Asthma and Obesity

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Asthma is a common chronic airway disease characterized by variable airflow limitation resulting from the combination of airway narrowing, airway hypersensitivity, airway wall thickening, and increased mucus hypersecretion. Airway narrowing results from both chronic inflammation and airway remodeling. Asthma is a heterogeneous disease with several distinct clinical presentations (phenotypes) and complex pathophysiological mechanisms (endotypes). Obesity is the consequence of an excessive body fat accumulation due to an imbalance of energy intake and energy expenditure. Diagnosis of obesity is usually established by assessing the body mass index (BMI) ≥ 30 kg/m^2.

Keywords: asthma ; cytokines ; phenotype

1. Asthma and Obesity Two Diseases on the Rise and Linked

Numerous epidemiological studies have reported the significant increase of asthma and obesity in most countries all over the world.

1.1. Asthma

Asthma is global health problem affecting almost 300 million people of all ages and ethnic groups worldwide [1]. In Spain, the prevalence of asthma ranges between 1.5 and 16.7% in the adult population, and about 10% in the pediatric population [2].

The prevalence of asthma has markedly increased over the last decades, especially in Westernized countries [3][4]. The causes of this increase are unclear but may be a consequence of changes in lifestyle and in environmental conditions. Lifestyle changes include modification of dietary habits, with decreased consumption of vegetables and fresh fruits, and increased access to processed saturated fats and carbohydrate sweeteners [5][6][7]. Several mechanisms have been proposed to explain the role of diet in asthma, including low vitamin D levels, oxidative stress, epigenetic regulation, and imbalance in the gut microbiome [5]. The environmental changes contributing to the increase in the prevalence of asthma include increased exposure to tobacco smoke, traffic pollution, and infectious agents [8]. However, the underlying mechanisms involved in the interaction of environmental pollution, allergen, and viral exposures with the immune system remains to be elucidated.

1.2. Obesity

Worldwide, the prevalence rate for being overweight or obese between 1980 and 2013 increased 27.5% for adults and 47.1% for children, resulting in a total of 2.1 billion individuals considered overweight or obese [9]. In Spain, the age-adjusted prevalence for being overweight or obese increased from 34.0% to 35.8%, and from 8.0% to 16.5%, respectively, between 1987 and 2012. Morbid obesity increased from 0.20% in 1993 to 0.88% in the same period. The growth rate was greater among males [10].

The increase in the prevalence of obesity has been associated with factors favoring a positive energy balance and weight gain, which include increased food consumption, particularly of high-calorie foods, and decreased time spent in occupational physical activities associated with increased sedentary activities. Various studies have shown that the rate of heritability of BMI ranges from 40 to 70%, supporting the existence of an underlying genetic mechanism that contributes to obesity. Over 300 loci have been identified, although these loci only account for less than 5% of individual variation in BMI [11][12].

1.3. Asthma and Obesity: Two Linked Diseases

The epidemiological link between asthma and obesity was first suggested in a study carried out by Camargo et al., involving 85,911 nurses in the United States [13]. The study found that the risk of developing late-onset asthma was significantly increased when the BMI was greater than or equal to 30 kg/m^2 with an odds ratio of 2.6. Subsequently,

several studies were carried out and corroborated the existence of an excess risk of developing asthma in obese subjects compared with subjects not overweight, regardless of gender or age [14][15][16][17][18][19][20][21]. The relationship also appears stronger for those with central versus general adiposity [22][23]. A study from the California Teachers Study cohort reported that increased waist circumference was associated with asthma even among those with BMI's within the normal range [22]. The European Community Respiratory Health Survey (ECRHS) found an association between asthma and obesity, but with a greater excess risk in females with respect to males [15][24]. The longitudinal cohort conducted in the city of Tucson in the United States [25] reported the persistence of symptoms into adulthood in obese children with asthma, and also found that being overweight is an independent risk factor for developing post-puberty asthma. Research has also shown associations between mothers' overweight status just before and during pregnancy and offspring's asthma [26][27]. A recent study found that fathers who were overweight during adolescence predispose their offspring to develop asthma [28].

Interestingly, a recent study suggests that asthma may also lead to obesity. The authors followed non-obese children for up to 10 years. Children with an initial diagnosis of asthma were approximately 50% more likely to become obese than children without asthma. The study also showed that the increased risk of obesity with asthma was driven by children who were already overweight at baseline. Since being overweight is a very strong predictor of subsequent obesity, these observations support the possibility that being overweight may drive both asthma and subsequent obesity, and that both obesity and asthma can interact by complex and multiple mechanisms [29].

1.4. Severe Asthma Is Associated with Obesity

Various recent studies that analyzed the profile of mild to severe asthma patients highlighted a subgroup of obese asthma patients, more often female, with late-onset, non-atopic asthma. Asthma in these patients is more difficult to control, lung function is impaired, they undergo more treatments with limited therapeutic effects, and suffer from more frequent exacerbations than the non-obese asthma population [30][31][32][33][34][35]. The frequent use of systemic corticosteroids that characterizes severe asthma may contribute to the development of obesity in these patients [36].

Two main sub-phenotypes of obese asthma have been described according to age. The first phenotype associating asthma and obesity of early onset affects children with asthma under 12 years old. It is characterized by obesity, which worsens pre-existing asthma [37]. Children are, in the majority of cases, allergic, and both sexes are affected equally. Asthma is associated with more severe airway obstruction, more marked airway hyperresponsiveness (AHR) compared with early non-obese asthma, and inflammation is predominantly eosinophilic [38]. The second main phenotype is characterized by delayed onset asthma developing, at least in part, as a consequence of obesity [36]. This asthma is generally non-allergic with pronounced symptomatology despite treatments with high doses of inhaled corticosteroids and long-acting bronchodilators [32][33]. There are, however, some discrepancies with respect to the type of airway inflammation associated with the obese phenotype. Some cluster analyses have shown that the association between obesity and neutrophilic inflammation is more common in women [33]. However, other studies have not found such an association between obesity and neutrophilic airway inflammation in adults with asthma [39][40].

2. Association of Obesity and Asthma: Genetics

A genetic predisposition has been suggested to explain why some obese subjects will develop asthma while others will not. A study on mice and human subjects found that CHI3L1 gene expression and the protein generated by its activation (chitinase 3-like 1) can be induced by a high-fat diet and thereby contribute both to obesity and to asthma development [41].

A recent study performed a large genome-wide association study (n > 450,000) to explore the genetic associations between obesity and early- versus late-onset asthma in an adult population, and between obesity and atopic versus non-atopic asthma. Limited evidence of shared genetic correlation between BMI and early-onset asthma was found. However, the results of the study were able to confirm causal effects of BMI on late-onset, atopic, and non-atopic asthma and identified 32 independent shared loci between these traits and the HLA (human leukocyte antigen) region, ERBB3 (regulation of bronchial epithelial repair and remodelling), and SMAD3 (regulation of inflammatory response) genes. These results provide support to the existence of a causal link between obesity and asthma. Moreover, the shared loci identified support the involvement of inflammation, airway repair, and the immune system in the underlying pathophysiological mechanisms shared by obesity and asthma [42].

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