Metabolic syndrome in hospitalized patients with chronic obstructive pulmonary disease

Evgeni Mekov, Yanina Slavova, Adelina Tsakova, Marianka Genova, Dimitar Kostadinov, Delcho Minchev, Dora Marinova

The metabolic syndrome (MS) affects 21-53% of patients with chronic obstructive pulmonary disease (COPD) with a higher prevalence in the early stages of COPD, with results being highly variable between studies. MS may also correlate with disease characteristics. The aim of the study is to examine the prevalence of MS and its correlation with comorbidities and COPD characteristics in patients with COPD admitted for exacerbation. 152 patients with COPD admitted for exacerbation were studied for presence of MS. All of them were also assessed for vitamin D status and diabetes mellitus type 2 (DM). Data were gathered for smoking status and exacerbations during the last year. All patients completed CAT (COPD assessment test) and mMRC (Modified Medical Research Council Dyspnea scale) questionnaires and underwent spirometry. Duration of current hospital stay was recorded. 25% of patients have MS. 23,1% of the male and 29,5% of the female patients have MS (p>0.05). The prevalence of MS in this study is significantly lower when compared to a national representative study (44,6% in subjects over 45 years). 69,1% of all patients and 97,4% from MS patients have arterial hypertension. The presence of MS is associated with significantly worse cough and sleep (1st and 7th CAT questions; p=0.002 and p=0.001 respectively) and higher total CAT score (p=0.017). Average BMI is 27,31. None of the patients have MS and BMI <25. There is a correlation between the presence of MS and DM (p=0.008) and with the number of exacerbations in the last year (p=0.015). There is no correlation between the presence of MS and the pulmonary function. This study among hospitalized COPD patients finds comparable but relatively low prevalence of MS (25%) compared to previously published data (21-53%) and lower prevalence compared to general population (44,6%). MS may impact natural course and the number of exacerbations of COPD. Having in mind that MS is more common in the early stages and decreases with COPD progression, the COPD patients admitted for exacerbation may be considered as having advanced COPD.

Metabolic syndrome in hospitalized patients with chronic obstructive pulmonary disease

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Abstract

Introduction: The metabolic syndrome (MS) affects 21-53% of patients with chronic obstructive pulmonary disease (COPD) with a higher prevalence in the early stages of COPD, with results being highly variable between studies. MS may also correlate with disease characteristics.

Aim: To examine the prevalence of MS and its correlation with comorbidities and COPD characteristics in patients with COPD admitted for exacerbation.

Material and methods: 152 patients with COPD admitted for exacerbation were studied for presence of MS. All of them were also assessed for vitamin D status and diabetes mellitus type 2 (DM). Data were gathered for smoking status and exacerbations during the last year. All patients completed CAT (COPD assessment test) and mMRC (Modified Medical Research Council Dyspnea scale) questionnaires and underwent spirometry. Duration of current hospital stay was recorded.

Results: 25% of patients have MS. 23,1% of the male and 29,5% of the female patients have MS (p>0.05). The prevalence of MS in this study is significantly lower when compared to a national representative study (44,6% in subjects over 45 years). 69,1% of all patients and 97,4% from MS patients have arterial hypertension. The presence of MS is associated with significantly worse cough and sleep (1st and 7th CAT questions; p=0.002 and p=0.001 respectively) and higher total CAT score (p=0.017). Average BMI is 27,31. None of the patients have MS and BMI <25. There is a correlation between the presence of MS and DM (p=0.008) and with the number of exacerbations in the last year (p=0.015). There is no correlation between the presence of MS and the pulmonary function.

Conclusions: This study among hospitalized COPD patients finds comparable but relatively low prevalence of MS (25%) compared to previously published data (21-53%) and lower prevalence compared to general population (44,6%). MS may impact natural course and the number of exacerbations of COPD. Having in mind that MS is more common in the early stages and decreases with COPD progression, the COPD patients admitted for exacerbation may be considered as having advanced COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with significant extrapulmonary effects that may contribute to the severity in individual patients. By 2030, COPD will be the fourth cause of mortality worldwide. The extrapulmonary comorbidities influence the prognosis of the patients with COPD (1).

Metabolic syndrome (MS) is common in patients with COPD. According to the available studies the prevalence of MS in COPD patients varies between 21-53% (2). The prevalence of MS in COPD patients is increased when compared to a control group (3-6).

Available studies suggest that MS may have impact on quality of life (7), lung function (8-12), natural course of COPD (number of exacerbations) (13,14) as well as to affect comorbidities in COPD patients (15).

Many studies examine prevalence of MS in COPD patients (3,4,6,13,16-21) with results being highly variable between studies. Prevalence of MS in an unselected Bulgarian population aged 20-80 years is 30,8%. The prevalence of MS for participants over 45 years (the most common age group for the COPD patients) is higher - 44,6% (22). An epidemiological study conducted in 2010 in Bulgaria in COPD patients (n=3598) showed that metabolic syndrome is found in 13.8% of the patients (23). These results differ significantly from the others probably because of the different criteria for metabolic syndrome. A more recent study indicates that the prevalence of metabolic syndrome is 41.8% in patients with COPD (n=141) compared to 39% in the control group (n=103). However this study was not conducted using a random sample (exclusion criteria was presence of DM, age 49-79 years for patients with COPD and 35-65 for controls) (24). The prevalence of MS in COPD patients, hospitalized for exacerbation is hard to predict because MS tends to be more prevalent in early stages of COPD while patients experiencing severe exacerbation often have advanced disease. On the other side MS may impact natural course of COPD and predispose to exacerbation which will lead to increased prevalence of MS in this group.

There is not enough data to determine whether the results from these studies are applicable to specific subgroups of patients such as COPD patients admitted for exacerbation. COPD is increasingly divided in subgroups or phenotypes based on specific features and association with prognosis or response to therapy, the most notable being the feature of frequent exacerbations (25). We hypothesize that the prevalence of MS in COPD patients admitted for exacerbation is low (because of the severity of COPD in this subgroup and the MS being more prevalent in the early stages). Presence of MS may also have distinctive characteristics for this subgroup ('severe' exacerbator phenotype). The aim of this study is to find out the prevalence of MS in patients with COPD admitted for exacerbation and the correlations of presence of MS with comorbidities and COPD characteristics.

Material and methods

A total of 152 COPD patients hospitalized for exacerbation were studied for the presence of MS, DM, and vitamin D deficiency and insufficiency using well-established criteria for:

- ❖ Presence of <u>MS</u>: at least 3 of the following: 1. Elevated waist circumference >102 cm in males, >88 cm in females; 2. Triglycerides >1.7 mmol/L (or on therapy); 3. HDL <1.0 mmol/L in males, <1.3 mmol/L in females (or on therapy); 4. Elevated blood pressure: systolic $\geq$130 and/or diastolic $\geq$85 mm Hg (or on therapy); 5. Fasting glucose >5.5 mmol/L (or on therapy) (26).

- ❖ Presence of <u>DM</u>: fasting plasma glucose ≥7.0 mmol/L OR 2-h plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT) OR HbA1c≥6.5% OR on therapy (27);
- ❖ Presence of <u>prediabetes</u>: fasting plasma glucose 5.6-6.9 mmol/L OR 2-h plasma glucose 7.8-11.0 mmol/L during an OGTT OR HbA1c 5.7-6.4% (27);
- ❖ Presence of <u>vitamin D deficiency</u>: 25(OH)D <25 nmol/L; <u>vitamin D insufficiency</u>: 25(OH)D 25-50 nmol/L; <u>vitamin D sufficiency</u>: >50 nmol/L (28,29).

The diagnosis of COPD was made according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria (DM1). Data were gathered for age, sex, smoking status and number of pack-years, number of bone fractures, therapy for arterial hypertension, therapy for DM, COPD therapy and number of exacerbations in the last year. The patients completed CAT and mMRC questionnaires and underwent pre- and post bronchodilatatory spirometry. Blood pressure was obtained according to the American Heart Association Guidelines (30). A patient was considered as having arterial hypertension if taking antihypertensives.

The inclusion criteria were post bronchodilator spirometry obstruction defined as FEV1/FVC<0.70. All participants in this study signed informed consent.

The exclusion criteria were failure to comply with study procedures (no completed questionnaires, no medical and demographic information, no spirometry, no lab tests) or FEV1/FVC ratio >0.70 after administration of bronchodilator.

Smoking status

Every participant was classified according to smoking status (31):
Never smoker – never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire lifetime.
Former smoker – smoked at least 100 cigarettes in their entire life but were not currently smoking.
Current smoker – had smoked at least 100 cigarettes in their entire life and were still smoking.
Numbers of pack-years were calculated using the formula:
Number of pack-years = years of smoking X number of daily smoked cigarettes/20

Anthropometric indices

Body weight and height were measured and the body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). According to BMI all patients were classified as underweight (<18,5), normal (18,5 – 24,99), overweight (25-29,99) and obese (>30). Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest according to the WHO STEPS protocol (32). Hip circumference was measured around the widest portion of the buttocks (32). Body adiposity index (BAI) was calculated as:
Hip circumference / (Height X √Height) – 18

COPD exacerbations and duration of hospital stay

Data were gathered for number of severe exacerbations (hospitalizations) and moderate exacerbations (antibiotic or/and systemic steroid treatment without hospitalization due to worsening of pulmonary symptoms) (1) in the previous year. The duration of the current hospital stay was recorded.

127

Quality of life

Quality of life was assessed with the mMRC scale and CAT questionnaire. Patients were instructed that there were no right or wrong answers. All patients' questions were answered. Patients were classified according to GOLD as having less symptoms (CAT <10) and breathlessness (mMRC grade 0-1) and more symptoms (CAT ≥10) and breathlessness (mMRC grade ≥2). Because all patients were hospitalized due to exacerbation there were only group C (high risk, less symptoms) and group D (high risk, more symptoms) patients according to GOLD (DM1).

Pulmonary Function Testing

The spirometry was performed using Minispir® New spirometer (MIR - Medical International Research, Italy). Patients were instructed to withdraw using short-acting β2-agonists at least 6 hours, long-acting β2-agonist at least 12 hours, long acting muscarinic antagonist 24 hours and short acting muscarinic antagonist 12 hours before the spirometry (33). Post bronchodilator spirometry testing was performed 15-30 min after inhalation of 400mcg Salbutamol according to ERS/ATS recommendations (33). Pre- and post- values were obtained for: FVC, FEV1, FEV1/FVC, FEV6, FEV1/FEV6, PEF, FEF2575, FEV3, FEV3/FVC as well as the difference between post/pre values (delta values). GLI (Global Lungs Initiative) predicted values were used (GLI-2012). Patients' obstruction were classified according to the severity of airflow limitation based on post-bronchodilator FEV1 as follows: mild (≥80% predicted); moderate (80>FEV1≥50% predicted); severe (50%>FEV1≥30% predicted); very severe (<30% predicted) (1).

Blood samples and analyses

A venous blood sample was collected from each subject after a 12-hour fasting. Blood samples were taken as late as possible before discharging (usually on 6th or 7th day). Plasma glucose, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol (tChol) were measured with a Roche COBAS INTEGRA® 400 plus analyzer and an enzymatic colorimetric assay and blood glucose was measured with an enzymatic reference method with hexokinase. Vitamin D was measured with Elecsys 2010 (Roche) and Electro-chemiluminescence immunoassay (ECLIA). Glycated hemoglobin (HbA1c) was measured with a NycoCard device and boronate affinity assay. For patients without established DM a 75g OGTT was performed with blood samples for glucose taken on first and second hour.

Statistical Analysis

Statistical analysis was performed with the SPSS for Windows software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and 95 Confidence intervals (95%CI) and categorical variables - as percentages. Chi-square test was used to determine the associations between categorical variables. Continuous variables were examined for normality by Shapiro-Wilk test. For normally distributed variables, differences between the groups were determined by independent-samples T test for two samples and analysis of variance (ANOVA) for more than 2 samples. Mann-Whitney U test was used for abnormally distributed variables with 2 samples and Kruskal-Wallis test for variables with more than 2 samples. Regression analyses were

169 used to determine risk factors for presence of DM or the consequences of having DM. Significance
170 value (p-value) was set at 0.05.
171
172   All patients signed informed consent. Medical University-Sofia Research Ethics Commission
173 approved the study.
174

Results and discussion

Sample characteristics

177   A total of 152 COPD patients admitted for exacerbation were recruited from University
178 Specialized Hospital for Active Treatment of Pulmonary Diseases 'Saint Sofia', Sofia, Bulgaria. Mean
179 age of patients in this study was 65,1±9,9 years. 71,1% (108/152) were males, 28,9% (44/152) were
180 females; mean post-bronchodilator FEV_1 was 55,34 ±19,5%. 15,8% from the patients were never
181 smokers, 57,9% - former smokers and 26,3% - current smokers.
182

Prevalence of MS

184   25,0% (38/152) of the patients have MS. 23,1% (25/108) of males have MS vs. 29,5% (13/44)
185 of females but this difference is not statistically significant (p=0.409) (table 1). Mean age does not
186 differ between the patients with and without MS (64,5 vs 65,3 years, p=0.688).
187

188 Table 1. Prevalence of MS according to different factors

	% MS	P value
All	25,0	
Sex		
Male	23,1	P=0.409
Female	29,5	
Smoking status		
Never	25,0	P=0.678
Former	27,3	
Current	20,0	
Arterial hypertension		
Yes	35,2	**P<0.0005**
No	2,1	
Vitamin D status		
>50 nmol/l	24,2	P=0.929
25-50 nmol/l	24,6	
<25 nmol/l	28,0	
DM		
Yes	37,7	**P=0.008**
No	18,2	
BMI		
Underweight	0	**P<0.0005**

Normal	0	
Overweight	27,3	
Obese	54,8	
BAI		
Underweight	0	**P=0.001**
Normal	17,5	
Overweight	28,9	
Obese	50,0	
Quality of life		
CAT 0-9	16,0	P=0.256
CAT ≥10	26,8	
mMRC 0 or 1	18,9	P=0.201
mMRC ≥2	28,3	
FEV1		
FEV1≥50%	21,3	P=0.390
FEV1<50%	27,5	
FEV1≥80%	11,8	P=0.852
80%>FEV1≥50%	28,8	
50%>FEV1≥30%	26,1	
FEV1<30%	25,0	

189 The prevalence of MS in COPD patients is summarized in table 2. It varies between 21-53%
190 (table 2). This study found comparable but relatively low prevalence of MS compared to previous
191 studies (fig. 1). The prevalence of MS in our study is significantly lower when compared to the general
192 Bulgarian population (44,6% in subjects over 45 years) (22). The odds ratio for COPD patients
193 admitted for exacerbation of having MS is 0.41 compared to general population (95% CI 0.28-0.61,
194 p<0.0005).
195

196 Table 2. Prevalence of MS in patients with COPD

Authors	N	Studied population	Prevalence of MS
Akpinar et al. (16)	133	Patients with COPD and controls	**44.6%**
Funakoshi et al. (3)	7189	Men aged 45-88 years	**16.8%**, OR 0.72 (95% CI 0.51-1.02) in GOLD I; **28.7%**, OR 1.33 (95% CI 1.01-1.76) in GOLD II-IV
Kupeli et al. (13)	106	Hospitalized patients with COPD	**27.3%**
Lam et al. (4)	7358	General population >50 years	**22.6%**; OR 1.47 (95% CI 1.12-1.92)
Marquis et al. (17)	72	Patients with COPD and controls	**47%**
Minas et al. (18)	114	Men with COPD	**21%**
Ozgen Alpaydin et al.	90	Patients with COPD and controls	**43%**

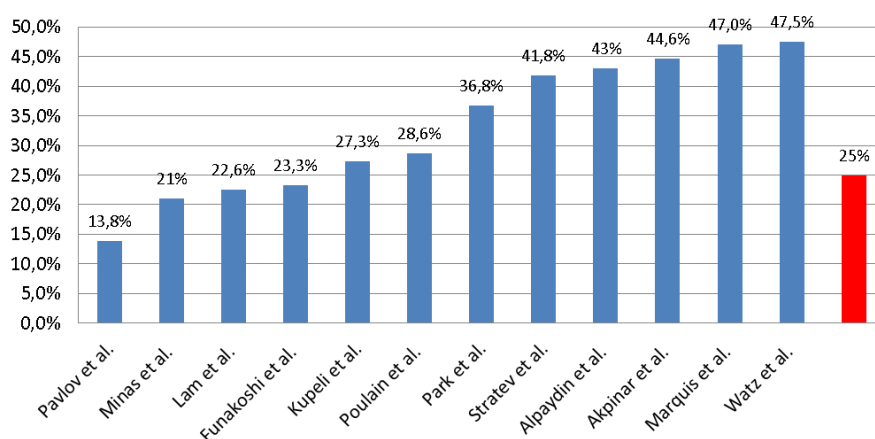|			
(19)			
Park et al. (6)	1215	Patients with COPD and controls >40 years	**33%** vs 22.2% for men; **48.5%** vs 29.6% for women OR 2.03 (95% CI 1.08-3.80)
Poulain et al. (20)	28	Patients with COPD	Overweight – **50%**; Normal weight – **0%**.
Watz et al. (21)	200	Patients with COPD and chronic bronchitis	GOLD I – **50%**; GOLD II – **53%**; GOLD III – **37%**; GOLD IV – **44%**; Chronic bronchitis – 53%

197

Fig. 1. Prevalence of MS in COPD patients

Two Bulgarian studies examined the prevalence of MS in COPD patients. An epidemiological study conducted in Bulgaria in COPD patients (n=3598) reported a prevalence of 13,8%. These results differ significantly from the literature data probably because of the different criteria for metabolic syndrome (presence of DM, BMI >30 and blood pressure >140/90 mmHg) which makes data comparing irrelevant (23). A more recent study indicates that the prevalence of metabolic syndrome is 41.8% in patients with COPD (n=141) compared to 39% in the control group (n=103). However this study was not conducted using a random sample (exclusion criteria was presence of DM, people were aged 49-79 years for patients with COPD and 35-65 years for controls) (24). However it uses similar criteria for MS and when comparing the results our study finds lower prevalence of MS.

Fulfilled criteria for MS (in all and in MS patients) are shown in table 3. Virtually all (37/38) patients with MS in this study have arterial hypertension, followed by elevated waist circumference (33/38). Arterial hypertension has greatest sensitivity but is not specific. Elevated waist circumference has greatest accuracy. Number of fulfilled criteria in all patients is given in table 4.

Table 3. Fulfilled criteria for MS in all patients and in patients with MS

MS criteria	All patients (n=152)	MS only (n=38)	Without MS (n=114)	Accuracy
Elevated blood pressure: systolic ≥130 and/or diastolic ≥85 mm Hg (or on therapy)	69,1% (n=105)	97,4% (n=37)	59,6% (n=68)	54,6%

Elevated waist circumference >102 cm in males, >88 cm in females	28,3% (n=43)	86,8% (n=33)	8,8% (n=10)	90,1%
Triglycerides >1,7 mmol/L (or on therapy)	29,6% (n=45)	60,5% (n=23)	19,3% (n=22)	75,7%
Fasting glucose >5,5 mmol/L (or on therapy)	34,2% (n=52)	65,8% (n=25)	23,7% (n=27)	73,7%
HDL <1.0 mmol/L in males, <1.3 mmol/L in females (or on therapy)	15,8% (n=24)	39.5% (n=15)	7,9% (n=9)	78,9%

216

217 Table 4. Number of fulfilled criteria for MS in all patients

Number of fulfilled criteria	%	n
0	13,8	21
1	33,6	51
2	27,6	42
3	13,2	20
4	10,5	16
5	1,3	2

218

219 The prevalence results could be explained with differences between the populations in different
220 studies (physical activity, diet, lifestyle etc.). For example, Bulgaria is low-income country, which may
221 impact diet preferences and treatment choices. Furthermore, patients in this study had been hospitalized
222 due to exacerbation, which represents the most severe group of COPD patients. Having in mind that
223 MS is more common in the early stages and decreases with COPD progression (21), COPD patients
224 hospitalized for exacerbation may be considered as having advanced COPD.
225 MS have low prevalence in COPD patients hospitalized due to exacerbation suggesting
226 advanced disease in these patients.

Lifestyle factors

228 According to NHANES III study smokers are more likely to develop MS than nonsmokers in
229 general populationand the risk increases with the number of pack-years even after adjusting for
230 covariates (34). Our study did not find significant differences in prevalence of MS according to
231 smoking status (p=0.678) and number of pack-years (p=0.682). These results could be explained with
232 smoke being the biggest factor in developing COPD and effect of developing MS could be reduced.
233 Moreover nicotine may be an appetite suppressant and lower the weight thus decreasing prevalence of
234 metabolic syndrome (35). Third, hospitalized COPD patients are patients with predominantly advanced
235 disease and prone to cachexia and wasting. Also lifestyle changes (quit smoking) in the presence of the
236 two diseases should be considered which may change the prevalence of MS.
237 Treatment with inhalatory corticosteroids (ICS) is not risk factor for MS (p=0.899) similar to
238 findings for DM (36). Fasting glucose level are not influenced by ICS (p=0.837).
239 MS is not associated with smoking status and treatment with ICS.

240

Comorbidity results

242 COPD is a disease that affects mainly the lungs, but is characterized by systemic inflammation
243 and a number of extrapulmonary manifestations. Only 1/3 of patients with COPD die due to respiratory
244 failure. Main cause of death is lung cancer and cardiovascular complications (37).

245   The vast majority of patients with COPD have a vitamin D deficiency (38). Aside from its role
246 in the metabolism of calcium and phosphorus, vitamin D is involved in the pathogenesis of multiple
247 diseases, including MS (39), mainly because it affects the secretion and the function of insulin (40).
248 However in our study vitamin D levels do not significantly differ in relation to presence of MS (32,11
249 vs 31,92 nmol/l, p=0.860). Presence of MS is also not related to vitamin D status (p=0.929) (table 1).
250   There are no studies that examine the relationship between osteoporosis and MS in patients
251 with COPD. However, both diseases share common risk factors such as smoking, lack of physical
252 activity, and treatment with corticosteroids. Some of the components of the metabolic syndrome
253 (arterial hypertension, elevated triglycerides, reduced HDL cholesterol) are risk factors for low bone
254 density. Systemic inflammation in MS plays a role in the pathogenesis of osteoporosis (41). On the
255 other hand, studies examining the relationship between MS and osteoporosis showed inconsistent
256 results, probably due to the protective effect of obesity (42,43). However number of fractures in our
257 study does not significantly differ regarding the presence of MS (p=0.443). Presence of at least one
258 fracture also does not differ significantly in relation to presence of MS (p=0.511).
259   Most patients with DM have MS, but the opposite is not necessarily true (44). In our study there
260 is a correlation between the presence of MS and DM (p=0.008). 52,6% (20/38) from patients with MS
261 have DM. BMI and BAI differ significantly according to presence of MS – 32,51 vs 25,58, p<0,0005
262 for BMI and 31,01 vs 25,58, p<0,0005 for BAI. There is also significant difference in prevalence of
263 MS in BMI and BAI groups (table 1). It is notable that none of the patients have MS and BMI <25
264 (table 1).
265   Linear regression showed presence of MS as risk factor for higher BMI (R=0.542, r^2=0.293,
266 p<0.0005, B=6.928, 95% CI 5.193-8.662) and BAI (R=0.406, r^2=0.165, p<0.0005, B=5.423, 95% CI
267 3.455-7.392).
268   A logistic regression analysis was conducted to predict presence of MS in a relation to presence
269 of other comorbidities. Presence of DM slightly improves the model (chi square = 6.818, p=0.009 with
270 df = 1). Nagelkerke's R2 of 0.065 indicates a weak relationship. Odds ratio was 2,73. Vitamin D status
271 does not improve the model (p>0.05).
272   The presence of MS is associated with presence of DM, higher BMI and BAI, but is not
273 associated with vitamin D levels, vitamin D status and number of fractures.
274

Exacerbations results and duration of hospital stay

276   Hyperglycemia is associated with elevated glucose concentrations in tissues and bronchial
277 aspirates (45) where it may stimulate infection by enhancing bacterial growth (46) and by promoting
278 bacterial interaction with the airway epithelium (47). Hyperglycemia also impairs both innate and
279 adaptive immunity, suppressing the host response to infection.
280   The presence of MS in patients with COPD increases the frequency of exacerbations (2.4 vs.
281 0.7) and their duration – (7.5 vs. 5.0 days) according to Kupeli et al. (13), and 8 versus 5.5 days,
282 according to Abdelghaffar et al. (14).
283   Our study found a significant difference between the number of total exacerbations according to
284 the presence of MS (table 5, p=0.015). The number of severe exacerbation, moderate exacerbation and
285 duration of hospital stay did not reach significance (p=0.130, p=0.188 and p=0.553 respectively).
286

287 Table 5. Number of severe, moderate and total exacerbations in previous year and duration of hospital
288 stay according to the presence of MS

	No MS	MS

Moderate exacerbations	0,61 (0,49-0,76)	0,92 (0,59-1,34)
Severe exacerbations	1,79 (1,61-1,97)	2,08 (1,71-2,50)
All exacerbations	**2,40 (2,19-2,61)**	**3,00 (2,56-3,52)**
Hospital stay (in days)	7,47 (7,24-7,70)	7,63 (7,28-8,05)

289

290   Triglycerides and blood glucose levels in our study did not correlate with number of
291 exacerbations as reported by other authors (13) (all p>0.05).
292   Linear regression showed presence of MS as risk factor for higher number of exacerbations
293 (R=0.207, r^2=0.043, p=0.010, B=0.596, 95% CI 0.143-1.050). From the MS components presence of
294 arterial hypertension is strongest risk factor for exacerbation (R=0.228, r^2=0.052, p=0.005, B=0.615,
295 95% CI 0.192-1.038).
296   MS is associated with increased number of exacerbations, but not with the duration of hospital
297 stay.
298

Quality of life results

300   The presence of MS is associated with significantly worse cough and sleep (1st and 7th CAT
301 questions; p=0.002 and p=0.001 respectively) and higher total CAT score (p=0.017) (table 6). This
302 confirms the data about reduced quality of life in patients with MS (7). However prevalence of MS is
303 not significantly different between patients with less symptoms (CAT 0-9) and breathlessness (mMRC
304 0 or 1) compared to patients with more symptoms (CAT ≥10) and breathlessness (mMRC ≥2) (all
305 p>0.05) (table 1). These mixed results may be explained with COPD having higher negative impact on
306 quality of life than MS (physical limitation due to shortness of breath) like suggested for DM (48) and
307 ameliorating the effect in patients having both diseases.
308
309 Table 6. Mean CAT score on every question and in total according to presence of MS

MS	Mean CAT score	N	P value
MS – no	CAT1 1,95	114	**P=0.002**
MS - yes	CAT1 2,63	38	
MS – no	CAT2 1,92	114	P=0.063
MS - yes	CAT2 2,34	38	
MS – no	CAT3 2,54	114	P=0.092
MS - yes	CAT3 2,97	38	
MS – no	CAT4 3,52	114	P=0.361
MS - yes	CAT4 3,74	38	
MS – no	CAT5 1,23	114	P=0.198
MS - yes	CAT5 1,66	38	
MS – no	CAT6 1,54	114	P=0.695
MS - yes	CAT6 1,68	38	
MS – no	CAT7 1,28	114	**P=0.001**
MS - yes	CAT7 2,21	38	
MS – no	CAT8 2,62	114	P=0.068
MS - yes	CAT8 3,08	38	
MS – no	Total CAT 16,61	114	**P=0.017**
MS - yes	Total CAT 20,32	38	

310   Regression analyses also showed that MS is a risk factor for reduced quality of life, measured
311 with total CAT score (R=0.205, r^2=0.042, p=0.011, B=3.711, 95% CI 0.859-6,562). Presence of MS
312 also impairs cough and sleep – first (R=0.285, r^2=0.081, p<0.0005, B=0.684, 95% CI 0.313-1,055) and
313 seventh (R=0.268, r^2=0.072, p=0.001, B=0.930, 95% CI 0.390-1,470) CAT questions.
314   In this study the presence of MS is associated with reduced quality of life, measured with CAT
315 questionnaire.

Pulmonary function test (PFT) results

317   COPD is characterized by airflow obstruction, which is not fully reversible. MS is associated
318 with a reduction of lung volumes (8-12). It should be noted that some studies found no association
319 between lung function and the presence of MS (49).
320   Our study did not find differences in FVC, FEV1, FEV1/FVC, FEV6, FEV1/FEV6, PEF,
321 FEF2575 and FEV3 according to the presence of MS. It should be noted that there is tendency for FVC
322 and FEV1/FVC ratio (p=0.094 and p=0.091 respectively). However, because of this there is significant
323 difference in FEV3/FVC ratio (p=0.033) (table 7).
324
325 Table 7. Mean PFT values according to the presence of MS

MS	Mean PFT value	N	P value
No	FEV1 55,56%	114	P=0.811
Yes	FEV1 54,68%	38	
No	FVC 80,46%	114	P=0.094
Yes	FVC 72,45%	38	
No	FEV1/FVC 0,53	114	P=0.091
Yes	FEV1/FVC 0,57	38	
No	FEV6 73,89%	114	P=0.277
Yes	FEV6 68,63%	38	
No	FEV1/FEV6 0,57	114	P=0.107
Yes	FEV1/FEV6 0,61	38	
No	PEF 55,62%	114	P=0.735
Yes	PEF 56,66%	38	
No	FEF2575 38,89%	114	P=0.316
Yes	FEF2575 40,95%	38	
No	FEV3 66,62%	114	P=0.601
Yes	FEV3 63,89%	38	
No	FEV3/FVC 0,81	114	**P=0.033**
Yes	FEV3/FVC 0,85	38	

326   Regression analyses also showed that MS is not a risk factor for reduced pulmonary function
327 (all p>0.05). However some of the components of MS are associated with reduced pulmonary function
328 with highest impact of HDL on FVC (R=0.183, r^2=0.033, p=0.024, B=-8.517, 95% CI -15.904;-1,130)
329 and FEV1 (R=0.251, r^2=0.063, p=0.001, B=-10.391, 95% CI -16.865;-3,918). Fasting glucose is
330 associated with increased FEV1/FVC ratio (R=0.186, r^2=0.035, p=0.022, B=1.238, 95% CI 0.183;
331 2.294) probably because of lowering FVC.
332   There is no difference in prevalence of MS in patients with FEV1 <50%, when compared to
333 patients with FEV1 >50% (p=0.390) or regarding GOLD stage (p=0.852) (table 1).
334   MS in our study is not associated with worsen pulmonary function. Prevalence of MS is not
335 different regarding GOLD stage.

336

Conclusions

337

338   This study finds 25% prevalence of MS in COPD patients admitted for exacerbation which is
339 significantly lower than general population. MS is more prevalent in females, but the gender difference
340 is not statistically significant. In this study most of the patients are former smokers and prevalence of
341 MS does not differ regarding smoking status and treatment with ICS.
342   The presence of MS is associated with presence of DM, higher BMI and BAI, more
343 exacerbations during the previous year and lower quality of life. MS is not associated with increased
344 hospital stay and lower pulmonary function.
345   This study finds comparable but relatively low prevalence of MS compared to previously
346 published data (21-53%). MS may impact natural course of COPD. Having in mind that MS is more
347 common in the early stages and decreases with COPD progression, the COPD patients admitted for
348 exacerbation may be considered as having advanced COPD.
349

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