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ORIGINAL

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND DIABETES MELLITUS –CONNECTION AND THERAPEUTIC DIFFICULTIES

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Introduction: There is the incompletely explored connection between chronic obstructive pulmonary disease [COPD] and diabetes mellitus type-2 [DM] that makes difficulties in the treatment of both in everyday clinical practice.

Objective of this study is to represent the number of patients with COPD associated with DM treated in Clinic for pulmonary diseases and TB "Podhrastovi" in four- year period-from 2012. to 2015.

Patients and methods: This is a retrospective study in which we analyzed the number of patients with COPD associated with DM according to age, sex, type of diabetes - insulin dependence treated in four-year period in Clinic "Podhrastovi.

Results: In four-year period [(2012.-2015.]there were 9709 patients treated in Clinic "Podhrastovi". 619 [6.38%] were discharged with diagnosis of COPD. Among them there were 362 males [58.48%] and 257 females [41.52%]. 70 [11.31%] patients with COPD had DM. 46 males or 12.71% of males with COPD had DM; 25 [54.35%] middle-aged 71.6 years were insulin dependent, and 21 [45.65%] middle-aged 64.8 years were insulin independent. 24 females or 9.34% of females with COPD had DM; 9 [37.5%] middle-aged 70.7 years were insulin dependent and 15 [62.5%] middle-aged 70.2 years were insulin independent.

Conclusion: Because of the link between COPD and DM, pulmonologist should actively perform screening for DM. Therapeutic options should be carefully contemplated. Patients with DM should be routinely screened for lung function for determining COPD risk. Collaboration between pulmonologist and diabetologist is fundamental for improving the treatment of these patients.

Key words: COPD, DM

INTRODUCTION

Sixty five million people are estimated to suffer from COPD. It is the fourth leading cause of death in the world [1] and is predicted to become the third in 2030. [1]. COPD is a pulmonary disease with significant extrapulmonary effects [2]. Its pulmonary component is characterized by irreversible progressive airflow limitation [3]. Systemic manifestations and comorbidities in COPD are body weight loss, skeletal muscle wasting, cachexia, osteoporosis, right heart failure, cardiac ischemia, cardiac arrhythmias, anemia, hypoalbuminaemia, diabetes, arterial hypertension, obstructive sleep apnea, cognitive deficits, depression [4, 5]. Cigarette smoking is the most common risk factor for COPD; various kinds of air pollution are also identified [2, 3, 6]. Acute exacerbation of COPD (AECOPD) is triggered mostly by respiratory infections.

In 2013. there was an estimated 382 million people [8, 3% of the adult population] with DM worldwide [1] . It is predicted that there will be around 600 million people with DM by 2035. [7]. DM-type-2 which represents about 90% of diabetes cases results from sedentary lifestyle, adiposity and genetic predisposition [7]. It is characterized by the failure of blood glucose control due to a combination of insulin resistance and pancreatic ß-cells not functioning. DM leads to serious complications. Approximately 10% of patients with DM suffer from COPD [8, 9]; DM can worsen the prognosis of COPD [10-12], but diabetes-associated adiposity can have a protective effect in some patients with COPD [13]. It is controversial whether there is a causal relationship between the DM and COPD; it is possible that this interaction occurs in a subset of patients [14]. It has been suggested that COPD is an important risk factor for the development and/or progression of DM [15 -18] .

Hyperglycaemia has adverse reaction on the lungs e.g. glycosylation of the connective tissues, reduced pulmonary elastic recoil, increased muscle weakness

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and inflammation [8] Pulmonary function tests are significantly decreased in subjects with DM in comparison to healthy controls [9, 20]. Metabolic syndrome, insulin resistance and systemic inflammation are risk factors for reduced lung function [21]. Reduced lung volume and airflow limitation might be considered as chronic complications of DM [22]. Hyperglycaemia can induce oxidative stress, structural changes in the lung tissue, alter gas exchange and increase levels of inflammatory cytokines - interleukin IL6 and IL18, Alfa tumour necrosis factor [TNFα], C-reactive protein [23

DM increases the mortality in patients with COPD [1]. Pulmonary hypertension is more severe in patients with COPD and DM [24]. DM with AECOPD elongates hospitalization and enhances mortality compared with patients without DM [11, 12, 25-28]. Hyperglycaemia can enhance the ability of bacteria to infect the lungs in COPD [11, 29, 30]. There is the diminished immunity in diabetics, including impaired polymorphonuclear leukocyte phagocitic functions [31].

DM can worsen COPD prognosis; COPD may be a valuable predictor for the development of DM. Several studies showed that the prevalence of DM is higher in COPD [16, 17, 32, 33] especially with GOLD stage 3 or 4 [15, 34]. Some studies [35, 36] observed that impaired lung function is the predictor of DM. A link between COPD and DM was not confirmed in other studies [37] that may be result of the large number of underweight examined individuals [1].

A plausible explanation for the association of COPD and DM may be that the COPD leads to diminished physical activity and the development of metabolic syndrome [1]. Metabolic syndrome in COPD may be linked to systemic inflammation [38, 39], supporting direct role for COPD in the induction of DM [40]. Others did not find that inflammation in AECOPD had effects on long-term glycaemia control [41].

Possible explanation for the increased prevalence of DM in COPD patients relates to therapy for AECOPD .Current international guidelines suggest a course of at least 7 days of systemic glucocorticoid therapy in AECOPD and high doses of inhaled corticosteroids are frequently used [1]. Prolonged exposure to corticosteroids can lead to considerable side effects [42, 43]. Treatment with a corticosteroid [prednisolone] leads to a circadian cycle with hyperglycaemia in the afternoon and evening [43] .The use of inhaled corticosteroids which are currently prescribed for COPD was associated with a 34% increase in the rate of DM [44]. Elderly patients using oral corticosteroids showed an increased risk for DM, inhaled- corticosteroids users did not [45, 46]. In one study, no connection between corticosteroids and DM could be confirmed [47].

The aim of this study is to represent the number of patients with COPD associated with DM treated in Clinic for pulmonary diseases and TB "Podhrastovi" in four- year period: from 2012. to 2015.

PATIENTS AND METHODS

This is a retrospective study in which we analyzed the number of patients with COPD associated with DM according to age, sex, type of diabetes - insulin dependence treated in four-year period in Clinic "Podhrastovi

RESULTS

In four-year period [2012.-2015.] there were 9709 patients treated in Clinic "Podhrastovi". 619 or 6.38% were discharged with diagnosis of COPD. There were 362 males [58.48%] and 257 females [41.52%]. 70 [11.31%] patients with COPD had DM : 46 males or 12.71% of males with COPD had DM; 25 of them [54.35%] middle-aged 71.6 years were insulin dependent, and 21 [45.65%] middle-aged 64.8 were insulin independent. 24 females or 9.34% of females with COPD had DM; 9 of them [37.5%] middle-aged 70.7 years were insulin dependent and 15 [62.5%] middle-aged 70.2 were insulin independent.

All of these 70 patients were smokers for more than 20 years. In all of them COPD was first diagnosis; after on average 6 years in men and 7 years in women DM was diagnosed. Men had on average four, and women three hospitalizations because of AECOPD before diagnosed DM. All of them were on continuous therapy –inhaled corticosteroids, β-2 agonists and antimuscarinics, teophyllin orally. During hospitalizations because of AECOPD they received corticosteroids intravenously (hydrocortisone; prednisolone; methyl prednisolone) with other appropriate treatment (teophyllin, inhaled β-2 agonists and antimuscarinics, antibiotics, oxygen therapy –if necessary, cardiac therapy - if necessary).

The results are shown in the figures 1, 2 and 3.

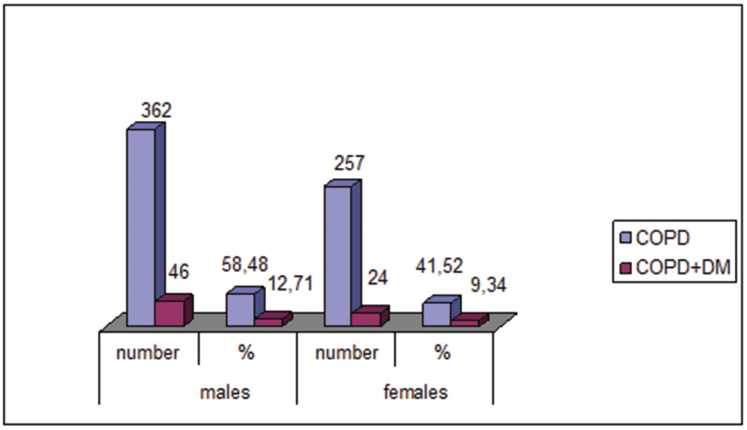

Figure 1. Patients with COPD and DM (males and females) treated in four-year period expressed in absolute number and percent

Among patients with COPD there were 362 males [58.48%] and 257 females [41.52%]. 70 [11.31%] patients with COPD had DM. 46 males or 12.71% of males with COPD had DM; 24 females or 9.34% of females with COPD had DM.

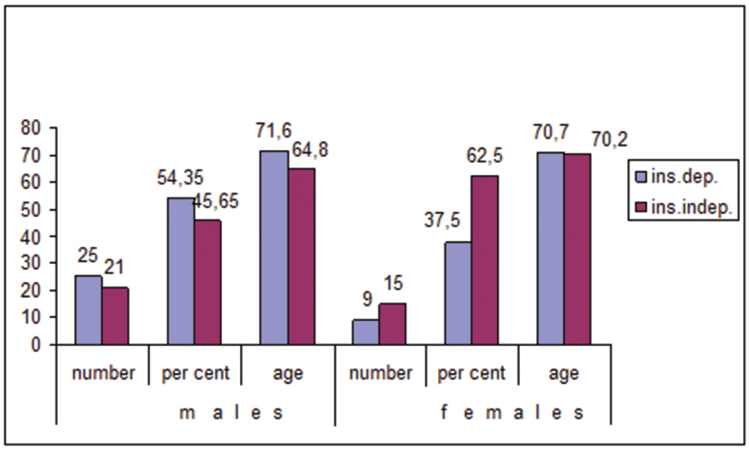

Figure 2. Patients with COPD and DM according to sex, age and insulin dependence

Among 46 males with COPD and DM 25 patients [54.35%] middle-aged 71.6 years were insulin dependent and 21 [45.65%] middle-aged 64.8 were insulin independent. Among 24 females with COPD and DM 9 patients [37.5%] middle-aged 70.7 years were insulin dependent and 15 [62.5%] middle-aged 70.2 were insulin independent.

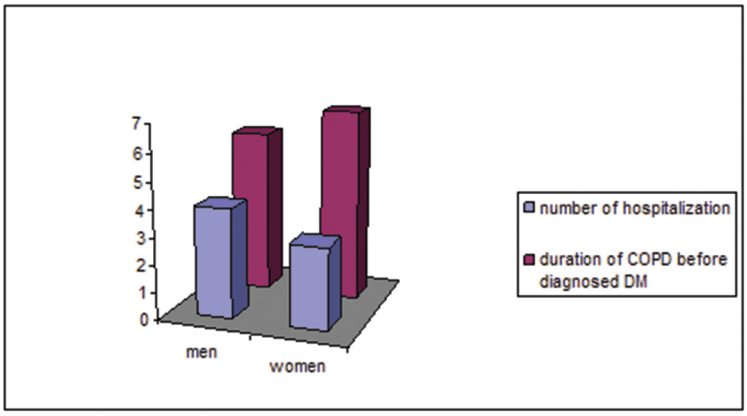

Figure 3. Number of hospitalisation because of AECOPD and duration of COPD before diagnosed DM in years

COPD was first diagnosed and after on average 6 years in men and 7 years in women, DM was diagnosed. Men had on average four, but women three hospitalizations because of AECOPD before diagnosed DM.

DISCUSSION

Although COPD and DM are distinct diseases, there might be a pathophysiological connection between them [1]. Hyperglycaemia can impact respiratory system by inducing oxidative stress, structural changes in the lung, altered gas exchange and can lead to increased levels of inflammatory cytokines [23]. Hyperglycaemia can enhance the ability of bacteria to infect the lungs of COPD patients [11, 29, 30] because of diminished immunity in diabetics [31].

A plausible explanation for the association of COPD and DM may be that the COPD leads to the development of metabolic syndrome which may be linked to systemic inflammation [38, 39], supporting direct role of COPD in the induction of DM [40]. Corticosteroids are very important in the treatment of COPD. Optimal dose of corticosteroids and the length of the treatment must be better defined [48]. Lowering steroid doses and shortening the duration of their use may be appropriate [49, 50] because it could diminish the potential side effects including the development of DM. A better understanding of how COPD therapies can influence the development and progression of DM can lead to safer and more effective patient care [1]. It is important to determine whether antidiabetic treatment might interact with COPD.

The investigations of the relationship between COPD and diabetes have analyzed the patients hospitalized for AECOPD which represent only a part of COPD patients [1]. Relationship between these two diseases may be result of other factors e.g. smoking. In most cases, COPD is the result of smoking, and some studies indicate that smoking may be a risk factor for DM [51]. Maybe the development of diabetes occurs in parallel and no as a consequence of COPD. Because of the link between COPD and DM, pulmonologist should actively perform screening for DM. Use of steroids should be carefully contemplated. Patients with DM should be routinely screened for lung function. Special attention should be given to the contraindication to metformin for patients with threatening hypoxic respiratory insufficiency [1].

Approximately 10% of patients with DM suffer from COPD [8, 9]. We found that 11.31% of patients with COPD had DM: 12.71% of males with COPD had DM and 9.34% of females. Insulin dependence was more expressed in males. All of our patients were smokers for more than 20 years. All of them were more than 64 year-old on average which is appropriate time for developing DM type-2; maybe in some number of our patients these two diseases developed in parallel independently of one another. In all of them COPD was first diagnosed and after on average 6 years in men and 7 years in women DM was diagnosed. Men had on average four, and women three hospitalizations because of AECOPD before diagnosed DM. All of them were on continuous therapy –inhaled corticosteroids, β-2 agonists and antimuscarinics, and teophyllin orally. During hospitalizations because of AECOPD they received corticosteroids intravenously with other appropriate treatment. All our patients with COPD and DM are inhaled- corticosteroids users but although some authors [44] found relationship of inhaled corticosteroids and DM we do not agree with it because very small quantity of steroids is absorbed in circulation in this way that is confirmed by other authors [45, 46]. In our practice we do not prescribe oral corticosteroids for COPD. It is known that prolonged exposure to corticosteroids can lead to hyperglycaemia [42, 43]. Is the treatment with systemic corticosteroids, during AECOPD treatment in hospital, long enough to cause DM which require continuous antidiabetic treatment is still open question.

CONCLUSION

There is the complex relationship between COPD and DM type -2. Most evidences suggest that DM can worsen the prognosis of COPD; this may result from the direct effects of hyperglycaemia on lung physiology, inflammation or susceptibility to bacterial infection. COPD increases the risk of developing DM as a consequence of inflammatory process and/or therapeutic side effects related to the use of high doses of corticosteroids. Although there are the evidences to support a connection between COPD and DM, additional research is required for better understanding these relationships, their possible implications and the potential consequences of therapeutic regimens. Collaboration between pulmonologist and diabetologist is fundamental for improving the treatment and quality of life of these patients.

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