43.41)	22 (31.88)	0.048
High (>5 mg L^{-1})	13 (43.33)	58 (48.33)	103 (56.59)	47 (68.12)	
Metabolic syndrome					
Present	17 (56.66)	78 (65.00)	110 (60.44)	32 (46.38)	0.180
Absent	13 (43.33)	42 (35.00)	72 (39.56)	37 (53.62)	
BMI (kg m^{-2})	24.8 (22.2–26.8)	28.0 (23.7–32.6)	24.4 (20.8–29.7)	22.2 (19.3–27.4)	<0.001
6MWD (m)	287 (200–400)	300 (177–365)	250 (150–325)	235 (130–300)	0.003
C-Reactive protein (mg L^{-1})	3.7 (1.7–13.4)	4.8 (1.7–16.1)	6.3 (2.2–15.7)	12.1 (4.4–27.7)	0.014
FEV_1 (ref%)	92 (84–100)	62 (54–69)	42 (36–46)	24 (21–26)	<0.001
FVC (%)	108 (100–116)	81 (70–90)	67 (59–76)	49 (43–55)	<0.001

Data are presented as median (IQR) or as frequency and percentage. GOLD: Global Initiative for Chronic Obstructive Lung Disease; CRP: C-reactive protein; BMI: body mass index; 6MWD: six-minute walking distance; FEV_1: forced expiratory volume in 1 s post-bronchodilator; FVC: forced vital capacity; P <0.05 means the two indicators were significantly correlated.

Table 4. Fulfilled criteria for Metabolic Syndrome

MetS criteria	With MetS *n* = 237	Without MetS *n* = 164	All patients *n* = 401
Elevated waist circumference ≥94 cm in males, ≥80 cm in females (*n*, %)	226 (95.36)	78 (47.56)	304 (75.81)
Elevated blood pressure: systolic ≥130 and/or diastolic ≥85 mmHg (or on therapy) (*n*, %)	213 (89.78)	80 (48.78)	293 (73.07)
Triglycerides ≥1.7 mmol L^{-1} (or on therapy) (*n*, %)	115 (48.52)	24 (14.63)	139 (34.66)
Fasting glucose≥ 5.6 mmol L^{-1} (or on therapy) (*n*, %)	188 (79.32)	51 (31.10)	239 (59.60)
HDL <1.03 mmol L^{-1} in males, <1.29 mmol L^{-1} in females (or on therapy) (*n*, %)	92 (38.82)	10 (6.01)	102 (25.44)

MetS: Metabolic Syndrome; HDL: high-density lipoprotein; The IDF (International Diabetes Federation) consensus worldwide definition of the metabolic syndrome. 2006.

Table 6 shows the Spearman rank correlation coefficients of serum cholesterin levels related to age, specific anthropometric, functional parameters in different stages of COPD. The serum levels of cholesterin was positively correlated to the serum levels of tryglicerides in each GOLD group.

Table 5. Characteristics of COPD patients with and without metabolic syndrome

	With MS $n = 237$	Without MS $n = 164$	*P*-value
Median Age (years) (IQR)	67 (61–72)	67 (62–73)	0.852
Men (*n*, %)	95 (40.08)	96 (58.54)	<0.001
Women (*n*, %)	142 (59.92)	68 (41.46)	
Smoking status			
Current smokers (*n*, %)	100 (42.19)	74 (45.12)	0.192
Former smokers (*n*, %)	127 (53.59)	79 (48.17)	
Never smokers (*n*, %)	10 (4.22)	11 (6.70)	
Quality of Life			
CAT (points)	26 (21–32)	24.5 (19–29)	0.049
FEV_1 (ref%)	43 (30–56)	47 (36–61)	0.028
FVC (%)	71 (55–84)	70 (60–83)	0.608
FEV_1/FVC (%)	50 (39–58)	54 (44–64)	<0.001
C-Reactive protein (mg L^{-1})	7.0 (2–18)	5.1 (1–17)	0.064
BMI (kg m^{-2})	28.0 (24–32)	21.6 (18–24)	<0.0001
6MWD (m)	250 (150–330)	277 (162–360)	0.235

Data are presented as median (IQR) or as frequency and percentage. CAT: COPD Assessment Test; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; BMI: body mass index; 6MWD: six minute walking distance; mMRC: modified Medical Research Council; $P < 0.05$ means the two indicators were significantly correlated.

Table 6. The correlation of cholesterol with age and anthropometric, functional parameters

	GOLD A		GOLD B		GOLD C		GOLD D	
	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value
Age (years)	−0.064	0.752	−0.087	0.355	−0.078	0.309	−0.040	0.746
FEV_1 (ref%)	−0.158	0.431	−0.049	0.601	0.041	0.587	0.028	0.821
FVC (%)	0.150	0.455	0.176	0.062	0.014	0.856	0.037	0.769
FEV_1/FVC (%)	−0.121	0.546	−0.236	0.011	0.034	0.661	−0.155	0.212
BMI (kg m^{-2})	0.052	0.797	−0.072	0.447	0.085	0.267	0.166	0.182
6MWD (m)	0.078	0.696	0.070	0.761	−0.043	0.567	−0.031	0.800
Triglycerides (mmol L^{-1})	0.279	0.157	0.243	0.009	0.361	<0.001	0.287	0.019

ρ: Spearman Correlation Coefficients; FEV_1: forced expiratory volume in 1 s post-bronchodilator; FVC: forced vital capacity; 6MWD: six-minute.

DISCUSSION

The aim of our study was to determine the prevalence of MetS among COPD patients with different nutritional status and GOLD stages. We also determined the extent of systemic inflammation and its association with prevalent MetS by measuring CRP levels. Abdominal obesity, hypertension, hyperglycemia and metabolic syndrome were also more common in the

overweight/obese group (BMI $\geq$ 25 kg m^{-2}; $P < 0.0001$). MetS showed a significant association with several cardiovascular comorbidities and type 2 diabetes. MetS was prevalent in 59.1% of COPD patients. This prevalence is close to those published in previous studies, ranging from 21% to 58% [21]. Prevalence of MetS in COPD patients appears to depend on the severity of COPD, the geographical location of the study, and also the diagnostic criteria of MetS used. In general, MetS is more common in patients with increasing severity of COPD. Patients with both MetS and COPD have worse physical status than the group of patients who have only COPD [21].

MetS as defined by IDF criteria, depends mainly on abdominal obesity. More studies indicated that the amount of abdominal - visceral - adipose tissue is increased in patients with COPD [8–11, 21]. The underlying mechanisms are multifaceted and likely include an unhealthy diet combined with an inactive lifestyle. It is remarkable that MetS patients with normal nutritional status had decreased physical exercising (6MWD) compared to those without MetS but with COPD. Our findings extend previous results that MetS reduces muscle mass, which may explain, at least in part, the aforementioned observation. The link between COPD and MetS is likely bi-directional as lower physical activity observed in COPD patients *per se* may contribute to the development of MetS [21, 22].

Numerous studies have shown that GOLD stage II patients have the highest MetS prevalence compared to more severe GOLD stage patients [8, 21, 23]. First, this observation may be due to the fact that in less advanced cases of COPD lifestyle has a greater effect on metabolism than other factors promoting the progression of the disease. Second, it is also possible that MetS has a higher cardiovascular risk in COPD and some of the patients may die earlier because of their comorbid cardiovascular disease and may not reach end-stage COPD.

Drugs can also directly affect the prevalence of MetS. For example, oral glucocorticoids used to treat COPD can increase LDL cholesterol levels, blood glucose levels, and appetite, and can lead to abdominal obesity and muscle atrophy [9]. Other medications commonly used to treat COPD, such as antidepressants, may also cause impaired glucose tolerance and thus contribute to the development of MetS [24].

We detected a significantly increased triglyceride level and significantly decreased HDL cholesterol level among overweight/obese patients and MetS patients had significantly higher BMI values than those without MetS. Our results are in line with the findings of many, but not all, previous studies [25–28]. Xuan et al. found that serum HDL levels were significantly lower, while triglyceride levels were significantly higher in stable COPD patients than in the control groups [25]. Can et al. described that there was no difference in serum total cholesterol and triglyceride levels between COPD patients and controls [26]. Breyer et al. reported that MetS was more common among obese COPD patients [27]. Reed and colleagues found that HDL cholesterol levels were significantly lower in the more severe stages of COPD than in controls [28]. Systemic inflammation in COPD is associated with elevated triglyceride levels and reduced HDL cholesterol levels [29]. It has also been shown that inflammatory cytokines disrupt lipid metabolism, and there is an inverse correlation between serum HDL and IL-6 levels [30]. COPD patients are physically inactive, which further increases the risk of dyslipidemia [2, 8, 30]. They often use corticosteroids, mainly in severe, and very severe COPD (GOLD C, D) which also increases the occurrence of dyslipidemia and obesity [31]. In addition, smoking as well as oxidative stress are possible mechanisms for the development of dyslipidemia, and altogether they contribute to the MetS development [32].

MetS appears to be more common in females with higher BMI values. In older female patients there is likely a significant decline in circulating estrogen levels, which may increase

adiposity, alter lipid metabolism, and promote a prothrombotic state. Female patients usually exhibit higher prevalence of abdominal obesity [12].

MetS and increased adiposity increases the the incidence of cardiovascular diseases in COPD patients [3]. The underlying mechanisms by which MetS and increased adiposity promotes the pathogenesis of cardiovascular diseases include vascular oxidative stress and inflammation [7], which promote accelerated atherogenesis [2, 5] mediated, in part, by pro-inflammatory adipokines secreted from the adipose tissue. These factors also increase blood pressure, exacerbate thrombogenesis and promote insulin resistance [5]. Decreased activity of fibrinolytic mechanisms contribute to the prothrombogenic state [2, 5, 7].

Nearly half of COPD patients in pulmonary rehabilitation programs are overweight or obese, which negatively affects their respiration and exercise tolerance, especially while walking [3]. Interestingly, the paradox phenomenon that patients with higher BMIs tend to live longer than patients with low or normal BMI has been well-documented in the literature [33]. This so called "obesity paradox" is not manifested in obese patients (BMI> 30 kg m^{-2}). Physical inactivity and comorbidities clearly negatively affect the survival of individuals with COPD [3, 6, 8, 33].

Recent studies have identified a so-called "co-morbidity predominant subtype" among COPD patients, characterized by a group of metabolic comorbidities, including CVD, T2DM, and obesity [6, 11, 31]. Patients with hypertension, T2DM, have been shown to be at increased risk of morbidity and mortality. Particular attention should be given to a sedentary life-style or decreased physical activity since these show a significant correlation with blood sugar levels and abdominal circumference. In Park and Larson's study [31], COPD patients were recorded as sitting in one place for more than 11 h per day. This is also harmful because prolonged sitting around or sedentary working *per se* have a strong impact on the MetS development. Even low-intensity physical activity can create a more favorable metabolic situation [31, 34].

In our study, we found significantly higher exacerbation rate (2 (1–3) vs.1 (0–2); $P < 0.05$) in COPD patients with MetS, which accord with the lower quality of life found in this patient group. Our findings extend the results of Kupeli et al. demonstrating that the prevalent MetS in COPD patients increases the number (2.4 vs. 0.7) and duration (7.5–8.0 vs. 5.0–5.5 days) of exacerbations [35]. However, it is unclear whether early diagnosis and treatment of MetS can improve long-term clinical outcomes. Weight loss alone affects a number of risk factors including hypertension, dyslipidemia, and insulin resistance. There are a number of studies demonstrating the beneficial effects of exercise in overweight and obese individuals on blood pressure, lipid profiles and glucose levels [36–38]. Improvement in glycated hemoglobin (HbA1c) and insulin sensitivity has been also described, and the total duration of exercise appears to be more important than the mode of its execution [39]. The available data suggest that in patients with COPD, a significant increase in abdominal fat is directly associated with the likelihood of developing acute myocardial infarction [6]. The physical workload and quality of life of COPD patients with MetS is also reduced [31]. Taken together, MetS in COPD patients should be considered by pulmonologists and treated as soon as possible.

Limitations of the study

Our study relied on a self-reported history of exacerbations, which may introduce a significant bias. Our present study was a single-centre, cross-sectional study, and therefore the cause and effect of relationship cannot be established. Further longitudinal prospective studies are needed

to examine the long-term effects of MetS on the cardiovascular system, the physical activity, quality of life, number of exacerbations and other comorbidities in COPD patients.

CONCLUSION

Among COPD patients, MetS is more likely to develop, especially in obese patients, with a prevalence of 59.1% in our study. The most common components of MetS are abdominal obesity, hypertension, hyperglycemia and hyperlipidemia, more common in women with high BMI values. COPD patients with MetS use more inhaled medications and have more co-morbidities, with a poorer quality of life and poorer physical capacity than those without MetS. Future follow-up and interventional studies are needed to determine the best treatment options. Also, additional studies are warranted to determine how MetS, obesity, COPD and COVID-19 morbidity and mortality relate [40, 41].

Ethics approval and consent to participate: The study was approved by the TUKEB Ethical Committee (Licence Number: TUKEB 44402-2/2018/EKU) and it complies with the Helsinki Declaration.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author [JTV].

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LIST OF ABBREVIATIONS

BMI	body mass index
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CVD	cardiovascular disease

FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDL	high-density lipoprotein
HbA1c	Hemoglobin A1c
IDF	International Diabetes Federation
IL-6	interleukin-6
IL-8	interleukin-8
ICS	inhaled corticosteroids
LABA	long-acting bronchodilators
LAMA	long-acting muscarinic antagonist
LDL	low-density lipoprotein
LTRA	leukotriene receptor antagonists
MetS	Metabolic syndrome
6MWT	six-minute walk test
OECD	Organisation for Economic Co-operation and Development
SABA	short-acting bronchodilators
T2DM	Type 2 diabetes mellitus
TG	triglyceride
TNF-α	tumor necrosis factor alpha
TUKEB	Regional Institutional Scientific Research Ethics Committee of Semmelweis University
VLDL	very low-density lipoproteins

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