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Obesity and asthma: beyond T_H2 inflammation

Luiz O.S. Leiria [a], Milton A. Martins [b], Mário J.A. Saad [a,*]

[a] Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas, Campinas, SP, Brazil
[b] Department of Medicine, School of Medicine, University de São Paulo, São Paulo, SP, Brazil

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ABSTRACT

Obesity is a major risk factor for asthma. Likewise, obesity is known to increase disease severity in asthmatic subjects and also to impair the efficacy of first-line treatment medications for asthma, worsening asthma control in obese patients. This concept is in agreement with the current understanding that some asthma phenotypes are not accompanied by detectable inflammation, and may not be ameliorated by classical anti-inflammatory therapy. There are growing evidences suggesting that the obesity-related asthma phenotype does not necessarily involve the classical T_H2-dependent inflammatory process. Hormones involved in glucose homeostasis and in the pathogeneses of obesity likely directly or indirectly link obesity and asthma through inflammatory and non-inflammatory pathways. Furthermore, the endocrine regulation of the airway-related pre-ganglionic nerves likely contributes to airway hyperreactivity (AHR) in obese states. In this review, we focused our efforts on understanding the mechanism underlying obesity-related asthma by exploring the T_H2-independent mechanisms leading to this disease.

1. Introduction

Obesity has emerged as an important risk factor for asthma [1,2]. There has been a remarkable increase in the prevalence of obesity worldwide as a consequence of the modern eating habits associated with a sedentary lifestyle [3]. Along with the growing prevalence of obesity and metabolic syndrome, a concomitant rise in the incidence of asthma has been observed in the last few years [1]. Nevertheless, obesity is known to increase disease severity in asthmatic subjects [4] and also to impair the efficacy of first-line medications to treat asthma, worsening disease control in obese and overweight patients [5–8].

Asthma is characterized by chronic inflammation in lung tissue, mucus production and abnormal bronchoconstriction. Inflammation includes the presence of CD4 T helper 2 (T_H2) cells and their associated cytokines, as well as eosinophilic infiltration. Effector T_H2 cells enhance the eosinophilic survival through the secretion of IL-5 and, in addition, facilitate mast cell survival by releasing IL-9. Likewise, eosinophils contribute to antigen specific production of IL-4 and IL-13, which in turn are required for increased muscle reactivity [9].

Abbreviations: AHR, airway hyperreactivity; AKT, RAC-alpha serine/threonine-protein kinase; AMPK, adenosine monophosphate-activated kinase; ARPF, airway-related pre-ganglionic fibers; ASM, airway smooth muscle; BAL, bronchoalveolar lavage; BMI, body mass index; BTSM, bovine tracheal smooth muscle; cGMP, cyclic guanosine monophosphate; CNS, central nervous system; eNOS, endothelial nitric oxide synthase; HMW, high molecular weight; IL, interleukin; ILC-3, innate lymphoid cells type 3; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS-1, insulin receptor substrate; LMW, low molecular weight; NFκB, nuclear factor kappa B; NLRP3, pyrin domain-containing protein 3; TH2, T helper 2; PI3K, phosphoinositide-3 kinase; PPARα, peroxisome-proliferator activated receptor alpha; sGC, soluble guanylyl cyclase; TNF-α, tumor necrosis factor alpha.

* *Corresponding author at:* Department of Internal Medicine, Faculty of Medical Sciences–FCM, State University of Campinas–UNICAMP, Rua Tessália Vieira de Camargo, 126 Cidade Universitária Zeferino Vaz, 13083-887 Campinas, SP, Brazil.
E-mail address: msaad@fcm.unicamp.br (M.J.A. Saad).

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Despite the established concept of asthma being the presence of local inflammation as basic criterion for the onset of disease, some asthma phenotypes are not accompanied by detectable inflammation [10]. There is an emerging theory supporting the idea that asthma phenotype incident in obese patients does not necessarily involve inflammatory lung injury [11–13]. Several researchers have found no relationship between obesity-associated asthma and eosinophilic inflammation, after measuring sputum eosinophils [14–16] or exhaled nitric oxide [16], while others have attributed airway hyperreactivity (AHR) in obese patients to obesity-related changes in lung mechanics as a consequence of the decreased pulmonary functional volume [11]. Individuals who are obese breathe with low lung volumes. This can lead to reduced airway caliber and increased airway resistance during tidal breathing. In addition, independently of lung volume, individuals who are obese also present increased elastic load [11,13].

Compared with subjects in the normal weight range, lung volume and airway caliber were reduced in subjects with increased body mass index (BMI), in a linear fashion [11]. Furthermore, studies support the idea that adipose tissue location is a determinant factor linking obesity and asthma, as abdominal fat mass was found to influence airway distribution more than for other fat locations [17,18], suggesting that adipokines released from these white fat deposits are likely to contribute to disease. Taken together, these studies have led to the general consensus that airway inflammation is not the unique and essential mechanism driving the association between obesity and asthma that it was first thought to be; the reason that corticosteroid anti-inflammatory drugs are less effective in the treatment of asthma in overweight and obese patients [5–8,19]. In accordance with those findings, a recent experimental study detected AHR in high-fat fed obese mice in an inflammation-independent manner [20], highlighting the possibility that metabolic changes induced by obesity/diabetes would mediate inflammatory-independent AHR phenotype in obese patients.

On the other hand, a number of clinical studies have suggested that obesity enhances inflammatory injury in the lungs of asthmatic patients [21–23] and, accordingly, experimental studies have also reported an increase in local inflammation in the lung from high-fat fed obese mice challenged with ovalbumin, compared to those from non-obese mice [24–26]. Another study with obese asthmatic patients revealed an increase in the eosinophil number located at the airway wall, but not at the lumen, suggesting that location of eosinophils in the lungs is crucial to the pathogeneses of disease [22]. Paradoxically, eosinophilic infiltration has a beneficial role in the adipose tissue, where it sustains alternatively activated macrophages, which importantly contribute to metabolic homeostasis. This way, it seems that at least in T_H2-dependent asthma in obese patients, redistribution of eosinophils from the adipose tissue to the lungs appears to be a plausible mechanism underlying this pathophysiology [27]. Nonetheless, it seems that either inflammation-dependent or -independent phenotypes could be detected in obese subjects and, for different reasons both of them lead to an impairment of asthma control in these patients. Although it is well-established that hormones that control metabolism such as insulin, leptin and adiponectin, modulate airway responsiveness, their functional role in asthma and their underlying molecular mechanisms remain unclear. Moreover, conflicting studies in the literature associate the hormone levels in obesity state that both T_H2-dependent or -independent asthma phenotypes exist [10,24,25]. In the next sections, we have focused our efforts on understanding the influence and contribution of the non-T_H2 components such as leptin, insulin, adiponectin and low-grade inflammation, to the pathophysiology of obesity-related asthma.

2. Early-onset *vs.* late-onset obese-asthma phenotypes

Asthma may develop in obese children or in obese adults for different reasons and it may involve different pathophysiological mechanisms. The most frequent asthma phenotype, early-onset asthma, occurs in a T_H2-dependent fashion, with children and adolescents often presenting with higher eosinophilic infiltration levels and/or activity in the lungs. Prospective studies with school-aged populations showed that asthma prevalence and incidence increase with the presence of obesity [28]. A recent study demonstrated that atopic asthmatic in obese children and adolescents presented an increased eosinophilic activity in comparison asthma in non-obese patients [23], which indicates that along with the increased incidence of asthma in obese children, disease severity is even higher in these subjects.

On the other hand, in some circumstances, such as for obesity, asthma may develop in the absence of T-helper 2 (T_H2)-inflammation in the lungs [10]. This peculiar asthma phenotype is known to have a later onset (~40 years) and to be minimally allergic and, as a consequence, has a worse response to glucocorticoid treatment. Several studies have recently explored the non-T_H2 components of obesity-related asthma and novel mechanisms (see next sections) have been recently described in order to explain the causative relationship between these two diseases. Therefore, taking into account the current state of knowledge, one could infer that while the T_H2-dependent early-onset asthma phenotype can be potentiated by obesity, the later-onset asthma phenotype is likely to be a consequence of obesity-induced metabolic changes and the condition appears to be driven by distinct mechanisms. Nevertheless, the mechanisms involved in both types of asthma need to be better comprehended in order to help drive new approaches to diagnosis and therapeutics.

3. Asthma control in obesity

Asthma is usually controlled with low doses of inhaled corticosteroids; this is regarded as first-line treatment for the disease. Approximately 10% of asthmatic patients need the maximum inhaled dose, and around 1% of the cases require chronic oral treatment with glucocorticoids (so-called glucocorticoid-dependent asthma). However, in some special cases the patients are glucocorticoid resistant. Glucocorticoid resistance is defined as asthma symptoms showing no clinical improvement after treatment with high-dose oral glucocorticoids. Notwithstanding, glucocorticoid resistance was reported to be prevalent in obese asthma patients [29].