THE EFFECT OF SMOKING ON ASTHMA PREVALENCE AND CONTROL

UTICAJ PUŠENJA NA PREVALENCIJU I KONTROLU ASTME

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Summary
Introduction. Determinants of asthma and its clinical course include the interaction between various intrinsic and extrinsic factors, of which exposure to harmful tobacco particles is one of the most important preventable causes of increased morbidity and mortality related to asthma. However, it is surprising that the prevalence of cigarette smoking among patients with asthma is equivalent to prevalence among the general population. Smoking as a Risk Factor for Development of Asthma. Exposure to tobacco smoke stimulates the immune response that can co-occur with asthma, leading to the development of bronchial hyperactivity and chronic inflammation of the respiratory tract, thus favoring the onset of asthma during childhood, as well as adulthood. Asthma Control in Relation to Smoking Habits. Continuous exposure to noxious particles of tobacco smoke, dysfunction of small airways as well as an altered inflammatory response result in irreversible changes. The worsening symptoms and signs of illness can easily remain unnoticed since they develop gradually, so the patients are often unaware of the severity of illness. The Prevalence of Asthma Symptoms Among Smokers. Compared to non-smokers, smokers have more prevalent and severe symptoms at all stages of disease, which is usually related to body weight and overall duration of smoking. Cigarette Smoking as a Risk Factor for Asthma Exacerbation. Current and former smokers are almost twice as likely to have asthma exacerbations and frequent relapses over a short period of time which increases the risk of requiring intensive care treatment The Effect of Smoking on Lung Function. Reduced airway sensitivity to the application of standardized inhalation therapy and the need for additional medications to achieve disease control can lead to irreversible changes and the development of fixed bronchial obstruction. Key words: Smoking; Asthma; Prevalence; Risk Factors; Signs and Symptoms; Respiratory Function Tests; Disease Progression

Introduction
Asthma is a chronic inflammatory disorder of the airways presenting with respiratory symptoms such as cough, shortness of breath, wheezing and chest tightness [1]. The symptoms vary over time in their occurrence and in intensity due to variable expira-

tory airway obstruction. Pathobiologically, asthma is characterized by a complex chronic inflammation that causes airway remodeling and hyperresponsive-ness of bronchial smooth muscles. Hyperresponsive-ness manifests itself as direct or indirect effects to stimuli, such as: allergens, viral infections, air pollution, tobacco smoke, stress, exercise, and others [2].
The primary goal of asthma treatment is to achieve good results in disease control, which means controlling actual symptoms (previously called current clinical control) and controlling the risks associated with adverse disease outcomes [1]. Assessment of symptom control has been carried out for the last 4 weeks, involving the absence of day and nighttime symptoms, the need for medications to eliminate symptoms more rapidly and no limitations in daily-life and workplace activities. Estimates are made on the basis of different questionnaires, among which Asthma Control Test [3] and Asthma Control Questionnaire [4] are the most commonly used. The presence of symptoms is often a predictor for disease worsening, but on their own they are not sufficient to predict risks. Namely, symptoms can be treated (and therefore may be completely absent) by using quick relief medications without affecting the time course of inflammation and the development of subsequent exacerbation [5] or may be present not because of asthma exacerbation but due to the presence of other related diseases (rhinosinusitis, obstructive sleep apnea, and similar) [6]. Another important domain related to asthma control assessments contains: (i) the risk of severe exacerbations, (ii) progressive and irreversible loss of pulmonary function, and (iii) the risk of developing adverse events caused by medications [1].

Generally, cigarette smoking is one of the most important preventable risk factors for morbidity and premature mortality [7]. Although the decrease in smoking prevalence in highly developed countries has been observed over the last decade [8], the number of smokers in the world has been rising steadily due to the increasing consumption of tobacco products in low- and middle-income countries [7]. The average prevalence of active smokers in the EU countries, according to the 2012 Eurobarometer survey requested by the European Commission was 28% (32% of male and 24% of female), but a high variability was observed among different countries (the prevalence in Russia was 60.2% and in the UK 22.4%) [8]. The number of smokers in Serbia is still high, according to the WHO data from 2013, the prevalence of smoking was 38.1% among men and 29.9% among women [9]. The surprising fact is that the percentage of smokers with asthma is almost the same as in the general population [10]. Although advice on smoking cessation is a part of daily practice, it is often forgotten that smoking is not only a bad habit, but also an addictive disease (MKB-10; F17.2) that causes mental and behavioral disorders, and relapses which commonly occur after smoking cessation. Thus, the aim of this paper is to point out the potential harmful effects of being a smoker with asthma and the need for more intense anti-smoking campaigns among these patients.

**Smoking as a Risk Factor for Asthma**

Smoking has a detrimental effect on the respiratory tract in infants and adults, in addition to irritant, toxic and carcinogenic effects [11], it stimulates the immune response that can be associated with asthma. Namely, exposure to tobacco smoke causes the activation of Th2 lymphocytes [12, 13], an increase in total IgE [14], allergic sensibilization [15], and an increase in bronchial hyperresponsiveness (BHR) [16]. In a study done by Pallasaho and associates [17], which involved 292 participants, a significant increase in BHR (p = 0.001) was associated with the onset of smoking before the age of 20, and the weight gain paralleled an increase in the number of packs/years (p = 0.001). In a multivariate analysis after the correction of independent determinants involving also a damaged lung function, smoking remained an independent risk factor for BHR (15 packs/year yielded OR 3; CI 95%, 1.33-6.76). In a study performed by Gilliland and associates [18] which included school children aged 8-15 years (during 8-year monitoring period), active smoking of at least 300 cigarettes per year coincided with 3.9-fold increased risk (95% CI, 1.7-8.5) for newly diagnosed cases of asthma. Compared with children without atopic disease, smokers were 5.2 (95% CI, 2.4-10.9) times more likely to develop asthma, and if they were also exposed to maternal smoke during gestation, the risk for asthma was nearly 9 times higher (RR, 8.8; 95% CI, 3.2-24.0). Children of non-smokers who were exposed to second-hand tobacco smoke at home also had an increased risk (OR, 1.22; 95% CI, 1.04-1.44), with the risk being higher in children exposed at pre-school age than at school age (OR 1.44 vs. 1.26). One of the first studies, published in 2004 by Pipari and associates [19], supported the hypothesis that smoking causes developing adult onset asthma and indicated that the risk of developing asthma was significantly higher among current (OR 1.33; CI 95%; 1.00-1.77) and former smokers (OR 1.49; 1.12-1.97) compared to non-smokers. Another interesting observation was that female smokers can have more adverse health effects to tobacco smoke and more severe nicotine addiction than men [20]. Risk of asthma among smokers is also associated with increased body mass index, but it is interesting that there is a positive correlation in women only (not in men) [21]. With respect to the incidence of asthma in adult women smokers, no statistically significant difference was found between white and black women [22].

**Relationship between Smoking Habit and Asthma Control**

Smoking has been cited as one of the most significant risk factors associated with poor asthma control, in addition to the severity of disease [23], female gender and presence of comorbidities. In a telephone survey conducted in the US, it was recorded that smokers had more nighttime symptoms (OR 1.783; 95% CI, 1.119-2.847) and disease exacerbations (OR 1.2; CI95%, 1.0-1.4) compared to non-smokers; moreover, a significant correlation was
found between disease control and the number of cigarettes smoked per day (p <0.001) [24]. Despite the fact that cigarette smoking undoubtedly increases asthma severity and morbidity [25], frequent visits to an infirmary and school absenteeism (p≥0.05 to <0.01), there is not always a clear correlation between Asthma Control Questionnaire and Asthma-specific Quality of Life Questionnaire and these events. This may be explained by patient’s adaptation to illness over time, and that questionnaires on the whole are not sensitive enough to measure control parameters over an extended time period.

Prevalence of Asthma Symptoms in Smokers

Studies conducted in Sweden in 1996 and 2006 [26] recorded a strong correlation among respiratory symptoms, cigarette smoking and asthma. Symptoms ranged from 9.8% to 25.5%, while current, as well as former smoking were continuously associated with recurrent wheeze in the chest. The increase in the Symptom Score was proportional to the number of cigarettes smoked per day, and the highest values were found in those smoking more than 14 cigarettes a day (OR=3). European Community Respiratory Health Survey (ECRHS) 1991-1993 (ECRHS) [27] and 1999-2002 (ECRHS II) studied 9,092 subjects without and 1,045 with asthma. The most common respiratory symptoms were chronic coughing and coughing up (p <0.01), and both current and former smokers with asthma had statistically significantly higher symptom scores (p <0.001) than non-smokers. It is noteworthy that there was no positive correlation between the effects of smoking on FEV1 decline and the presence of asthma [28]. According to a study conducted in Belgrade [29], based on ECRHS screening questionnaire, the most frequent respiratory symptoms were longstanding cough (32.2%), sputum production (30.4%) and wheezing (30.3%), and the majority of respiratory symptoms were associated with current or former smoking (37.5% versus 17.5%). Contrary to these studies, Boulet [30] obtained a statistically insignificant difference between smokers and non-smokers regarding asthma control, quality of life, FEV1, bronchodilator and methacholine responsiveness, number of exacerbations, use of prednisolone or absenteeism in the workplace, while there was a statistically significant difference to the advantage of smokers in terms of respiratory symptoms (p <0.05), the FEV1 / FVC ratio, diffusing capacity, sputum induction, and high-resolution chest CT. The author stated that smokers with asthma have features that are more characteristic of COPD than of asthma.

The increase in symptoms and the worsening of asthma control in smokers is probably the result of changes in the respiratory epithelium that becomes thickened and proliferated with increased number of foam and mast cells and lower eosinophil values [31]. These changes are less visible in former smokers, whereas in non-smokers they are not visible, which leads to the conclusion that these changes can be at least partially reversible. The cause of the occurrence of a number of symptoms may also be the dysfunction of small respiratory tract, since tobacco smoke particles are 2.5-0.1 mcg in diameter. This is supported by studies that examined the efficacy of systemic anti-inflammatory therapy [32] distributed equally to small and large airways, as well as the application of inhalation therapy with fine and ultrafine particles distributed to small airways [33, 34] compared to standard inhalation therapy.

Smoking as a Risk Factor for Asthma Exacerbation

The frequency and severity of asthma exacerbation are significant factors associated with asthma control because it directly influences the quality of life, costs of asthma treatment and asthma-related mortality. Exacerbations more often develop in severe forms of the disease in the patients with impaired lung function; however, it should not be forgotten that they are not rare even in the patients with a mild form of asthma and these patients account for up to 40% of visits to emergency departments [35]. Thereby, the risk of exacerbation in current and former smokers is twice as great in comparison with non-smokers (RR, 1.71; 95% CI, 1.48-1.97) [36]. In a retrospective study conducted in the United States and the United Kingdom, including 5,167 and 2,904 patients, respectively, which focused on asthma-related ED visits/hospitalizations, it was defined that 9.2 of American study sample patients and 4.7% of British study sample patients had asthma-related re-admissions within 30 days due to disease exacerbation [37], whereas one of the most important predictors was exacerbation frequency (apart from disease severity) which increased with the number of exacerbations in the previous period. Accordingly, Kauppi mentioned that independent risk factors for severe exacerbations requiring treatment in intensive care units are former (HR 1.9, CI 1.3-3.1) and current smoking (HR 3.6, CI 1.6-8.2), poor quality of life (HR 2.5, CI 1.5-4) and poor lung function (FEV1<65%, HR 2.2, CI 1.3-3.7) [38]. Rabinovitch and associates performed a five-month study on a sample of asthmatic children that suggested that passive exposure to tobacco smoke led to an increased urinary excretion of LTE4, which is a predictor of potential exacerbations [39].

The Effect of Smoking on Lung Function

One of the key features of asthma is the presence of completely reversible bronchoopstruction, which implies a preserved pulmonary function found during a stable phase of disease. In practice, however, we often come across patients with fixed airway obstruction and irreversible changes arising from airway remodeling, which is the risk factor for poor disease control and frequent exacerbations. These changes have been linked with longer disease duration, cigarette smoking and neutrophilic inflammation. FEV1 values <60% are considered to be a risk factor for the occurrence of exacerbation [40] and
have a better predictive value than disease symptoms. ICS has a protective effect on a mean annual FEV1 decline (The Forced Expiratory Volume at first second), but it disappears in long-time smokers. In a longitudinal study done by Dijkstre and associates [41] the patients were followed up for more than 23 years, and consequently the initiation of ICS led to a reduction in mean annual decline in FEV1. As a result, annual FEV1 decline in men was 20.6 ml (p = 0.011), whereas in women it was 3.2 ml. The recorded FEV1 changes were highly statistically dependent on the dosing and administration of ICS. The author of the study identified sex hormones, uneven airway caliber and inhaled air distribution inequalities between males and females as potential causes of this phenomenon. However, this significant protective effect of ICS was observed only in non-smokers or former smokers with less than 5 packs/years of smoking, while in long-standing former smokers and current smokers it disappeared.

There is no doubt that cigarette smoking has a detrimental effect on the course and outcome of asthma. Therefore, it is imperative that all health professionals should be aware of this problem and accordingly assess patients with asthma regularly, pointing out negative effects of cigarette smoking habit as well as benefits of quitting it.

References


