



Smoking asthma phenotype: diagnostic and management challenges

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Purpose of review

The prevalence of active smoking in adults with asthma is similar to the general population. Smoking asthma is associated with poorer disease control, impaired response to corticosteroid therapy, accelerated decline in lung function, and increased rate of healthcare utilization. Current asthma guidelines do not provide specific treatment advice for smoking asthmatic patients. There is an urgent need for better understanding of the underlying mechanisms and effective treatment for smoking asthmatic patients.

Recent findings

An association between both active and passive smoking and adult-onset asthma is supported by many studies.

The asthma-COPD overlap syndrome (ACOS) has recently gained particular interest and smoking asthmatic patients should be evaluated for ACOS.

Treatment regimens for smoking asthma include higher doses of inhaled corticosteroids (ICS), extrafine particle ICS formulations, antileukotrienes, and combinations of these options.

Asthma is associated with increased risk of cardiovascular comorbidities whereas smoking is an additional strong independent risk factor for pulmonary and cardiovascular diseases. Tobacco smoking and not asthma per se seems to be the reason of poor prognosis, especially with regard to lung cancer, cardiovascular diseases, and mortality in asthmatic patients.

Summary

Smoking asthma represents a common challenge to the clinician both in terms of diagnosis and management. These aspects have not been thoroughly evaluated and deserve further investigation.

Keywords

asthma-COPD overlap syndrome, asthma, smoking, treatment

INTRODUCTION

Tobacco smoking is associated with poor asthma control, worsening symptoms, impaired response to corticosteroid therapy, accelerated decline in lung function, and increased healthcare utilization [1–3].

The prevalence of active smoking in adults with asthma is similar to the general population, with rates ranging from under 20% to over 35% [1].

Current guidelines do not provide specific treatment advice for smoking asthmatic patients. This is partly attributed to the exclusion of smokers and exsmokers with at least 10 pack-year history from clinical trials in asthma [4,5]. Therefore, prescription to smoking asthmatic patients may impose a challenge on clinicians lacking strong evidence of effectiveness of available treatment options. This stresses the urgent need for a better understanding of the underlying mechanisms and treatment options for smoking asthmatic patients.

ASSOCIATION BETWEEN TOBACCO SMOKING AND ADULT-ONSET ASTHMA

Whether tobacco smoking is linked to the development of adult-onset asthma is not clear. Despite a large body of evidence supporting a causal relationship between parental smoking and the development of asthma in children [3,6], the evidence for an association of smoking and adult-onset asthma is inconsistent [3,7]. The 2014 Report of the Surgeon General on the Health Consequences of Smoking deemed the overall evidence ‘suggestive but not sufficient to infer a causal relationship between

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Curr Opin Pulm Med 2016, 22:53–58

DOI:10.1097/MCP.0000000000000221

KEY POINTS

- Active and passive smoking are associated with adult-onset asthma.
- Asthmatic patients who smoke should be evaluated for asthma-COPD overlap syndrome.
- Treatment choices for smoking asthmatic patients include higher doses of inhaled corticosteroids, extrafine particle inhaled corticosteroid formulations, antileukotrienes, and combinations of these options.
- In smoking asthmatic patients, tobacco smoking and not asthma per se seems to be the reason of poor prognosis including the risk of COPD, lung cancer, cardiovascular disease, and mortality.

active smoking and the incidence of asthma in adults.' [8] In a 15-year follow-up of African-American women the incidence of adult-onset asthma was increased by, approximately, 40% among active smokers and by 20% among passive smokers, compared with women with no active or passive exposure to tobacco smoke; additionally, incidence increased as the pack-years increased. The association of active and passive smoking with increased asthma incidence was most apparent among non-obese women and women 50 years of age or older [9[¶]]. Although the precise mechanisms linking smoking to the development of adult-onset asthma remain uncertain, its detrimental effects on the airway epithelium, immune cells, and airway smooth muscle may play a role [1,3].

Continued maternal smoking throughout pregnancy was associated with increased risk of asthma, whereas maternal smoking during the first trimester only or paternal smoking was not [10]. Interestingly, grandmother's smoking when the mother is pregnant increased the risk of asthma in the grandchild, independent of the mother's smoking status, indicating a transgenerational influence of prenatal tobacco smoke exposure on asthma development [11]. A recent systematic review confirmed an important role of prenatal exposure to maternal smoking on the induction of wheezing and asthma in offspring, particularly in the first years of life [12].

Understanding the association between exposure to tobacco smoke and incident asthma has significant implications for public health. First, on the assessment of the global burden of disease and the health costs related to tobacco and second to provide insight into asthma endotypes, for example, the variance of the relation between smoking and asthma by age and BMI in the study by Coogan

et al. [9[¶]] strongly supports that smoking is linked to particular asthma endotypes.

THE OVERLAP BETWEEN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A CONTINUING CHALLENGE

Differential diagnosis with other conditions and overlap with chronic obstructive pulmonary disease (COPD) remains a challenge for the diagnosis of smoking asthma. The term asthma-COPD overlap syndrome (ACOS) is being increasingly applied to patients with airflow obstruction related to smoking who have features of asthma (reversibility, eosinophilia, and atopy) or who have a known past history of asthma [13]. Distinguishing asthma from COPD may be problematic particularly in smokers. ACOS is identified by the features that it shares with asthma and COPD [14]. Current Global Initiative for Asthma (GINA) and Global Initiative for Obstructive Lung Diseases (GOLD) guidelines suggest a stepwise approach to the diagnosis of ACOS, starting from the recognition of the presence of a chronic airway disease, then confirmation by spirometry and eventually referral to a specialist for specific investigations [14]. There is accumulating evidence that patients with ACOS have poor quality of life, more exacerbations and more rapid decline in lung function compared with asthma or COPD patients [14]. In the COPD Gene study, patients who had had asthma before the age of 40 years in combination with at least 10 pack-years of smoking exposure had more exacerbations, less emphysema, and greater airway wall thickness for any degree of lung function impairment compared with those with COPD alone, suggesting that asthma drives both symptoms and disorder in these 'ACOS' patients [15].

It is noteworthy that chronic airflow obstruction in smokers should not be diagnosed as COPD, without considering concomitant asthma. However, it is obvious that smoking adversely impacts lung function in asthmatic patients, either by adding another airway disease (COPD), or by worsening pre-existing asthma. In a cross-sectional study in primary care investigating the prevalence of ACOS among asthmatic patients with a smoking history of at least 10 pack-years almost 25% were considered as having ACOS. In this study age over 60 years and a smoking history of more than 20 pack-years were the best predictors of ACOS [16].

Distinguishing between COPD and asthma in large epidemiologic studies using self-report without pulmonary function tests or physician diagnosis remains arbitrary as was, for example, the case in the large longitudinal study by Coogan *et al.* [9[¶]] This is

further strengthened by the finding that the hazard ratio between smoking and incident asthma was highest in patients more than 50 years old, who are at higher risk for the development of COPD [9[¶]].

There is evidence that asthma is an important risk factor for the development of airway obstruction and COPD later in life [17,18]. However, it is not fully clear how smoking impacts pre-existing asthma. Understanding the relationship between asthma, smoking and airway obstruction might provide important information in identifying target groups for COPD prevention. In a recent study exploring these interrelationships, it was found that airway obstruction was rare (0.4%) in never-smoking patients without asthma, and most prevalent among former and current smokers with asthma (>12%) [19[¶]]. In early-onset asthma, the risk of airway obstruction was increased by more than 20-fold, regardless of the smoking status. More importantly, current smokers with late-onset asthma had a higher risk of airway obstruction compared with never-smokers with late-onset asthma. The interaction between late-onset asthma and current smoking was present both when smoking was initiated before and after asthma onset. The effect of current smoking and late-onset asthma in the risk of airway obstruction was larger in patients without atopy [19[¶]]. This may either indicate that atopy (partially) protects against the impact of smoking, or that the atopic airways may already be chronically inflamed, rendering additional damaging effects of tobacco smoke less evident [3].

The above findings are of particular interest in our effort to understand the natural history and development of COPD. The age group in which current smoking interacted with asthma onset to increase risk of airway obstruction coincided with the age of maximal lung growth, thus, patients with asthma onset during adolescence and during the age of the most rapid lung growth might be particularly vulnerable to smoking [13]. Another intriguing point is that in this particular study the term 'airway obstruction' instead of COPD was used because only prebronchodilator measurements were performed. The strict definition of COPD in treatment guidelines has been criticized [20] mainly because a definition based upon postbronchodilator values may capture the majority of, but far from all, patients with COPD, as asthma and COPD may coexist or overlap (ACOS) [13]. According to the findings of the present study, asthma might evolve into COPD by increasing susceptibility to smoking. Whether the natural history of chronic airflow obstruction evolving from asthma is similar to the natural history of COPD caused by smoking is unknown.

TREATMENT OF SMOKING ASTHMA

The current concept of asthma treatment is to intensify pharmacotherapy until full control has been achieved [14]. Asthma exacerbations and hospitalizations usually reflect a failure in asthma management [21]. In a recent study, it was demonstrated that asthma patients who are current or exsmokers are more likely to require emergency room care compared with never smokers. Previous and current smoking was an independent risk factor for emergency room visits [22].

A recent observational database study showed that current smoking was associated with significantly higher mean daily rescue medication usage compared with that of exsmokers and nonsmokers [23]. This is indicative of more frequent and severe asthma symptoms and greater dependence on rescue medication among asthmatic smokers.

Another study evaluating the emergency care utilization by asthmatic patients demonstrated that current and former smokers were more likely to need emergency care than never smokers. Actually, former smokers had 1.30 times the odds and current smokers had 1.46 times the odds of visiting the emergency room compared with never smokers. Moreover, former smokers had 1.28 times the odds and current smokers had 1.29 times the odds of urgent visits compared to never smokers [24].

It is known that the oxidative stress from tobacco smoke impairs histone deacetylase-2 (HDAC2) via phosphorylation of phosphoinositide-3-kinase (PI3K)/Akt activation, leading to corticosteroid insensitivity [25]. In agreement with previous studies in adults, passive smoking exposure in children impairs HDAC2 function via PI3K signaling activation [25]. This finding highlights the need for parental education regarding the effects of tobacco smoke exposure on their children with asthma.

Observational studies and pragmatic trials including smoking asthmatic patients provide a way of assessing the relative effectiveness of different pharmacotherapeutic options for the treatment of this frequent phenotype. Exploratory studies of possible treatment options for smoking asthma suggest potential effectiveness of higher doses of ICS, in extrafine particle ICS formulations targeting the small airways, and antileukotrienes, whereas combinations of these options could also be considered.

The first treatment recommendation for smoking asthma patients should be smoking cessation including environmental control if passive smoking is involved. Smoking cessation needs to be a key strategy in the management of asthma, as it has been reported to be associated with better lung

function in asthmatic patients compared with those asthmatic patients who continue to smoke [26,27]. A 6-week study showed that smoking cessation was associated with a significant improvement in forced expiratory volume in the 1st second (FEV1) and a significant reduction in sputum neutrophils [28,29]. Many smoking asthmatic patients claim that smoking often worsens their asthma and increases the frequency and severity of their symptoms, whereas fear of asthma-related exacerbations and poor self-control appeared to be the major triggers for quitting smoking [30].

Current smoking has been associated with impaired response to inhaled corticosteroids even in mild asthma [26]. Use of ICS therapy at higher doses may be a treatment choice in patients with smoking asthma [26]. It should be stressed that current GINA strategy suggests that high ICS doses provide little additional benefit and there is increased risk of side-effects [14]. Exposure to even low levels of tobacco smoke is known to induce small airways inflammation [31,32]. It has been suggested that targeting inflammation in both the central and peripheral airways may be beneficial for asthma phenotypes wherein small airways involvement is particularly implicated [33]. Therefore, ICS deposition in small airways might be an important determinant of ICS effectiveness in smokers with asthma, providing also the potential for lowering ICS doses and prevention of possible adverse events. An observational study explored the real-life effectiveness of extrafine hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) and standard particle size fluticasone across different smoking subgroups (nonsmokers versus current and exsmokers). Using database measures of asthma control and exacerbations, current/exsmokers receiving extra-fine HFA-BDP had significantly lower exacerbation rates and significantly higher odds of gaining asthma control compared with patients on fluticasone. The difference was less marked in never smokers than in current/exsmokers [34]. These findings suggest a possible differential treatment effect with regard to smoking status and particle size of ICS, showing a greater beneficial effect of small particle ICS in current and exsmokers. This could be explained by small airway disease induced by smoking and improved targeting of this airway compartment by smaller ICS particles. These findings also extend previous results from a prospective observational study exploring the real-life effectiveness of the combination of extrafine HFA BDP with the long-acting β -agonist formoterol in smokers with moderate-to-severe persistent asthma [35]. The one-year outcomes were improvement in lung function as well

as in asthma control, evaluated by the 6-question Asthma Control Questionnaire in smoking asthmatic patients [35].

The addition of a long-acting β -agonist (salmeterol) to fluticasone provided greater improvements in airway hyperresponsiveness and airway caliber in a small study in smoking asthmatic patients compared with doubling the dose of fluticasone [36].

In a recent study, the effect of tobacco smoking on a range of arachidonic acid metabolites involving both lipoxygenase and cyclooxygenase pathways was examined in urine, sputum, and blood of asthmatic patients and healthy individuals. Urinary leukotriene E4 and prostaglandin D2 concentrations were significantly increased in smokers with asthma compared with never smokers with asthma whereas sputum PGE2 concentration was significantly lower in smokers with asthma compared with never smokers with asthma [37[¶]]. These findings demonstrate a different effect of smoking in arachidonic acid metabolism in asthma and suggest that targeting specific lipoxygenase and cyclooxygenase pathways activated by asthma and by tobacco smoking may optimize therapeutic responses [37[¶]].

A large, randomized, double-blind, parallel-group study evaluated the efficacy and safety of montelukast (10 mg once daily) and high-dose inhaled fluticasone (250 μ g twice daily) compared with placebo in smoking asthmatic patients [38]. Over a 6-month period, patients in both the fluticasone and montelukast treatment arms demonstrated significantly more days of asthma control and significant improvement in the mean daytime symptom score change from baseline. There were no differences between montelukast and fluticasone arms. Interestingly, smoking appeared to play a role in the response to treatment, thus patients with a smoking history less than 11-pack years showed a trend toward more benefit from fluticasone whereas those with a smoking history more than 11-pack years tended to show greater numerical benefit with montelukast [38]. Accordingly, montelukast could be a treatment option for chronic smoking asthma.

PI3K- δ inhibitors may provide a novel approach to reversing corticosteroid insensitivity and such inhibition has been shown to attenuate allergic airway inflammation [39,40]. Although more data are becoming available, it is clear that larger prospective real-life trials are needed to compare treatment options in smoking versus nonsmoking asthma. Moreover, new (targeted) treatments may become available when underlying mechanisms of smoking asthma are further elucidated.

OTHER SMOKING-RELATED COMORBIDITIES IN ASTHMA

Previous studies suggest that asthma is associated with increased risk of cardiovascular comorbidities [41–43]. Common risk factors, systemic inflammation, or effect of asthma medication have been proposed as three potential explanations of this association [41]. However, most of these studies were cross-sectional or retrospective and some of these findings were limited to women [42,43].

Tobacco smoking is a strong risk factor for pulmonary and cardiovascular diseases. Accordingly, it is truly difficult to separate the effect of asthma per se and that of tobacco smoking in the development of cardiovascular comorbidities and mortality among asthmatic patients. In the Copenhagen General Population Study, tobacco smoking strongly influenced the prognosis of asthma in terms of restricting the risks of lung cancer, cardiovascular comorbidities, and death to former and current smokers with asthma [44[■]]. These findings indicate that tobacco smoking and not asthma per se is the reason of poor prognosis, especially with regard to lung cancer, cardiovascular diseases, and mortality in asthmatic patients. This is compatible with a recent meta-analysis, which concluded that there is a lack of evidence to support asthma as an independent risk factor for lung cancer and suggested that such an association may be a result of residual confounding and/or reverse causation [45].

CONCLUSION

In conclusion, smoking asthma represents a complex phenotype with several challenges to the clinician. The recent introduction of ACOS with a clinical approach has complicated the situation even more. The results of pragmatic trials including smoking asthmatic patients have shed some light toward more evidence-based management of this frequent asthma phenotype. However, more and larger real-life trials are needed in the future in order to clarify differences in treatment responses between smoking and nonsmoking asthma. Smoking cessation, including lifestyle changes but also legislation, should be the first recommendation in the management of smoking asthma. Finally, targeted therapies are a new perspective that may become applicable once the underlying mechanisms in smoking asthma are more clearly elucidated.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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