ORIGINAL ARTICLE, MEDICINE

Comorbidities of COPD in Bulgarian Patients – Prevalence and Association with Severity and Inflammation

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Background: COPD is a disease with constantly rising economic and social burden; it is associated with multiple comorbidities which contribute to the disease severity.

Aim: To investigate the prevalence of co-morbidities in COPD patients and their association with the disease severity and CRP levels.

Patients and methods: We conducted a retrospective study among 338 COPD patients (mean age 65.2±7.6 years) with assessment of comorbidities, spirometry measurements and serum levels of CRP. In 183 patients we found metabolic syndrome (MS) according to IDF criteria.

Results: We found prevalence of cardiovascular diseases (CVD) of 73.5% (hypertension 70.4%, CHF 47.4%, ischemic heart disease 37.5%, and cardiac arrhythmias 12.6%), with higher prevalence in patients with more severe disease. We found prevalence of type 2 diabetes of 21.1%, and 12.4% prevalence of bronchiectasis. In a subpopulation of the patients we found 48.1% prevalence of MS and the serum levels of CRP were significantly higher in patients with COPD and MS compared to those without the syndrome: 7.4 (3.14 – 11.54) mg/ml vs 4.06 (2.64 – 6.93) mg/ml, p=0.006.

Conclusion: The present study suggests high prevalence of CVD comorbidities in COPD patients and association with the disease severity. Metabolic syndrome is a common comorbidity and is associated with increased inflammatory response.

BACKGROUND

COPD is a disease with rising social burden due to increasing mortality and the disabling course of the disease. There are expectations of rising morbidity in the future as a result of the increasing number of active smokers and the aging of the general population.¹ Although COPD affects primarily the lungs, it is assumed nowadays that it is a systemic and multifaceted disease, which is characterized with systemic inflammation often associated with other conditions as comorbidities. The peripheral inflammation spills over into the circulation, resulting in systemic inflammation that may worsen comorbidities, such as cardiovascular diseases, diabetes and osteoporosis. Comorbidities contribute to the disease severity in the individual patients and the treatment of comorbidities may have positive

effect on the course of the disease, because COPD patients usually die of complications associated with the accompanying conditions.² Comorbidities are present in every stage of the disease as they are important determinants of the disease course and have great economic consequences.³ Historically, the term comorbidity was defined as ‘any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study’.⁴ The most common comorbidities of COPD are cardiovascular diseases (CVD), metabolic disorders, osteoporosis, skeletal muscle dysfunction, anxiety/depression, cognitive impairments, gastrointestinal diseases and other respiratory diseases as bronchiectasis, lung fibrosis and lung carcinoma.⁵ Population based studies confirm this thesis: an epidemiological study

conducted in Switzerland found that 2.3% of the hospitalizations in the country in the period between 2002 and 2010 were due to COPD and the number increased to 6.1% in patients over the age of 70 years. In hospitalized patients the highest comorbidity was associated with hypertension (35%), followed by ischemic heart disease (14.4%), cardiac rhythm abnormalities – atrial fibrillation and flutter (~10%) and type II diabetes mellitus (~10%).⁶ In Bulgaria there are inconsistent data about the prevalence of COPD comorbidities. Some studies discussed below present different aspects of the problem.

AIM

The aim of the present study was to assess the prevalence of the most common comorbidities in COPD patients in Varna region, Bulgaria and find their correlation with the disease severity and the levels of CRP.

PATIENTS AND METHODS

We performed a retrospective study among 338 COPD patients (mean age 65.2 ± 7.6 years, 67.4% males) after approval from local ethical committee (N 4/10.10.2009). 250 of the patients were hospitalized in the pulmonary clinic of St. Marina University Hospital, Varna and in the Clinic of Internal Diseases of Varna Naval hospital between 2010 and 2016, for COPD exacerbation. 88 subjects were stable COPD patients from follow up visits. Inclusion criteria for the study were: established COPD diagnosis, post-bronchodilator obstructive spirometry according to ATS/ERS criteria and use of inhalation therapy either LABA, LAMA, or combination with ICS. Patients showing reversibility of FEV_1 more than 12% and 200 ml were excluded from the study. The presence of comorbidities was assessed by medical records, concomitant medications and self-reported. Prevalence of comorbidities was compared to other studies in Bulgaria and epidemiological studies and meta-analyses. The level of obstruction was assessed with spirometry. As an inflammatory marker we used the serum levels of CRP. In 183 of the patients we defined the presence of metabolic syndrome according to IDF criteria: presence of central obesity (waist circumference > 94 cm for males and > 80 cm for females) in combination of two or more of the following: increased arterial blood pressure $> 130/85$ or treatment for hypertension; increased levels of triglycerides > 1.7 mmol/l; low levels of HDL cholesterol < 1.03 mmol/l for males and < 1.29 mmol/l for females; increased levels of blood glu-

cose > 5.6 mmol/l or previously diagnosed type 2 diabetes.⁷ Data were analysed with IBM SPSS for Windows, v. 19.

RESULTS

The mean FEV_1 % predicted of patients with exacerbated COPD was 50.91 ± 13.19 % vs. 62.7 ± 17.6 % in stable COPD patients. Most of the patients (56.8%) had no exacerbations in the previous year, 25.9% had one exacerbation, 15.1% had two exacerbations and 2.2% had three or more exacerbations.

We found total prevalence of cardiovascular comorbidities of 73.5% with hypertension accounting for 70.5%, followed by chronic heart failure (47.4%), ischemic heart disease (37.5%) and cardiac arrhythmias (12.6%). The prevalence of type 2 diabetes mellitus was 21.1% and bronchiectasis accounted for 12.4%. In a subset of 183 patients we found 48.1% prevalence of MS. When selecting the patients with severe and very severe obstruction (GOLD stages III and IV) we found significantly higher comorbidity rates of cardiovascular diseases compared to the patients with lower levels of obstruction ($p < 0.05$).

In the present study we found significantly increased serum levels of CRP even in the stable phase of the disease (7.96 ± 14.1 in stable COPD vs. 19.9 ± 34.7 mg/ml in exacerbated COPD). In patients with COPD who presented with MS we found significantly higher levels of CRP compared to those without the syndrome: 7.4 (3.14 – 11.54) mg/ml vs. 4.06 (2.64 – 6.93) mg/ml, $p = 0.006$. Correlation analysis showed that levels of CRP correlate positively with the GOLD spirometry stage of the disease ($r = 0.308$, $p < 0.0001$) and negatively with FEV_1 % predicted ($r = -0.259$, $p < 0.0001$).

DISCUSSION

I. CARDIOVASCULAR COMORBIDITIES

In the present study the cardiovascular diseases were the most common comorbidities among the investigated patients with the highest prevalence of hypertension (**Fig. 1**). Similar results were found by other Bulgarian researchers (Mekov et al.) who investigated 375 COPD patients and found comorbidity of hypertension in 68% of the patients.⁸ During follow up of 226 COPD patients in Pleven region, Bulgaria, Yanev et al. established accompanying cardiovascular comorbidity in 78.5% of the patients with highest rates found for hypertension (48.1%), followed by ischemic heart disease (21.4%), CHF (21.4%) and cardiac rhythm disorders (20.6%).⁹

Cardiovascular comorbidity in Bulgaria is similar and even higher than that reported in international population studies and meta-analysis. For example, in recent meta-analysis Miravitles et al. included 25 550 patients with COPD who participated in randomized tiotropium trials and 61 361 COPD patients in observational studies and found that hypertension is the most common accompanying disease with prevalence between 41% and 60.6%, followed by ischemic heart disease (12.5-41%) and cardiac arrhythmias with prevalence 7.8-15.8%.¹⁰ In the ARIC and CHS population based cohorts, the prevalence of hypertension was 34% in normal subjects but 40% in GOLD stage I COPD patients, 44% in GOLD stage II and 51% in GOLD stage III and IV COPD patients.¹¹ In the present study we also found increased incidence of hypertension in more severe disease (**Fig. 2**). The increased comorbidity with hypertension and cardiovascular diseases can be explained on one hand with the fact that they are the most common diseases in the general population and on the other hand accelerated ageing with degradation of elastin and increased deposition of collagen resulting in increased arterial stiffness may play a role. Arterial stiffness was reported to be increased in COPD patients, and is related to FEV₁ levels and emphysema.¹² In a large UK database of primary care medical records, comprising 1,204,110

patients aged over 35 years, 29,870 patients were identified with COPD and these patients were five times more likely to have cardiovascular disease compared with those without COPD.¹³ It appears that reduced lung function is an independent risk factor for developing cardiovascular diseases. In the Baltimore Longitudinal Study of Aging, patients with the greatest decline in FEV₁ over a 16-year follow-up period were three to five times more likely to die from a cardiac cause than those with the lowest decline in FEV₁.²⁸ Even among lifetime nonsmokers, an increased decline in FEV₁ was associated with a five to 10-fold increase in risk of cardiac death, suggesting that the relationship between changes in FEV₁ and cardiovascular events is independent of the effects of smoking.¹⁴

II. SYSTEMIC INFLAMMATION

Systemic inflammation is an extra-pulmonary manifestation of COPD and is characterized by increased inflammatory markers. It has been proven that raised levels of CRP and systemic inflammatory response are major risk factors for development of atherosclerosis and contribute to the increased risk of cardiovascular diseases.¹⁵ In the present study we found elevated levels of CRP even in stable COPD patients and association with disease severity. Systemic inflammation is defined as two

Figure 1. Prevalence of cardiovascular comorbidities in COPD patients.

Figure 2. Cardiovascular comorbidities according to COPD severity.

to four-fold increase of the levels of the circulating pro-inflammatory and anti-inflammatory cytokines (interleukin-6, interleukin-1 β , TNF- α), and acute phase plasma proteins (CRP, serum amyloid-A).¹⁶ Study of Thomson et al. demonstrates that simultaneous increase of the serum levels of CRP, fibrinogen and leucocytes is associated with two- to four-fold increased risk of comorbidities, including ischemic heart disease, myocardial infarction and heart failure.¹⁷ Additional mechanisms are tissue hypoxia and oxidative stress, which are present also in IHD and cardiac arrhythmias, as well as impaired vasodilative capacity observed in bronchial arteries.¹⁸ Considering the increased rates of chronic inflammation, Fabbri and Rabe introduced the term “chronic systemic inflammatory syndrome” which is characterized with presence of COPD, chronic heart failure, increased levels of CRP, smoking history over 10 pack years and metabolic syndrome.¹⁹ Study among 4132 patients with CHF followed up for 8 years showed that patients with comorbidity of COPD had higher mortality rates compared to those without airflow limitation.²⁰ Decreased lung function is associated with increased cardiovascular morbidity proved a large population based study among over 6000 participants. They were followed for 14 years and the results showed that decreased values of FEV₁ were independent risk factor for the development of cardiovascular disorders and death from myocardial infarction.²¹

III. METABOLIC SYNDROME (MS)

In the present study we investigated a subgroup of participants for the presence of metabolic syndrome and 48.1 % of the patients were consistent with the IDF criteria for MS. Similar results were reported by Watz et al. who found presence of MS in 47.5% of the investigated 170 COPD patients with prevalence between 40 and 50% when dividing the patients into groups according to the spirometry GOLD stages.²² In Turkish population Akpınar et al. found 44.6% prevalence of MS in 91 patients with stable COPD versus 17.1% in control group.²³ Study performed in Korea among 133 newly diagnosed patients with COPD reports similar results – prevalence of MS of 36.8%.²⁴ In Bulgaria, Mekov et al. found 25% prevalence of MS in 155 COPD patients²⁵, and epidemiological study in Pleven region, Bulgaria found MS in 13.8% of the investigated 3598 COPD patients. The lower prevalence reported in the latter study could be explained with using the body mass index (BMI) instead of waist circumference as a major criterion for defining MS.²⁶ These studies show that metabolic syndrome is 1.3–1.5-times more common in COPD patients than in people with normal lung function.

The possible mechanisms which associate central obesity with airflow limitation are still not well understood. It is established that abdominal obesity changes the compliance of the diaphragm and chest wall through mechanical forces. Chen et al. found

that 1 cm increase in the waist circumference is associated with 13 ml reduction in FVC and 11 ml fall in FEV₁.²⁷ Reduced ventilation in the lung basis can lead to altered ventilation/perfusion ratio and arterial hypoxemia in recumbent position of the body.²⁸ On the other hand, both COPD and MS are associated with chronic systemic inflammation which suggests that probably they share similar pathogenic mechanisms. It is established that fat tissue is metabolically and endocrinal active organ with significant production of adipocytokines like IL-6, TNF- α and leptin and its mass enlargement is associated with increased levels of these proteins as well as raised levels of CRP.²⁸ COPD disease severity and metabolic syndrome, as well as physical inactivity, were independent predictors of systemic inflammation measured by high-sensitivity C-reactive protein (hs-CRP) and IL-6.⁴² Accordingly, in the present study we found increased inflammatory response in patients having both COPD and MS. Thus, common pathogenic mechanisms of MS and COPD may be responsible for the association between central obesity and airflow limitation.

IV. DIABETES MELLITUS TYPE 2

In the present study we found 21.1% prevalence of diabetes mellitus type 2 (DM type 2) in COPD patients. Yanev et al. established similar prevalence of 17.6%⁹ which was comparable to other studies conducted in Bulgaria – Mekov et al. found prevalence of type 2 diabetes mellitus accounting for 21.7% in 152 COPD patients.²⁹ Results from randomized and observational studies of COPD patients report prevalence of diabetes mellitus type 2 between 10.3 – 38.9%¹⁰ which is significantly higher compared to the prevalence in the general population in Europe (6.8 – 13%) according to the data from 2015 world diabetes atlas.³⁰ A systematic review on diabetes epidemiology found that patients with COPD have increased risk of developing DM type 2 and reduced lung function measured with FEV₁ and FVC may precede the development of DM type 2. Moreover, the presence of asthma and COPD was independently associated with an increased risk of DM type 2.³¹ The possible relating mechanism between the two conditions is the effect of smoking, a major risk factor for COPD, on the development of insulin resistance. Study of Borissova et al. demonstrates that smoking of 4 cigarettes for an hour is resulting in significant reduction of the insulin receptor's affinity to glucose.³² This insulin resistance in smokers may also be the reason for

the decreased HDL-cholesterol and raised levels of triglycerides which increase additionally the risk of cardiovascular diseases. Chronic hypoxia also may play significant role in the impaired glucose metabolism through rise of plasma epinephrine levels. An impaired glucose tolerance is found in COPD patients with low blood oxygen saturation, compared to those with normal arterial oxygenation.³³ It has been shown that pancreatic β -cells are very sensitive to hypoxia-induced damage as a result of intermittent (sleep apnea) or chronic hypoxia in COPD patients.³¹ On the other hand the persisting systemic inflammation in COPD patients expressed with raised levels of CRP, TNF- α , IL-6 and other factors is an established pathogenic mechanism for development of both COPD and insulin resistance which may explain increased glucose levels and the higher prevalence of diabetes mellitus type 2 in patients with airflow limitation.³⁴

V. BRONCHIECTASIS

In the present study the prevalence of bronchiectasis amongst COPD patients was 12.4% while other study in Bulgaria found slightly higher prevalence of 16% among 226 COPD patients.⁹ With the increasing use of high resolution CT bronchiectasis are more commonly recognized and diagnosed as a comorbidity of COPD. A systematic review and meta-analysis included 14 studies of total 5329 patients and found that 1572 (29.5%) of the patients were comorbid with bronchiectasis with prevalence between 20% and 69% in different studies.³⁵ Seven studies found association between the presence of bronchiectasis and the exacerbations of COPD.³⁵ The two diseases have similar clinical presentation with symptoms of cough with or without purulent expectoration as well as similar pathogenic mechanisms, including persistent chronic inflammation and fibrotic changes in the airways. There is some evidence that patients with COPD and bronchiectasis have worse clinical characteristics and increased risk of chronic sputum production, more frequent exacerbations and increased levels of inflammatory markers compared to patients without bronchiectasis.¹ Recently the co-existence of the two diseases was defined by many authors as a distinct “infectious” phenotype of COPD, which requires different therapeutic approach. The deteriorated clinical course of COPD in the presence of bronchiectasis is associated mostly with the colonization of the bronchial tree with potentially virulent microorganisms, of which *Pseudomonas* species being most frequently isolated.³⁵

CONCLUSION

The results of the present study suggest that COPD is associated mostly with cardiovascular comorbidities and these findings are consistent with the data of similar studies in Bulgaria and in the world literature with greater prevalence in patients with more severe disease. Metabolic syndrome is present in nearly half of the patients and is associated with increased inflammatory response. Other common comorbidities are diabetes mellitus type 2 and bronchiectasis. Defining the comorbidities and their treatment is of great importance for the prognosis of COPD patients as they have negative impact on the course of the disease, quality of life and mortality.

STUDY LIMITATIONS

Diagnoses and comorbidities are retrospectively collected; the diagnostic criteria for COPD and assessed comorbidities may vary.

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Сопутствующие заболевания при хронической обструктивной болезни лёгких (ХОБЛ) у болгарских больных – распространение и взаимосвязь с тяжестью заболевания и воспаления

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Введение: ХОБЛ является заболеванием с постоянно нарастающей социально-экономической тяжестью со множеством сопутствующих заболеваний, усугубляющих тяжесть заболевания.

Цель: Проследить распространение сопутствующих заболеваний у пациентов с ХОБЛ и их взаимосвязь с тяжестью заболевания и уровнями CRP (С-реактивный белок) .

Пациенты и методы: Нами было проведено ретроспективное исследование среди 338 больных с ХОБЛ (средний возраст 65.2±7.6 лет) и осуществлена оценка сопутствующих заболеваний, спирометрических данных и сыровоточных уровней CRP. У 183 больных было установлено наличие метаболического синдрома (МС) согласно критериям МФД (Международная федерация диабета).

Результаты: Нами было установлено распространение сердечно-сосудистых заболеваний (ССЗ) среди 73.5 % больных (гипертония - 70.4 %, ЗСН (застойная сердечная недостаточность) - 47.4 %, ишемическая болезнь сердца - 37.5 % и сердечная аритмия - 12.6 %) с более широким распространением среди больных, страдающих заболеванием в более тяжелой форме. Установлено распространение диабета 2 типа в 21.1 % и 12.4 % распространения бронхоэктазии. В субпопуляции больных установлено 48.1 % распространения МС с

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сывороточными уровнями в значительной степени более высокими у больных с ХОБЛ и МС по сравнению с теми, у которых отсутствует наличие синдрома - 7.4 (3.14 – 11.54) mg/ml и 4.06 (2.64 – 6.93) mg/ml, $p=0.006$ соответственно.

Заключение: Настоящее исследование устанавливает высокую степень частоты ССЗ сопутствующих заболеваний у больных с ХОБЛ и взаимосвязь с тяжестью заболевания. Метаболический синдром является часто встречающимся сопутствующим заболеванием и связывается с повышенным воспалительным ответом.