

CHILD OBESITY AND BRONCHIAL ASTHMA

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ABSTRACT

Obesity and bronchial asthma have suffered a sustained increase in its prevalence worldwide. The relationship between both entities has been widely studied especially in the adult population. Obesity has been shown to be a risk factor for new bronchial asthma diagnoses and vice versa; and that both alter the evolution of the other. The relationship between them is based on systemic inflammatory factors and cardiometabolic factors rather than the fat load. In this review we will focus on the pathophysiology of metabolic and immunological alterations that link both diseases.

Keywords: obesity, bronchial asthma, inflammation.

INTRODUCTION

The relationship between obesity and bronchial asthma is complex to establish. Both morbidities have behaved epidemically in the last three decades and are currently a public health problem. The current prevalence of childhood asthma in Chile is 17.9% in children 6 to 7 and 15.5% in children 13 to 14 years old (1). Chile currently ranks fifth in the world in childhood obesity, with a prevalence of over 20% in preschool age and over 25% in school age (2).

Obesity, as an independent clinical entity, adds to the symptoms of asthma and has negative effect on a child's health with consequences: obstructive sleep apnea, high blood pressure, diabetes, dyslipidemia, liver disease, mental health disorders and orthopedic problems (3). Comorbidities such as gastroesophageal reflux, obstructive sleep apnea, metabolic syndrome and depression are especially important as they worsen the evolution of bronchial asthma (4).

Although overweight / obesity and bronchial asthma may simply coexist in some children, growing evidence highlights the existence of a special "asthma-obesity" phenotype, where high body weight affects and modifies the characteristics of asthma (5). This specific asthma phenotype can be divided into two categories: bronchial asthma complicated by the coexistence of obesity and asthma due

to obesity (6). The first group refers to patients with early onset bronchial asthma, usually atopic, and in whom obesity has been associated with an increased risk of exacerbation, emergency consultations and / or hospitalization (7), lower response to inhaled corticosteroids (8), lower response to bronchodilator treatment (9), lower control of symptoms (10), lower quality of life (11) and poor evolution during hospitalizations for bronchial asthma (12). In regards to the second group, these are patients with a later diagnosis, generally non-atopic, in whom adiposity would be the main risk factor for developing bronchial asthma (13) (Figure 1).

The relationship between obesity and bronchial asthma has also been described in reverse, that is, bronchial asthma as a risk factor for developing obesity in children (14). The bidirectional association is due to independent factors that increase body weight: reduced physical activity, increased sedentary time and use of oral corticosteroids during exacerbations.

Since 2015, the Center for Disease Control and Prevention (CDC) lists obesity as a major risk factor for childhood bronchial asthma (15). Currently, obesity is considered a risk factor for developing bronchial asthma and a risk factor for modifying the course of the disease, worsening its control.

Longitudinal studies in adults report that obesity precedes and increases the risk of non-atopic bronchial asthma especially in females (16). A recent meta-analysis in children demonstrates a significant association between being overweight or obese and the risk of new diagnoses of bronchial asthma at follow-up, the odds ratio for this group of

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Figure 1. Obesity Phenotype / Bronchial Asthma. Abbreviations: FEV1, forced expiratory volume in one second ; FVC, Forced vital capacity; Th1, T helper type 1; Th2, t helper type 2
Adapted from Di Genova L, Penta L, Buscarini A, Di Cara G, Esposito S. Children with Obesity and Asthma: Which Are the Best Options for Their Management. *Nutrients*. 2018, Nov, 10 (11)

Obesity Phenotype / Bronchial Asthma

Characteristics	Early onset asthma	Late onset asthma
Starting age	< 12 years	> 12 years
Sex	Female = Male	Female > Male
Lung function (FEV1, FVC)	Decrease in lung function	Minimal alteration of lung function
Atopic condition	Atopic	Non atopic
Hyperreactivity of the airway	Severe hyperreactivity of the airway	Mild hyperreactivity of the airway
Score symptom control questionnaire	High score	Low score
Inflammation of the airway	Eosinophilic airway infiltration	Neutrophilic airway infiltration
Th1-Th2 profile	Biomarkers Th2 high	Biomarkers Th2 low

patients was 1.30 (95% confidence interval = 1.23-1.39; $p < 0.001$) (17). The association of obesity and new diagnoses of asthma has been demonstrated in different age ranges, from the first three years of life to school age (18) and from school age to adolescence (19). Most longitudinal prospective studies report that obesity would be an independent risk factor for developing bronchial asthma in specific groups of patients, such as children with high birth weight (20), children of obese mothers or with exaggerated weight gain during pregnancy (21), children with insufficient breastfeeding (22) and girls with precocious puberty (23).

Classically, studies that relate obesity and bronchial asthma have focused on the Body Mass Index (BMI). More recent studies have focused on investigating the mechanisms linked to obesity that could explain the pathophysiology of obesity asthma, including the role of metabolic deregulation, systemic immune disorders (24) and the mechanical effect of the obesity burden, especially torso adiposity (25). However, the relationship between both pathologies seems to be more complex and multifactorial. There are genetic, epigenetic, environmental, inflammatory, metabolic, dietary and microbiome factors involved (Figure 2).

In this review we will focus on the pathophysiology of metabolic and immunological alterations that link both diseases.

OBESITY, INFLAMMATION, CARDIOMETABOLIC FACTORS AND BRONCHIAL ASTHMA

In the pathogenesis of obesity, rapid proliferation of adipose tissue occurs. The resulting hypoxic environment, product of the delay in the neovascularization of adipose tissue, is the most potent stimulus to initiate an inflammatory reaction. Through its endocrine function, reflected by the production of adipokines, and possibly some other factors,

adipose tissue influences immune and metabolic responses, and can generate a pro-inflammatory environment (26). Adipokines are peptide substances produced by adipose tissue; they have the properties of cytokines, chemokines and classical hormones (27). Adiponectin is the most abundant adipokine in adipose tissue, responsible for regulating energy balance by, for example, stimulating insulin secretion or increasing fatty acid oxidation (28). It has anti-inflammatory effects, mediated by the stimulation of interleukin 10 (IL-10), synthesis and endogenous production of IL-1 receptor antagonists, as well as by the inhibition of nuclear factor signaling κB (NF- κB) (29). In addition, adiponectin further suppresses proinflammatory effects by inhibiting IL-6 and Tumor Necrosis Factor alpha (TNF- α) (26).

Adiponectin concentrations are higher in women than in men, a difference that arises after puberty, since testosterone inhibits the synthesis of adiponectin (30). In obese patients the levels of adiponectin are reduced, therefore decreasing its anti-inflammatory effects, which could contribute to the increase in inflammation present in asthma associated with obesity (31).

Another important mediator produced by adipose tissue is leptin, a hormone that regulates energy balance and appetite. Leptin is transported to the brain, where it binds to its receptor in the hypothalamus and generates the sensation of satiety thus reducing food intake (32). A larger proportion of adipose tissue in the body composition of obese patients leads to an increase in leptin levels. Individuals with overweight and obesity develop resistance to leptin, which causes greater weight gain due to increased appetite. Leptin also exerts immunomodulatory effects of the proinflammatory type, such as increased Interferon-mediated responses (IFN- γ), increased immunity of T helper cells CD4+, mast cell activation, as well as the activation of transcription factors such as NF κB . It is not surprising, therefore, that leptin can contribute to the development of asthma or increase its severity in obese people (33).

Figure 2.

Relationship between bronchial asthma and obesity. Abbreviations: M1, type 1 macrophages; M2, type 2 macrophages; Th1, T helper type 1; Th2, t helper type 2; BHR, bronchial hyperreactivity; Sd syndrome.

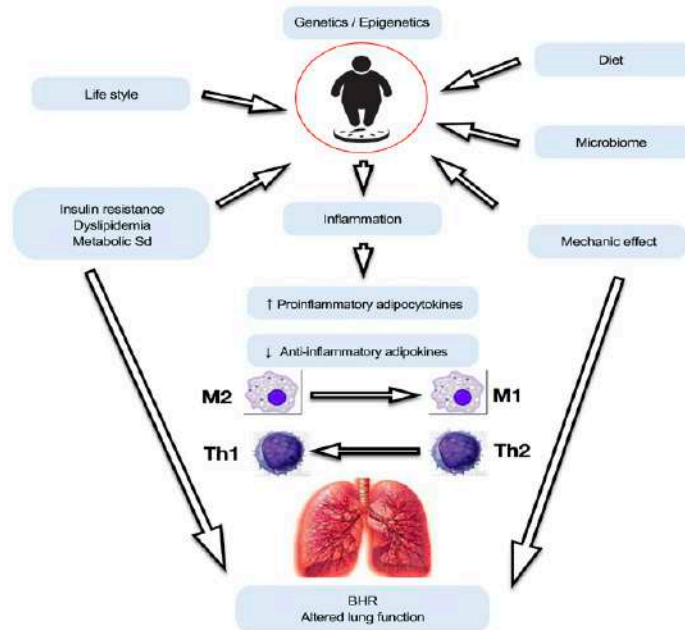
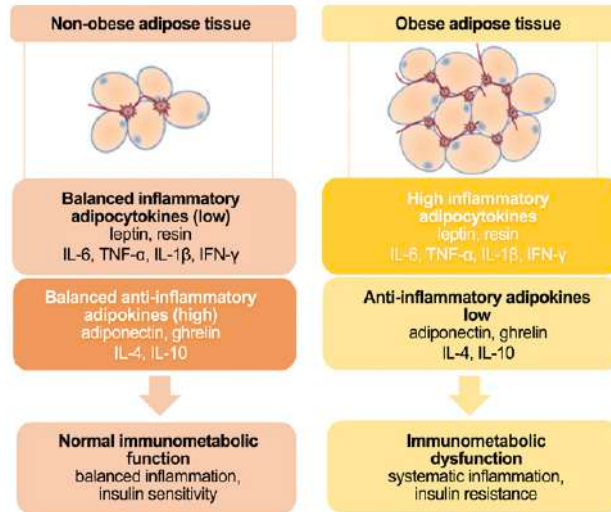


Figure 3.

Tissue immunometabolic response. Abbreviations: IL-1 β , interleukin beta; interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10; IFN- γ , interferon gamma; TNF- α , tumor necrosis factor α . Adapted from: Miethe S, Guarino M, Alhamdan F, Simon HU, Renz H, Dufour JF, Potaczek DP, Garn H. Effects of obesity on asthma: immunometabolic links. Pol Arch Intern Med. 2018 Aug; 128 (7-8): 469-477.



Resistin is another hormone produced by adipose tissue that modifies insulin resistance. Resistin levels increase in obese patients and lead to insulin resistance (34). In addition, it triggers the activation of NF κ B and the production of cytokines, which promotes pro-inflammatory effects (35), which in turn is believed to contribute to more severe exacerbations of asthma in obese patients (36). Ghrelin is another important appetite hormone involved in metabolism and energy balance (37). It is responsible for the increase in food intake and the decrease in fat utilization. In addition, ghrelin can inhibit the expression of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α (38). However, in obese individuals, ghrelin levels decrease,

which is believed to be a physiological protection mechanism that regulates energy balance (39) (Figure 3).

In the pro-inflammatory cascade of asthma in obesity there is an increase in the pool of proinflammatory adipose tissue M1 macrophages and a decrease in anti-inflammatory M2 macrophages, with the release of proinflammatory adipocytokines and a decrease in anti-inflammatory adipokines (40).

In relation to the immunological alterations, an inflammatory state with polarization towards the T helper type 1 - Th1- lymphocyte pathway in obese asthmatics is described. In asthmatic and obese adolescents, polarization of systemic Th1 inflammation is associated with deterioration of pulmonary function,

and high levels of circulating IL-6, produced by adipose tissue macrophages associated with worse asthma control (41).

The cytokine imbalance described translates into a low-grade pro-inflammatory state that is directly and indirectly related to immune and metabolic alterations that contribute, not only to the development of bronchial asthma, but also to the development of atherosclerosis, arterial hypertension, insulin resistance, type 2 diabetes and dyslipidemia (42). In effect, adipokines are involved in the development of metabolic syndrome (MS) whose essential components are glucose intolerance, central obesity, high blood pressure and dyslipidemia. At present, the need to add non-alcoholic fatty liver disease and the determination of biomarker levels as adipokines (43), is suggested since these would also negatively impact patients' cardiovascular health.

To date, according to our knowledge, the effect of nonalcoholic fatty liver disease in the course of bronchial asthma has not been described.

Experimental models have provided some explanations for the relationship between cardiometabolic factors and airway dysfunction. In the bovine airway smooth muscle, hyperinsulinemia and the increase in insulin-like growth factors have been shown to induce a remodeling of the airway characterized by respiratory epithelial metaplasia and myofibroblast proliferation that ultimately results in hypercontractibility. (44).

PUMONARY FUNCTION IN AN OBESE ASTHMATIC CHILD

Obesity alters lung function regardless of the presence of bronchial asthma symptoms. In adults, obesity has a restrictive effect, decreasing lung volumes (45). In the obese child it is reported that the forced expired volume in one second (FEV1) and forced vital capacity (FVC) remain normal, but the FEV1 / FVC ratio decreases. This functional alteration, called "dysanapsis", compatible with an obstructive pattern, is due to an incongruity between the growth of the lung parenchyma and the airway (46). The presence of "dysanapsis" in an obese child suggests a genetically determined somatic growth pattern that defines an increased weight gain and a lung growth disorder. In asthmatic patients this functional disorder is associated with a higher frequency of asthma exacerbations and use of systemic corticosteroids (47).

In relation to cardiometabolic factors and asthma, in prepubertal children it has been shown that insulin resistance and hyperglycemia are associated more closely with airway hyperreactivity than with obesity itself. Metabolic deregulation, defined by insulin resistance and dyslipidemia, worsens lung function and promotes bronchial hyperreactivity, independent of BMI. In children with asthma, leptin and adiponectin levels correlate with exercise-induced changes in lung function; in adults, leptin expression of visceral fat correlates with increased bronchial hyperreactivity. Dyslipidemia in adolescents has been associated with asthma risk, independently of BMI (48). Therefore, in the decrease of the pulmonary function of the asthmatic patient, specifically in the decrease of the FEV1 / FVC ratio and bronchial hyperreactivity, obesity, dyslipidemia and insulin resistance would act synergistically (46), although in some cases the components of MS act by affecting respiratory function independent of adiposity.

CONCLUSIONS

Current evidence strongly suggests that the effects of obesity on asthma, both in its incidence and severity, are mediated by an inflammatory and cardiometabolic pathway. Adipokines secreted

by adipose tissue exert significant effects not only on the metabolism but also on the immune system and, although it is still necessary to establish detailed mechanisms of their contribution, they seem to represent important mediators in asthma associated with obesity. The metabolic health of adipose tissue seems more important than the fat mass itself; in fact, the negative effect of torso adiposity in the asthmatic obese, rather than a mechanical effect, is due to the inflammation associated with central obesity.

Conflicts of interest

The authors have no conflicts of interest.

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