Metabolic and Inflammatory Profile in Patients with COPD

Monika Fekete (feketemonika78@gmail.com)
Semmelweis Egyetem
Gergo Szollosi
Debreceni Egyetem
Stefano Tarantini
Oklahoma City University
Anna N Nemeth
Semmelweis Egyetem
Csenge Bodola
Semmelweis Egyetem
Luca Varga
Semmelweis Egyetem
Janos Tamas Varga
Orszagos Koranyi Tbc es Pulmonologiai Intezet

Research

Keywords: COPD, metabolic syndrome, prevalence, inflammation, exacerbations, SGRQ-C

Posted Date: June 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-36903/v1

Abstract

Background: In COPD, aside from obesity, decreased physical activity significantly increases the probability of developing metabolic syndrome, which can have a great impact on the natural course of COPD.

Objective: The purpose of our study was to evaluate the prevalence of metabolic syndrome and whether it is related to age, sex, comorbidities, drug intake, degree of impairment of lung function, nutritional status, physical activity and quality of life.

Methods: A cross-sectional study was performed on patients in Budapest at the Department of Pulmonary Rehabilitation of the National Koranyi Institute of Pulmonology between March 1, 2019 and March 1, 2020. The anthropometric and respiratory function tests and laboratory parameters of a random sample of 401 patients were known. Metabolic syndrome was determined according to IDF criteria and by definition CRP levels above 5.0 mg/L were considered elevated.

Results: Metabolic syndrome occurred in 59.1% of COPD patients, male: 49.7% female: 67.6% ($p < 0.001$). Patients with metabolic syndrome had worse FEV_1%pred (43 (30-56) vs. 47 (36-61); p=0.028), lower 6MWD (250 (150-330) vs. 277 (162-360); p=0.235), lower quality of life, and significantly higher number of exacerbations (3 (1-6) vs.1 (0-3); $p < 0.001$), than patients without metabolic syndrome. C-Reactive protein level was elevated in 55.1% of patients, higher in patients with metabolic syndrome, but the difference was not significant (7.0 (2-18) vs. 5.1 (1-17); p = 0.064).

Conclusions: MetS can affect respiratory function, physical activity, quality of life and the number of exacerbations and is related to nutritional status and the level of systemic inflammation.

Introduction

Chronic obstructive pulmonary disease is a terminal disease of the respiratory system, in addition it is currently the fourth leading cause of death worldwide, however according to some predictions it will become the third leading cause of mortality until 2030 [1]. One of the most important risk factors of developing chronic obstructive pulmonary disease is smoking [2]. Patients living with COPD are also at higher risk of developing cardiovascular diseases, osteoporosis, anxiety and depression, pulmonary cancer, metabolic syndrome, anemia and other diseases [3]. Patients with COPD frequently (65–80%) suffer from at least one or two comorbidities, and the common reason behind the evolvement of these additional malformations is the local and systemic inflammatory response to inhalational particles (eg. cigarette smoke, air pollution) which have a wide range of destructive effects on the body [4]. It is still under discussion whether metabolic syndrome can be interpreted as an independent entity or as a collection of different diseases (Table 1). An increase in the abdominal fat shows a direct connection between the odds of developing heart diseases (especially myocardial infarction) caused by atherosclerotic arterial damage; in the background of these changes adipokines stand, which are polipeptides secreted by fat tissue (Table 2) and which have elevating effects on blood pressure, atherogenic and thrombogenic mechanisms and they also increase the potential of the developing insulin resistance, multiplying the chances of atherosclerotic arterial damage [5]. Hyperinsulinaemia results in higher VLDL production by the liver and also the accumulation of triglyceride rich in atherogenic lipoproteins (small, dense LDL, decreased levels of HDL, long lasting hypertriglyceridaemia). The key component of atherogenic dyslipidaemia in metabolic syndrome is the small, dense LDL, which can hardly bind to LDL receptors due to its malformed molecular

structure, and it is also sensitive to oxidative changes. As a result of the transfigured structure of LDL molecules, despite being eliminated through LDL receptors, small, dense LDL is consumed by macrophages, which creates the bases of atherosclerotic plaques [6]. The decreased activity of fibrinolitic mechanisms (e.g. plasminogen activator factor (PAI-1) production) results in prothrombogenic state. Overall these changes create an increased oxidative stress and lead to arterial inflammation (Fig. 1) [7]. Observations in the recent past note that overweight patients suffering from COPD have a higher prevalence of metabolic syndrome compared to the healthy group of similar age and BMI [8] and patients with both metabolic syndrome and COPD had lower physical persistence compared to the group of patients who only had COPD. The increased BMI and abdominal fat further increase the cardiovascular incidence in COPD patients. Some research suggests that COPD patients with higher serum cholesterine and triglyceride levels have more severe stage of disease and worse exacerbations [9]. The purpose of our study was to evaluate the prevalence of metabolic syndrome, and whether it is related to age, sex, comorbidities, drug intake, degree of impairment of lung function (FEV_1%pred), nutritional status (BMI), physical activity (6MWD) and quality of life (SGRQ-C).

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

Basic ingredients	Additional ingredients	Other factors
insulin resistance	hyperuricemia	smoking
hyperinsulinaemia	CRP-growth	oxidative stress
glucose intolerance	hyperhomocysteinaemia	increase in resistin
hypertension	PCOS	increase in TNF-alfa, IL-6
dyslipidaemia	hyperfibrinogenaemia	abnormal endothelial function
diabetes mellitus	microalbuminuria	decrease in adiponectin
obesity (cental type)	sleep apnoe syndrome	leptin growth
CRP: C-reactive protein; PCOS: Polycystic ovary syndrome; TNF-alfa: Tumor necrosis factor-alpha; IL-6: Interleukin-6;		

Table 2
Bioactive substances produced by adipose tissue (adipokines)

IGF-1, IGFBP	TNF-alpha, Interleukines, TGF-ß
Bone morphogenetic protein (BMP)	FGF, EGF
Resistin	Fatty acids, Lysophosholipids
Adiponectin	Lactate, Adenosin, Prostaglandin
Oestrogen	Glutamine
ANG-II.	Agouti Protein
Angiotensin	Retinol

IGF: insulin-like growth factor-1; IGFBP: insulin-like growth factor-binding protein; TNF-alpha: tumor necrosis factor alpha; TGF-ß: transforming growth factor ß; FGF: fibroblast growth factor; EGF: epidermal growth factor; PAI-1: plasminogen activator inhibitor-1; ASP: acylation stimulation protein; ANG-II: angiotensin-II;

Methods

Study Design and Population

A cross-sectional study was performed on COPD patients at the National Koranyi Institute of Pulmonology. Patients were given oral and written information prior to the assessment, and then they signed a statement of consent. The study was approved by the TUKEB Ethical Committee (Licence Number: TUKEB 44402-2 / 2018 / EKU) and it complies with the Helsinki Declaration. The inclusion criteria were: age over 40 years and diagnosis of COPD (post-bronchodilation of $FEV_1/FVC < 70\%$) [10].

Measurements

We measured the post-bronchodilator FEV_1 (forced expiratoty volume in the first second) in each patient and we provided all estimated data in percentage. We classified patients in GOLD A-D stages according to the current and the future risk parameters, like spirometric values, symptoms and exacerbation rate [10]. We assessed the quality of life with the hungarian translated version of the disease specific Saint George Respiratory Questionnaire (SGRQ-C) [11], which contained 40 questions. This questionnaire analyzes the influencing factors of quality of life in three categories: symptomatic, activity related and the respiratory diseases impact on everyday life. The weightnumber values of individual answers were used to calculate weightnumbers of different dimensions, and with the summation of weightnumbers as the overall score were calculated. Higher scores suggest worse quality of life in the questionnaire. It was completed by participants in the institute under the supervision of the coordinators. During the 6-minute walking test we asked participants to walk for six minutes in the corridor while we measured the walking distance [12]. We divided the weight of the patients (kg) by the square of their height (m) (kg/m^2) to measure BMI. We conducted the fasting blood test in the National Koranyi Institute of Pulmonology central laboratory, and measured serum CRP with high sensitivity (hs) immunoassay method and the lipid profile (total cholesterine, triglyceride, LDL and HDL). Patients were in clinically stable condition, in the absense of fever and respiratory infection throughout the measurements. The diagnosis of metabolic syndrome was made on the basis of a set of diagnostic criteria 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:

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

Statistical Analysis

Since most of the continuous data did not follow the normal distribution (which was verified by using the Sapphiro-Wilk test), non-parametric statistical methods were used. Continuous variables were interpreted and represented by medians and interquartile ranges. The categorical data were presented with case numbers and proportions. Mann-Whitney tests were used to detect the differences of continuous variables between two groups; if more than two groups were present, then Kruskal-Wallis ANOVA tests were conducted. The differences in frequencies of categorical variables were examined using Fisher's exact test. Spearman's correlation was used to test the relationship between continuous variables, which were interpreted by Spearman's rho and it's p-values. Univariate logistic regression model was formed using the variables, all statistical analyses were conducted with STATA SE-10.0 (StataCorp, College Station, TX).

Results

Fourhundreds one stable COPD patients were involved to the study. The median age of patients was 67 (61–73), 47.6% of the participants were men and 52.4% were women, the patients demographic characteristics and their information on smoking are shown in Table 3. 5.2% of the patients have never smoked, 51.4% of the patients quit smoking and 43.4% are currently active smokers. The distribution of patients in GOLD standardization are the following: GOLD A: 7.5% GOLD B: 29.9% GOLD C: 45.4% and GOLD D: 17.2%.

Regarding BMI, we assessed the risk groups, and found that 22.2% of the involved COPD patients had lower BMI than 21 kg/m², a quarter (27.4%) had a BMI between 21 and 25 kg/m², and more than half of the patients (50.4%) fell into the obese cathegory (BMI > 25 kg/m²). The evaluated BMI values showed a significant correlation with the status of smoking ($p = 0.006$), also with 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 (total score on SGRQ-C: 72.2 vs. 64.6; $p = 0.006$) and with comorbidities: hypertension ($p < 0.0001$), diabetes ($p = 0.003$) and ischemic heart disease ($p = 0.014$). The prevalence of metabolic syndrome ($p < 0.0001$) and the rate of medication use (SABA, LAMA, LABA, ICS, Theophylline) was higher in the obese group of patients (BMI > 25 kg/m²) (Table 3). It is interesting that the rate of vaccination against pneumococcus and influenza was significantly lower ($p < 0.05$) in malnourished patients (BMI > 21 kg/m²) than in patients who had average BMI values or who were obese. Serum levels of LDL in obese patients were higher (2.7 vs. 2.9, $p = 0.547$), and we found significantly lower levels of HDL in this group (1.5 vs.

1.3, $p < 0.0001$) additionally we also discovered that the serum levels of trygliceride showed a significant difference in this group (1.1 vs. 1.6, $p < 0.0001$) compared to the adequatly nourished group of patients (Table 3).

Table 3
Characteristics of the patients by BMI categories.

	Underweight BMI < 21 kg/m² n = 89	Normal weight BMI 21–25 kg/m² n = 110	Overweight BMI > 25 kg/m² n = 202	p-value
Median Age (years) (IQR)	66.0 (60–71)	69.5 (63–74)	67.0 (61–72)	0.026
Men (n, %)	47 (52.80)	56 (50.91)	88 (43.56)	0.232
Women (n, %)	42 (47.20)	54 (49.09)	114 (56.44)	
Smoking status				
Current smokers (n, %)	51 (57.30)	40 (36.36)	83 (41.09)	0.006
Former smokers (n, %)	36 (40.45)	60 (54.55)	110 (54.46)	
Never smokers (n, %)	2 (2.25)	10 (9.09)	9 (4.45)	
SBP/DBP (mmHg)	136.1/80.6	140.9/81.3	146.8/86.6	< 0.001
FEV_1 (ref%)	36.0 (28–48)	45.5 (35–58)	49.0 (39–63)	< 0.0001
FVC (%)	68.0 (54–79)	73.5 (60–85)	70.0 (58–83)	0.062
FEV_1/FVC (%)	42.0 (38–52)	49.0 (42–62)	56.5 (48–66)	< 0.0001
GOLD stage (n, %)				
A	3	12	15	< 0.001
B	14	28	78	
C	47	49	86	
D	25	21	23	
C-Reactive protein (mg/L)	4 (1–21)	6 (2–16)	7 (2–18)	0.481
Metabolic variables				
Triglycerides (mmol/L)	1.1 (0.9–1.7)	1.3 (1–2)	1.6 (1.2–2.1)	< 0.0001
HDL-cholesterol (mmol/L)	1.5 (1.2–1.8)	1.4 (1.2–1.7)	1.3 (1.0-1.6)	< 0.0001
LDL-cholesterol (mmol/L)	2.7 (2.0-3.3)	2.8 (2.3–3.4)	2.9 (2.2–3.5)	0.547
Fasting glucose (mmol/L)	5.1 (4–7)	6.0 (5–7)	6.6 (5–8)	< 0.001
HbA1c (mmol/mol)	37.1 (33.1–40.4)	37.4 (34.4–40.3)	39.0 (34.7–45.2)	0.005
Dyspnea Severity (n, %)				

Mild dyspnea (mMRC score of 0–1)	23 (25.85)	41 (37.27)	68 (33.66)	0.150
Moderate dyspnea (mMRC score of 2–3)	43 (48.30)	56 (50.91)	98 (48.51)	
Severe dyspnea (mMRC score of 4)	23 (25.85)	13 (11.82)	36 (17.82)	
Quality of Life (median)				
Total score on SGRQ-C	72.2	65.4	64.6	0.006
Impact score on SGRQ-C	72.4	64.9	65.8	0.014
Activity score on SGRQ-C	48.5	33.4	34.8	0.002
Symptom score on SGRQ-C	56.8	48.7	49.8	0.002
Comorbidity				
Hypertension (n, %)	51 (57.30)	76 (69.09)	166 (82.18)	< 0.0001
Diabetes (n, %)	6 (6.75)	16 (14.55)	51 (25.25)	0.003
Metabolic syndrome (n, %)	20 (22.47)	57 (51.81)	161 (79.70)	< 0.0001
Ischemic heart disease (n, %)	43 (48.30)	44 (40.00)	119 (58.91)	0.014
Psychiatric history (n, %)	10 (11.24)	11 (10.00)	29 (14.36)	0.390
Medication (n)				
SABA	30	41	74	<0.001
LAMA	5	5	19	0.216
LABA	4	3	5	0.397
LABA and LAMA and ICS	4	6	13	0.604
ICS and LABA	9	19	26	0.136
LABA and LAMA and ICS	22	26	50	0.837
Supplemented with Theophylline	36	39	61	0.178
Annual influenza vaccination (n, %)	16 (17.98)	42 (38.18)	56 (27.72)	0.002
Pneumococcal vaccination (n, %)	8 (8.99)	22 (20.00)	20 (9.90)	0.010

Data are presented as median (IQR) or as frequency and percentage; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SGRQ-C: Saint-George Respiratory Questionnaire for COPD patients; 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 haemoglobin; SABA: short-acting bronchodilators; LABA: long-acting bronchodilators; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids; $p < 0.05$ means the two indicators were significantly correlated;

The prevalence of MetS and the elevated levels of CRP in the different groups of GOLD staging can be found in Table 4. The serum levels of C-reactive protein were elevated in 55.1% of the patients, the highest values were in GOLD C and GOLD D. The prevalence of MetS was the following in the different groups of GOLD staging: GOLD A: 56.6%, GOLD B: 65.0%, GOLD C: 60.4%, GOLD D: 46.4%, and we found the highest prevalence of MetS in groups B and C.

Table 4. Patient severity classification and comparison of parameters according to GOLD stages.

	GOLD A	GOLD B	GOLD C	GOLD D	p-value
n (%)	n=30 (7.48)	n=120 (29.93)	n=182 (45.39)	n=69 (17.21)	
CRP					
Normal (≤ 5 mg/L)	17 (56.67)	62 (51.67)	79 (43.41)	22 (31.88)	0.048
High (> 5 mg/L)	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/m²)	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)	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 5 shows the Spearman rank correlation coefficients of serum cholesterin levels in relation with age, different antropometric, functional parameters in different stages of COPD. The serum levels of cholesterin

showed a negative correlation with the age of patients and showed positive correlation with the serum levels of tryglicerides, LDL and HDL in each GOLD group.

Table 5. The correlation of cholesterol with age and antropometric, 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/m²)	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)	0.279	0.157	0.243	0.009	0.361	<0.001	0.287	0.019
HDL-cholesterol (mmol/L)	0.247	0.214	0.340	<0.001	0.290	<0.001	0.352	0.003
LDL-cholesterol (mmol/L)	0.897	<0.001	0.706	<0.001	0.731	<0.001	0.845	<0.001

ρ: Spearman Correlation Coefficients; FEV_1: forced expiratory volume in 1 s post-bronchodilator; FVC: forced vital capacity; 6MWD: six-minute walk distance; BMI: Body Mass Index; HDL: high density cholesterol level; LDL: low-density cholesterol level;

The most profound IDF criteria of metabolic syndrome are shown in Table 6. The most common prevailed criterion of metabolic syndrome was the elevated waist circumference (95.4%), and among the MetS components the other most relevant criteria were hypertension (89.8%) and hyperglicemia (79.3%), in spite of this, the elevated levels of serum tryglicerides (48.5%) and the decreased levels of serum HDL (38.8%) were not significantly common (Table 6).

Table 6. Fulfilled criteria for Metabolic Syndrome.

MetS criteria	With MetS	Without MetS	All patients
	n=237	n=164	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 (or on therapy) (n, %)	115 (48.52)	24 (14.63)	139 (34.66)
Fasting glucose≥ 5.6 mmol/L (or on therapy) (n, %)	188 (79.32)	51 (31.10)	239 (59.60)
HDL <1.03 mmol/L in males, <1.29 mmol/L 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.

The prevalence of MetS in the entire patient population was 59.1%: it was significantly more common in women (67.6%) (142/210) than in men (49.7%) (95/191; $p < 0.001$) (Table 6). CRP serum levels were measured higher in patients with metabolic syndrome, however the difference was not significant (7.0 (2–18) vs. 5.1 (1–17); $p = 0.064$) (Table 7).

Table 7
Functional characteristics of the COPD patients by metabolic syndrome.

	With MS	Without MS	p-value
	n = 237	n = 164	
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)	
Dyspnea Severity (n, %)			
Mild dyspnea (mMRC score of 0–1)	76 (32.07)	56 (34.15)	0.714
Moderate dyspnea (mMRC score of 2–3)	117 (49.37)	80 (48.78)	
Severe dyspnea (mMRC score of 4)	44 (18.56)	28 (17.7)	
Quality of Life (median)			
Total score on SGRQ-C	67.6	66.1	0.871
Impact score on SGRQ-C	67.9	65.5	0.579
Activity score on SGRQ-C	35.8	34.2	0.436
Symptom score on SGRQ-C	51.6	50.1	0.605
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)	7.0 (2–18)	5.1 (1–17)	0.064
BMI (kg/m²)	28.0 (24–32)	21.6 (18–24)	< 0.0001
6MWD (m)	250 (150–330)	277 (162–360)	0.235
Exacerbations in previous year (range)	3 (1–6)	1 (0–3)	<0.001

Data are presented as median (IQR) or as frequency and percentage. SGRQ-C: Saint-George Respiratory Questionnaire for COPD patients; 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;

Some of the patients who had metabolic syndrome, obtained worse respiratory function: (FEV_1/FVC: (50 (39–58) vs. 54 (44–64); $p < 0.001$). This particular group also performed shorter 6-minute walking distance (250 (150–330) vs. 277 (162–360); $p = 0.235$), they experienced worse dyspnoe on the mMRC ($p = 0.714$), they also had lower quality of life and they had significantly more exacerbations in the previous years (3 (1–6) vs. 1 (0–3); $p < 0.001$) compared to those who did not suffer from MetS (Table 7).

We calculated the odds ratio (OR) with logistic regression model (Table 8). Female gender (OR: 2.11; $p < 0.001$), higher BMI (OR: 1.20; $p < 0.001$), the use of inhaled corticosteroids (OR: 1.66; $p = 0.003$) significantly elevated the odds of developing metabolic syndrome, whereas among the comorbidities, diabetes (OR: 2.51; $p < 0.001$) and ischemic heart disease (OR: 2.43; $p < 0.001$) increased the probability of developing MetS.

Table 8
Logistic regression with metabolic syndrome as dependent variable.

	OR	p-value
Age (years)	0.99	0.968
Females/Males	2.11	< 0.001
Smoking	1.12	0.561
FEV_1 (ref%)	1.00	0.104
BMI (kg/m²)	1.20	< 0.001
6MWD (m)	1.01	0.250
C-Reactive protein (mg/L)	1.01	0.580
Total score on SGRQ-C	1.39	0.583
Ischemic heart disease	2.43	< 0.001
Diabetes	2.51	< 0.001
Psychiatric history	0.99	0.711
ICS	1.66	0.003
OR: Odds Ratio; FEV_1: forced expiratory volume in the first second; ICS: inhaled corticosteroids; BMI: body mass index; 6MWD: six minute walking distance; $p < 0.05$ means the two indicators were significantly correlated;		

Discussion

The aim of our study was to determine the prevalence of MetS in COPD patients with different nutritional states and GOLD stages. We also determined the extent of systemic inflammation and its association with the presence of MetS by measuring high-sensitivity CRP levels. Abdominal obesity, hypertension, hyperglycemia and metabolic syndrome were also more common in the overweight/obese group (BMI ≥ 25 kg/m^2; $p < 0.0001$). Metabolic syndrome occurred simultaneously with several cardiovascular comorbidities and type 2 diabetes. Metabolic syndrome was found in 59.1% of patients with COPD, this prevalence is higher than in previous studies, which showed a value between 21% and 58%. It also depended on the severity of the disease, the geographical location

of the research, and the definition used, and suggested that metabolic syndrome is more common in patients with more severe respiratory disease [14].

The metabolic syndrome, defined by IDF criteria, mainly depends on abdominal obesity.

Studies have shown that the quantity of abdominal - visceral - adipose tissue is increased in patients with pulmonary obstructive diseases. The exact cause and mechanism are unspecified, but presumably unhealthy diet and inactive lifestyle play a major role in its development.

Interestingly, patients with normal nutritional status and metabolic syndrome had decreased physical performance (6MWD) compared to patients without metabolic syndrome but with COPD. Metabolic syndrome is known to reduce muscle mass, which may explain the experience mentioned above, and it is confirmed by our present research as well. The correlation is also reversed, because the low physical activity observed in COPD can be the cause of the development of the metabolic syndrome [15].

The most recent GOLD recommendation on the diagnosis, treatment and prevention of COPD [16] highlighted the importance of comorbidities. In particular, cardiovascular disease, hypertension, lung cancer, depression, osteoporosis, and metabolic disorders such as type 2 diabetes, metabolic syndrome, as they significantly affect the prognosis, and some of them are the most common causes of death even in mild COPD [17].

Nearly half of COPD patients participating in a pulmonary rehabilitation program are overweight or obese, which negatively affects respiration and exercise tolerance, especially while walking, however, a contradiction was described that patients with higher BMIs live longer than patients with low or normal BMI. This paradox, the so called “Obesity paradox” disappears above 30 BMI and physical inactivity and comorbidities clearly negatively affect the survival of individuals with COPD [18].

The term metabolic syndrome, or “cardiometabolic syndrome,” is often used today to describe the interaction of cardiovascular, renal, metabolic, prothrombotic and inflammatory disorders that result in increased morbidity and mortality in patients with COPD.

Several studies have evaluated the lipid profile of COPD patients, but the results remain contradictory. Sibel et al. found that serum HDL levels were significantly lower, while TG levels were significantly higher in patients with stable COPD than in controls [19]. Jiayu et al. described that there was no difference in serum TG, total chol, and LDL levels between COPD patients and controls [20]. Breyer et al reported that metabolic syndrome was more common among overweight and obese COPD patients [21]. Ummugulsum Can et al. examined disease severity and serum lipid levels and found that HDL levels were significantly lower in more severe COPD stages (GOLD III. and IV.) than in control subjects [22].

We detected a significantly increased TG level and a significantly decreased HDL cholesterol level among overweight patients (BMI > 25 kg/m²), patients with MetS had significantly higher BMI than patients without MetS in the lipid profile in our present study.

Systemic inflammation itself is associated with decreased serum HDL and increased TG levels in COPD [23], it has been shown that inflammatory cytokines disrupt lipid metabolism, there is an inverse correlation between serum HDL and IL-6 levels [24]. Patients with COPD are physically inactive, which further increases the risk of dyslipidemia, and they often use corticosteroids, which also increases the occurance of dyslipidemia and obesity

[25]. In addition, smoking as well as oxidative stress are possible mechanisms for the development of dyslipidemia, and all together they contribute to the development of MetS [26].

MetS appears to be more common in female patients with higher BMI. This allegation was confirmed by our present study as well. Numerous studies have shown that GOLD stage II patients have the highest MetS prevalence compared to more severe GOLD stage patients [27]. First, this observation may be due to the fact that the role of lifestyle in less advanced COPD disease has a greater effect on metabolism than other factors in the progression of the disease. Second, assuming that MetS has a higher cardiovascular risk in COPD, they may die earlier because of their CVD and may not reach end-stage COPD.

Drugs can directly affect the prevalence of MetS, e.g. oral glucocorticoids increase blood glucose levels, LDL levels and appetite, and can cause muscle atrophy and abdominal obesity. Other common drugs in the treatment of COPD, such as antidepressants, can cause decreased glucose tolerance, thus contributing to the development of MetS [28].

Recent studies have identified a so-called “co-morbidity predominant subtype” in COPD patients, characterized by a group of metabolic comorbidities, including CVD, T2DM, and obesity. Patients with CVD, hypertension and T2DM have been shown to be at increased risk for morbidity and mortality. Particular importance should be given to sitting position or stillness because the duration of sitting position shows a significant correlation with blood sugar levels and abdominal circumference. In Park and Larson's study, more than 11 hours of on-site sessions per day were recorded for people with COPD. This is also disadvantageous because studies in the healthy population suggest that prolonged sitting or sedentary work has a strong effect on the development of metabolic syndrome, regardless of moderate or intense physical activity. Even low-intensity physical activity can create a more favorable metabolic situation [29, 30].

Kupeli et al. and Abdelghaffar et al. reported that the presence of 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 [31]. In our study, we found a higher mMRC score in the presence of MetS and a significantly higher exacerbation rate, confirming the observations of a lower quality of life in COPD patients with MetS.

However, it is unclear whether early identification and treatment of metabolic syndrome in patients reduce the risk of developing cardiovascular disease and improves long-term clinical outcomes. Weight loss alone affects a number of risk factors that are very common in obesity, such as hypertension, dyslipidemia, and insulin resistance.Various studies have examined the effect of exercise in overweight and obese individuals through blood pressure, lipid profiles and glucose [32, 33]. Improvement in glycated hemoglobin (HbA1c) and insulin sensitivity has been described, and the total duration of exercise appears to be more important than the mode of exercise [34].

Our results show that the co-morbidity index increases in patients with metabolic syndrome, especially in patients who are overweight or obese, therefore, metabolic syndrome should be recognized early, and treated appropriately in patients with COPD. Our present study was a cross-sectional study, further longitudinal prospective studies are needed to study the long-term effects of metabolic syndrome on cardiovascular and other diseases in COPD patients.

Conclusion

In COPD patients, metabolic syndrome is more likely to develop, especially in obese patients. The most common components of MetS are abdominal obesity, hypertension, hyperglycemia and hyperlipidemia, more common in women with high BMI. In addition to obesity, decreased physical activity greatly increases the risk of developing metabolic syndrome and cardiovascular comorbidities. Reducing immobility and increasing the duration and intensity of physical activity significantly reduce the probability of developing metabolic syndrome. COPD patients with metabolic syndrome take more medication and have more comorbidities than those without MetS. Future follow-up and intervention studies are needed to survey the best treatment options.

List Of Abbrevations

ANOVA = Analysis of variance; 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 = glycated haemoglobin; IDF = International Diabetes Federation; IL-6 = interleukin-6; IL-8 = interleukin-8; ICS = inhaled corticosteroids; IL-15 = interleukin-15; LABA = long-acting bronchodilators; LAMA = long-acting muscarinic antagonist; LDL = low-density lipoprotein; MetS = Metabolic syndrome; mMRC = Modified Medical Research Council Dyspnea Scale; OR = odds ratio; PAI-1 = Plasminogen activator inhibitor-1; QoL = Quality of Life; 6MWT = six-minute walk test; ROS = reactive oxygen species; SABA = short-acting bronchodilators; SGRQ-C = St. George's respiratory questionnaire for COPD patients; 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.

Declarations

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. Patients were given oral and written information prior to the assessment, and then they signed a statement of consent.

Consent for publication:

Not applicable.

Availability of data and materials:

The data that support the findings of this study are available on request from the corresponding author [MF].

Competing interests:

The authors declare that they have no competing interests.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions:

MF and JTV developed the hypotheses, designed the study, performed the tests, wrote and published the manuscript. ANN and GSZ analyzed statistical data, prepared the tables and diagrams. CSB and LV drafted the manuscript and prepared the manuscript for publication. ST: supplemented and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

References

1. Varga J, Casaburi R, Ma S, et al. Relation of concavity in the expiratory flow-volume loop to dynamic hyperinflation during exercise in COPD. Respir Physiol Neurobiol. 2016;234:79-84. https://doi.org/10.1016/j.resp.2016.08.005
2. Varga JT. Smoking and pulmonary complications: respiratory prehabilitation. J Thorac Dis. 2019;11(Suppl 5):S639-S644. https://doi.org/10.21037/jtd.2018.12.11
3. Böszörményi Nagy Gy, Balikó Z, Kovács G, et al. Egészségügyi szakmai irányelv a krónikus obstruktív tüdőbetegség (COPD) diagnosztikájáról és kezeléséről, az alap, a szak és a sürgősségi ellátás területén. [Guideline for the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) in primary care, specialist- and emergency care.] Med. Thor. 2014;67:76112. Available from: https://www.copdplatform.com/res/file/national-documents/hun-guidelines.pdf [accessed: May, 3, 2020].
4. Márton J, Farkas G, Nagy Z, et al. Plasma levels of TNF and IL-6 following induction of acute pancreatitis and pentoxifylline treatment in rats. Acta Chir Hung. 1997;36(1-4):223-225. PMID: 9408354. https://pubmed.ncbi.nlm.nih.gov/9408354/
5. Doehner W, Haeusler KG, Endres M, Anker SD, MacNee W, Lainscak M. Neurological and endocrinological disorders: orphans in chronic obstructive pulmonary disease. Respir Med. 2011;105 Suppl 1:S12-S19. https://doi.org/10.1016/S0954-6111(11)70005-1
6. Krychtiuk KA, Kastl SP, Pfaffenberger S, et al. Association of small dense LDL serum levels and circulating monocyte subsets in stable coronary artery disease. PLoS One. 2015;10(4):e0123367. https://doi.org/10.1371/journal.pone.0123367
7. Yara S, Lavoie JC, Levy E. Oxidative stress and DNA methylation regulation in the metabolic syndrome. Epigenomics. 2015;7(2):283-300. https://doi.org/10.2217/epi.14.84
8. Clini E, Crisafulli E, Radaeli A, Malerba M. COPD and the metabolic syndrome: an intriguing association. Intern Emerg Med. 2013;8(4):283-289. https://doi.org/10.1007/s11739-011-0700-x

9. Pako J, Barta I, Balogh Z, et al. Assessment of the Anti-Aging Klotho Protein in Patients with COPD Undergoing Pulmonary Rehabilitation. COPD. 2017;14(2):176-180. https://doi.org/10.1080/15412555.2016.1272563
10. Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53(5):1900164. https://doi.org/10.1183/13993003.00164-2019
11. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-1327. https://doi.org/10.1164/ajrccm/145.6.1321
12. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test [published correction appears in Am J Respir Crit Care Med. 2016 May 15;193(10):1185]. Am J Respir Crit Care Med. 2002;166(1):111-117. https://doi.org/10.1164/ajrccm.166.1.at1102
13. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366(9491):1059-1062. https://doi.org/10.1016/S0140-6736(05)67402-8
14. Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review. COPD. 2016;13(3):399-406. https://doi.org/10.3109/15412555.2016.1140732
15. van den Borst B, Gosker HR, Koster A, et al. The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. Am J Clin Nutr. 2012;96(3):516-526. https://doi.org/10.3945/ajcn.112.040774
16. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195(5):557-582. https://doi.org/10.1164/rccm.201701-0218PP
17. Varga JT. Smoking and pulmonary complications: respiratory prehabilitation. J Thorac Dis. 2019;11(Suppl 5):S639-S644. https://doi.org/10.21037/jtd.2018.12.11
18. Fekete M, Pongor V, Fehér Á, Veresné Bálint M, Varga JT, Horváth I. Krónikus légzőszervi betegek tápláltsági állapotának vizsgálata – klinikai megfigyelések [Relationship of chronic obstructive pulmonary disease and nutritional status - clinical observations.] Orv Hetil. 2019;160(23):908-913. https://doi.org/10.1556/650.2019.31386
19. Xuan L, Han F, Gong L, et al. Association between chronic obstructive pulmonary disease and serum lipid levels: a meta-analysis. Lipids Health Dis. 2018;17(1):263. https://doi.org/10.1186/s12944-018-0904-4
20. Can U, Yerlikaya FH, Yosunkaya S. Role of oxidative stress and serum lipid levels in stable chronic obstructive pulmonary disease. J Chin Med Assoc. 2015;78(12):702-708. https://doi.org/10.1016/j.jcma.2015.08.004
21. Breyer MK, Spruit MA, Hanson CK, et al. Prevalence of metabolic syndrome in COPD patients and its consequences. PLoS One. 2014;9(6):e98013. https://doi.org/10.1371/journal.pone.0098013
22. Reed RM, Iacono A, DeFilippis A, Eberlein M, Girgis RE, Jones S. Advanced chronic obstructive pulmonary disease is associated with high levels of high-density lipoprotein cholesterol. J Heart Lung Transplant. 2011;30(6):674-678. https://doi.org/10.1016/j.healun.2010.12.010

23. Novgorodtseva TP, Denisenko YK, Zhukova NV, Antonyuk MV, Knyshova VV, Gvozdenko TA. Modification of the fatty acid composition of the erythrocyte membrane in patients with chronic respiratory diseases. Lipids Health Dis. 2013;12:117. https://doi.org/10.1186/1476-511X-12-117
24. Varga J, Palinkas A, Lajko I, Horváth I, Boda K, Somfay A. Pulmonary Arterial Pressure Response During Exercise in COPD: A Correlation with C-Reactive Protein (hsCRP). Open Respir Med J. 2016;10:1-11. https://doi.org/10.2174/1874306401610010001
25. Park SK, Larson JL. The relationship between physical activity and metabolic syndrome in people with chronic obstructive pulmonary disease. J Cardiovasc Nurs. 2014;29(6):499-507. https://doi.org/10.1097/JCN.0000000000000096
26. Vujic T, Nagorni O, Maric G, Popovic L, Jankovic J. Metabolic syndrome in patients with chronic obstructive pulmonary disease: frequency and relationship with systemic inflammation. Hippokratia. 2016;20(2):110-114. PMID: 28416906; PMCID: PMC5388510. https://pubmed.ncbi.nlm.nih.gov/28416906/
27. Díez-Manglano J, Barquero-Romero J, Almagro P, et al. COPD patients with and without metabolic syndrome: clinical and functional differences. Intern Emerg Med. 2014;9(4):419-425. https://doi.org/10.1007/s11739-013-0945-7
28. Khoza S, Barner JC. Glucose dysregulation associated with antidepressant agents: an analysis of 17 published case reports. Int J Clin Pharm. 2011;33(3):484-492. https://doi.org/10.1007/s11096-011-9507-0
29. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(7):728-735. https://doi.org/10.1164/rccm.201209-1665OC
30. Vágvölgyi A, Rozgonyi Z, Vadász P, Varga JT. A mellkassebészeti műtéti teherbíró képesség megítélése, perioperatív légzésrehabilitáció [Risk stratification before thoracic surgery, perioperative pulmonary rehabilitation]. Orv Hetil. 2017;158(50):1989-1997. https://doi.org/10.1556/650.2017.30862
31. Küpeli E, Ulubay G, Ulasli SS, Sahin T, Erayman Z, Gürsoy A. Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. Endocrine. 2010;38(1):76-82. https://doi.org/10.1007/s12020-010-9351-3
32. Varga J. Mechanisms to dyspnoea and dynamic hyperinflation related exercise intolerance in COPD. Acta Physiol Hung. 2015;102(2):163-175. https://doi.org/10.1556/036.102.2015.2.7
33. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol. 2013;3(1):1-58. https://doi.org/10.1002/cphy.c110062
34. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002;347(19):1483-1492. https://doi.org/10.1056/NEJMoa020194

Figures

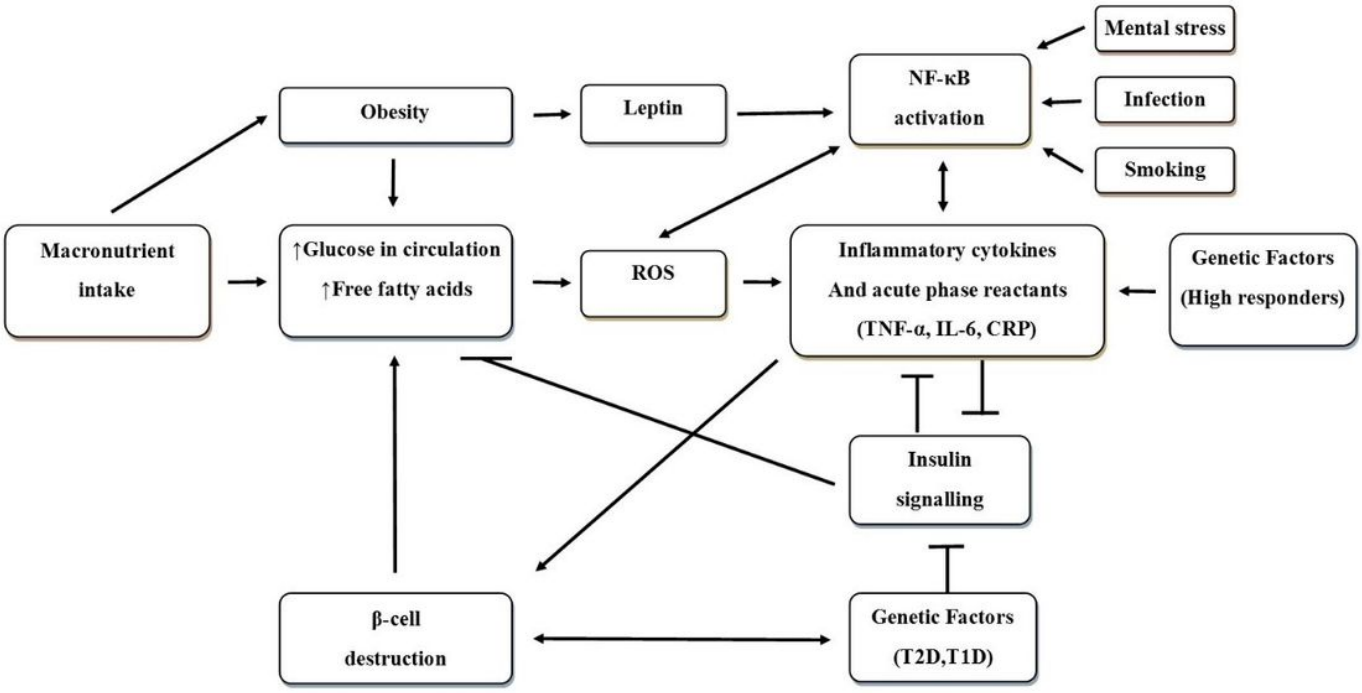

Figure 1

The suggested mechanism of inflammation in obesity of COPD patients. ROS: reactive oxygen species; TNF-alpha: tumor necrosis factor alpha; IL-6 = interleukin-6; CRP=C-reactive protein; NF-κB: Nuclear Factor Kappa B; T1D: Type 1 diabetes mellitus; T2D: Type 2 diabetes mellitus;