

# Asthma and Smoking: An Unfortunate Combination

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Asthma is an inflammatory disease of the airways in which a key role is played by certain cells and mediators (T-helper 2 cells, mast cells, eosinophils, interleukin 4 and 5). In certain disorders, such as irritant-induced asthma, reactive airways dysfunction syndrome, and asthma due to toluene diisocyanate, inflammation is mediated predominantly by T-helper 1 cells, macrophages and neutrophils. Smoking also produces bronchial inflammation, in this case mediated primarily by macrophages and neutrophils although eosinophil predominance has also been observed in some smokers (an allergic response to certain antigens). The remodeling of the airway wall that accompanies the chronic inflammatory cascade may alter the cell response profile making it difficult to determine which type of inflammatory infiltrate is predominant. The association of asthma and smoking is a reality in our society, and it is a combination that substantially modifies pathogenic mechanisms and gives rise to a more severe clinical picture. Resistance to some of the pharmacotherapies used routinely in the treatment of asthma (corticosteroids) has also been observed and this has favored the use of other drugs (antileukotrienes). One of the preventative measures that should be used more energetically is to encourage patients to stop smoking, paying particular attention to asthmatic smokers.

**Key words:** *Asthma. Smoking. Inflammation. Eosinophils. Neutrophils. Prevention.*

## Introduction

Asthma is a chronic disease of the airways characterized by a disproportionate inflammatory response to specific or nonspecific stimuli.<sup>1</sup> Some of the agents that provoke this response are known while others are not. After repeated exposure, these agents eventually trigger sustained inflammation that gets progressively worse, producing secondary alterations in the physiology of the bronchial response. The clinical manifestations of asthma are daily respiratory symptoms (cough, wheezing, dyspnea, and chest tightness), which affect the patient's quality of life. During an attack these symptoms become more severe and endanger

## Asma y tabaco: una unión inconveniente

El asma es una enfermedad inflamatoria de las vías aéreas en la que desempeñan un papel primordial determinadas células y mediadores (linfocitos T *helper*-2, mastocitos, eosinófilos, interleucinas-4 y 5). En algunas situaciones la inflamación predominante está mediada por linfocitos T *helper*-1, macrófagos y neutrófilos, como en el asma por irritantes, el síndrome de disfunción reactiva de las vías aéreas, el asma por diisocianato de tolueno (TDI), etc. Por otra parte, también el tabaco produce inflamación bronquial, fundamentalmente mediada por macrófagos y neutrófilos, aunque en algunos fumadores se observa también un predominio de eosinófilos (respuesta inmunoalérgica a determinados antígenos). El remodelado bronquial que acompaña a la cascada inflamatoria crónica puede modificar la respuesta celular y confundir sobre el predominio de uno u otro tipo de infiltrado inflamatorio. La asociación de asma y tabaco constituye una realidad en nuestro medio, a la vez que modifica sustancialmente los mecanismos patogénicos, produce una clínica más florida y se observa resistencia a ciertos tratamientos habituales en el asma (corticoides), lo que ha propiciado la utilización de otros fármacos (antileucotrienos). Una de las medidas preventivas que deben utilizarse con más energía es propiciar el abandono del hábito tabáquico, prestando especial atención a los asmáticos fumadores.

**Palabras clave:** *Asma. Tabaco. Inflamación. Eosinófilos. Neutrófilos. Prevención.*

the patient's life.<sup>1</sup> However, there is some debate about whether asthma should be considered a single disease.<sup>2,3</sup>

Tobacco smoke, a toxic agent containing high levels of harmful substances, directly affects the airways, where it triggers a very strong local inflammatory response, independently of any concurrent secondary systemic reaction. Constant aggression against the airways through cumulative exposure to smoke from daily tobacco consumption leads to the onset of chronic bronchial hypersecretion and obstructive pulmonary disease, with chronic airflow limitation or chronic obstructive pulmonary disease (COPD) in many cases. COPD is an entity characterized by irreversible bronchial lesions and progressive destruction of the lung parenchyma once the process has begun.<sup>4</sup>

Both asthma and smoking-related lung disease are characterized by the presence of permanent airway inflammation and, according to current pathophysiologic knowledge, both asthma and COPD can be considered to

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be components—each with its own entity—of airway disease: components that may coexist and share common biological inflammatory mechanisms.<sup>5</sup>

In this review we will give a brief overview of the most relevant scientific evidence and describe the most important findings relating to the biology of inflammation in the presence of asthma and smoking. We will place particular emphasis on the description of the peculiarities of the different inflammatory phenotypes described to date, considered separately and together.

### **Inflammation in Asthma**

Inflammation in asthma is triggered by the presence of an antigen, which can be either a known or an unknown allergen. The inflammatory response, which affects both the central and peripheral airways, is activated when dendritic cells in the bronchial submucosa recognize the aggressive agent and present the appropriate antigen. T-helper (Th) 2 cells play a role in this phase by producing interleukin (IL) 4 and 5, which activate B-lymphocytes, eosinophils, and mast cells locally or at distance, thereby triggering the inflammatory cascade and the recruitment of infiltrated cells in the submucosal layer; this leads to the release of multiple inflammatory mediators, including colony-stimulating growth factor and tumor necrosis factor alpha (TNF- $\alpha$ ).<sup>6,7</sup> Following cell recruitment, extravasation of molecules and pro-inflammatory substances, and local production of inflammatory mediators, the inflammatory process enters a second phase in which a specific selection occurs determining the response type. Several specific response patterns have been reported (for example involving Th1 or Th2 cells), and each pattern would give rise to different inflammatory phenomena, determine which response predominates and, consequently, define which inflammatory profile occurs.<sup>8-10</sup> All of these findings have been confirmed by the analysis of biopsy samples from asthmatic patients. Morphological and anatomical changes in bronchial mucosa and submucosa have also been described. These alterations disrupt the integrity of the epithelium and the basement membrane and affect underlying capillary vascularization, glandular structures, smooth muscle, the extracellular matrix, and the infiltration of circulating inflammatory cells. Predominantly eosinophilic or neutrophilic infiltrations, whether or not accompanied by remodeling, are the most relevant in this context.<sup>11</sup>

#### *Eosinophil Infiltration*

Eosinophilic inflammation is considered to be a consequence of the differentiation of Th2 cells, and the role these cells play in the pathogenesis of asthmatic disease has been well documented through analysis of the products of degranulation.<sup>12,13</sup> Moreover, the eosinophils and neutrophils involved in the inflammation express a different pattern of surface markers,<sup>14</sup> and the biological environment of the mediators involved in their recruitment, activation, and apoptosis is rather complex.<sup>15,16</sup> There is a large body of scientific evidence in both animal and human models implicating eosinophils in different components of asthma,

such as bronchial hyperreactivity and clinical deterioration. However, eosinophils may not be the only inflammatory cells implicated in inflammatory activity since we have so far been unable to investigate whether the total elimination of eosinophils from the site of inflammation can cure asthma or the side effects such suppression would produce.<sup>16</sup>

#### *Neutrophil Infiltration*

Neutrophil infiltration is also found as the predominant inflammatory pattern in certain circumstances. It has been associated with the infectious—predominantly viral—etiology of asthma attacks and with near-fatal asthma.<sup>17</sup> The mechanism that activates and perpetuates this pattern in these situations is poorly understood and the extent of direct tissue damage attributable to the mechanism is unclear. It has been suggested, however, that the course of the neutrophil clearance mechanism after initiation of apoptosis may be a crucial factor in the appearance of permanent anatomical airway damage.<sup>18,19</sup>

### **Bronchial Remodeling**

The process of bronchial remodeling refers to the anatomical and functional loss of airway structure secondary to repeated cycles of inflammation caused by persistent aggressions or inflammatory triggers when such inflammation persists over time and resolves without complete repair. Remodeling is characterized by the appearance of permanent changes in the bronchial epithelium and the basement membrane as well as the underlying submucosa, capillaries, and smooth muscle.<sup>11</sup> These changes permanently and irreversibly impair the correct functioning of the airways in almost all cases, and in most patients the airways are not susceptible to “*restitutio ad integrum*” even with long-term treatment.

Apart from these anatomical changes, remodeling is accompanied by inflammatory cell infiltration and a complex proinflammatory environment in which the inflammatory mediators constantly modify the biochemical interactions and signaling of different cell types. Bronchial remodeling is characteristic of both eosinophilic and lymphocytic inflammation, but other inflammatory mechanisms may be present.<sup>20,21</sup> The pathogenic significance of remodeling in the natural history of the disease is poorly understood, but such remodeling probably limits the effectiveness of current asthma drugs.<sup>11</sup>

### **Smoking-Related Airway Inflammation**

Tobacco smoke is responsible for the development and persistence of airway inflammation. It contains a large number of substances that are toxic, carcinogenic, and damaging to the bronchial mucosa in the short and medium term,<sup>22</sup> and the biological and molecular mechanisms that produce the damage are varied and work together synergistically.<sup>23</sup> In summary, the pathophysiologic alterations of greatest interest are the functional changes in the bronchial epithelium and the dysfunction of macrophages and other inflammatory cells in the

reestablishment of molecular repair mechanisms. These changes are implicated in the constant aggression produced by the exacerbated repair mechanisms and in the dysfunction of the physiology of programmed cell death. This last aspect in particular is currently the subject of intense research, as are the biochemical pathways that perpetuate inflammation through an imbalance between the mechanisms of cell removal by apoptosis, macrophage phagocytosis, and initiation of cell necrosis, the final result of which is irreversible bronchial obstruction.<sup>19,24,25</sup> The results of this research reinforce the hypothesis of a biochemical balance in the activation and deactivation of the most important molecular pathways in the pathogenesis of chronic airway inflammation.

### Asthma and Smoking

Only limited scientific information is available concerning the effects of smoking on asthma and its consequences, although certain aspects are better understood than others. In this section we will briefly discuss the main findings of interest in this context, which have revealed an important association between these 2 entities in the development of airway disease.

#### *The Pathophysiology of Inflammatory Airway Disease in the Presence of Asthma and Smoking*

Asthma and tobacco addiction are both prevalent in the general population.<sup>26,27</sup> While their prevalence varies by geographical area, the rates for both are clearly high. Only scant information is available on the prevalence of the combination of the 2, and the figure varies greatly between epidemiological studies.<sup>28,29</sup> It is estimated that around 50% of adult asthmatics in the developed world probably are or have been smokers.<sup>30</sup> The high coincidence of asthma and smoking favors the development of a complex pathophysiology of inflammatory airway disease, the pathophysiologic and clinical expression of which is also diverse and multifaceted and so still poorly understood today. Different inflammatory phenotypes of the diseased airway have been investigated and described in the literature. Some authors, for example, found smoking-related inflammatory activity to be closely and causally related to the onset of the nonatopic asthma phenotype,<sup>31</sup> and others found an association with greater impairment of lung function.<sup>32</sup> However, many aspects of airway inflammation and its link with asthma and smoking remain unclear.

#### *Clinical Characteristics, Lung Function, and Pathophysiologic Aspects Common to Asthma and Smoking*

Asthmatic smokers have more symptoms, greater morbidity, and poorer health-related quality of life as measured by direct and indirect questionnaires than asthmatics who do not smoke.<sup>33</sup> In some asthmatic smokers, direct toxic exposure to tobacco smoke is associated with a higher degree of immediate bronchial hyperresponsiveness and lower baseline lung function,<sup>34</sup> an indirect indication of the existence of an inflammatory

base different from that of nonsmoking patients with allergic asthma.<sup>35</sup> Some authors report greater use of emergency health care among patients with asthma who smoke,<sup>33,36</sup> although it is still unclear whether smoking is a risk factor for the onset of near-fatal asthma.<sup>37</sup>

A noteworthy finding is that, over the long term, there is a synergy between asthma and the effects of prolonged exposure to tobacco smoke, and this effect can be observed in the sustained decline in lung function among these patients; it is estimated that the combination produces a decline of approximately 18% in forced expiratory volume in 1 second in 10 years.<sup>38</sup>

#### *Diagnosis and Pathophysiology of Asthma and Tobacco as the Cause of Inflammatory Airway Disease*

Asthmatic smokers differ in certain ways from patients with COPD caused by cumulative and prolonged exposure to tobacco smoke. Most of these individuals test positive on a methacholine challenge test or demonstrate a greater than 15% improvement after inhaling a short-acting  $\beta$ -agonist. However, no information is currently available on the possible confounding effect of the intensity and level of cumulative tobacco consumption over many years on the elimination or disappearance over time of variability in the results of these tests. Furthermore, we do not know whether transient resistance to the antiinflammatory effect of corticosteroids is a consequence of heavy smoking alone, or a characteristic acquired by smokers over time.<sup>39</sup> Many mechanisms of corticosteroid resistance have been posited.<sup>30</sup> Little is known about the mechanisms that modify diagnosis in the natural history of inflammatory airway disease, that is, about the predominant mechanism (asthma, COPD, bronchitis) involved in the inflammatory activity.<sup>5</sup> Likewise, the effect of smoking cessation on the alterations associated with airway inflammation in asthmatic smokers is poorly understood.<sup>25</sup> It has been suggested that lung function could improve to some degree once the efficacy of oral corticosteroid treatment is reestablished and the tobacco-related resistance to these agents has disappeared.<sup>40,41</sup> A progressive improvement in chronic respiratory symptoms has been observed among asthmatic smokers who stop smoking,<sup>42</sup> although, paradoxically, in some of these patients symptoms worsen as a result of onset of chronic bronchitis<sup>43</sup> and/or the characteristic bronchial obstruction associated with COPD.

#### *Biological Mechanisms Common to the Inflammatory Pathophysiology of Both Asthma and Tobacco*

The proinflammatory activity of tobacco in airways already inflamed by asthma is poorly understood. It is known that smoking favors a cell phenotype in normal individuals characterized by a predominance of CD8<sup>+</sup> T-lymphocytes, neutrophilia, and higher macrophage counts within the most central airway wall, and by an increase in eosinophils in the peripheral lung.<sup>30</sup> Almost no precise histological information is available on the natural history of airway inflammation in the presence of asthma and smoking. Only indirect and partial data is available on

differences between inflammatory activity in current smokers and nonsmokers.<sup>39</sup> For example, findings concerning inflammatory cell phenotypes show that eosinophil counts in induced sputum are higher among asthmatic smokers than among nonsmokers with asthma,<sup>44</sup> whereas neutrophilia is more pronounced among asthmatic smokers.<sup>45</sup> A greater variability in exhaled nitric oxide levels has also been found in asthmatic smokers, a phenomenon conditioned by the short and long-term effects of smoking.<sup>46,47</sup> Certain proinflammatory transcription factors (nuclear transcription factor- $\kappa$ B) and cell signaling systems specific to both inflammatory activity (phosphorylation of the p38 mitogen-activated protein kinase enzyme) and certain very potent inflammatory mediators (for example IL-4, TNF- $\alpha$ , and IL-8) are elevated in the bronchial secretions of asthmatic smokers.<sup>30,48</sup> IL-8 has been shown to correlate positively with neutrophilia and negatively with forced expiratory volume in 1 second.<sup>45</sup> IL-8 is also associated with corticosteroid resistance, while TNF- $\alpha$  is associated with macrophage metalloelastase activity.<sup>49</sup> It has also been reported that bronchial remodeling is highly dependent on the intensity of tobacco consumption, although exhaustive data are not available to indisputably support this affirmation. Similarly, it has been hypothesized that tobacco smoking may regulate the type 1 immune response to common allergens.<sup>50</sup> The generation of leukotriene B<sub>4</sub> by circulating leucocytes is also increased in asthmatic smokers.<sup>51</sup>

Several experimental studies in animals and clinical studies in humans, as well as *in vitro* experiments, have attempted to determine the degree of oxidative stress and the predominant inflammatory profile in the mucosa inflamed by asthma, and to study the modifications produced by smoking in order to determine its role in the mechanisms that produce inflammatory airway disease<sup>52</sup> and to gain a better understanding of the biological conditions of its expression in the onset of bronchitis, COPD, and asthma.<sup>30</sup>

#### *Treatment of Asthma in Smokers*

While very few studies have evaluated the effects of inhaled or oral corticosteroids in asthmatic smokers, the findings generally indicate that these patients only achieve partial recovery of lung function and limited symptom control with these antiinflammatory agents.<sup>40,53</sup> This finding contrasts with the very high level of control achieved in asthmatic patients who do not smoke.<sup>30,41,54</sup> While certain factors related to the correct treatment of asthmatic patients and the cumulative exposure of years of smoking may interfere with and limit the effectiveness of corticosteroid therapy, and resolving such problems would improve efficacy, current research into the antiinflammatory therapeutic effect is mainly focused on achieving a better understanding of the biological molecular inflammatory mechanisms involved and how these could be regulated.<sup>55</sup> Specific research is targeting both inhaled and oral corticosteroids as well as the newer antiinflammatory drugs.<sup>55</sup> The partial antiinflammatory effect found for corticosteroid treatment of certain groups of asthmatic smokers has led to a search for other antiinflammatory

molecules that may be effective in this situation. The antileukotrienes are one potentially useful therapeutic option (Table). This therapy would be useful in asthmatic smokers in whom the activity of the leukotriene pathway is predominant and corticosteroids have only limited and inadequate efficacy in the control of the smoking-related inflammation.

#### **Immediate Clinical Implications of Smoking for Patients With Asthma: Where is the Dilemma or What is the Best Solution to This Puzzle?**

It is reassuring to discover that we are continuously improving our scientific understanding of the biological processes and pathogenic mechanisms responsible for asthma and smoking addiction and that this improvement will in the future lead to more effective drugs for this combination of diseases. It will surely be possible, to a great extent, to control most of the biological mechanisms of inflammation with harmful repercussions on the patient's health in each stage of the natural history of both these diseases. But this statement inevitably raises the question of whether all the effort invested in increasing our knowledge and making available medical and health resources will have been sufficient to reduce the morbidity and mortality associated with this combination of diseases? It is a question that we can deliberate carefully, but the answer will most likely be "no." We cannot escape the epidemiological and daily clinical reality of asthma and smoking—that the morbidity and mortality associated with both these diseases can be prevented using simple measures. An example of this can be found in the article published recently by Harrison and colleagues,<sup>56</sup> who studied asthma deaths recorded on death certificates in the United Kingdom. Asthma deaths continue to be largely associated with behavioral factors and behaviors known to be harmful to health, including noncompliance with therapy. However, those authors found that up to 46% of

TABLE  
Potentially Useful Treatments  
for Asthmatic Smokers\*

Long-acting $\beta_2$ receptor agonists alone or in combination with inhaled corticosteroids
Theophyllines
New glucocorticoid receptor agonists
Selective phosphodiesterase-4 inhibitors
Mediator antagonists
Leukotriene receptor antagonists
Histamine-H <sub>1</sub> receptor antagonists
Interleukin-2 receptor blockade
Tumor necrosis factor- $\alpha$ , leukotriene B <sub>4</sub> , or interleukin 8 receptor antagonists
Other antiinflammatory therapies
Interferon- $\alpha$ Interleukin-10 agonists
Mitogen-activated protein kinase inhibitors
Nuclear factor- $\kappa$ B inhibitors
Macrolide antibiotics
Inducible nitric oxide blockers
Antioxidants

\*Taken from Thomson et al<sup>30</sup>.



asthma deaths were associated with smoking (a socially acceptable drug addiction).<sup>56</sup> Overlooking this important clinical and epidemiological observation of the daily medical reality of these 2 diseases so prevalent in Spain will make it more difficult to implement the most effective solution to the pathophysiologic puzzle posed by asthma and smoking (in contrast to the biological challenge posed by achieving a greater understanding of its pathogenesis). We should not, therefore, lose sight of the common sense solution to this supposed dilemma in the clinical management of these patients, that is, we should remember the following: if you have asthma and smoke, rapidly alleviate your suffering and improve your asthma control by stopping smoking now!

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