



Association between obesity and asthma – epidemiology, pathophysiology and clinical profile

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Abstract

Obesity is a risk factor for asthma, and obese asthmatics have lower disease control and increased symptom severity. Several putative links have been proposed, including genetics, mechanical restriction of the chest and the intake of corticosteroids. The most consistent evidence, however, comes from studies of cytokines produced by the adipose tissue called adipokines. Adipokine imbalance is associated with both proinflammatory status and asthma. Although reverse causation has been proposed, it is now acknowledged that obesity precedes asthma symptoms. Nevertheless, prenatal origins of both conditions complicate the search for causality. There is a confirmed role of neuro-immune cross-talk mediating obesity-induced asthma, with leptin playing a key role in these processes. Obesity-induced asthma is now considered a distinct asthma phenotype. In fact, it is one of the most important determinants of asthma phenotypes. Two main subphenotypes have been distinguished. The first phenotype, which affects adult women, is characterised by later onset and is more likely to be non-atopic. The childhood obesity-induced asthma phenotype is characterised by primary and predominantly atopic asthma. In obesity-induced asthma, the immune responses are shifted towards T helper (Th) 1 polarisation rather than the typical atopic Th2 immunological profile. Moreover, obese asthmatics might respond differently to environmental triggers. The high cost of treatment of obesity-related asthma, and the burden it causes for the patients and their families call for urgent intervention. Phenotype-specific approaches seem to be crucial for the success of prevention and treatment.

Key words: Obesity: Overweight: Asthma: Phenotypes: Obesity-induced asthma

Introduction

Obesity and asthma are conditions that have been increasing in recent decades. This sudden increase is most probably caused by the shift towards the Westernised lifestyle and rapid urbanisation. Strong association has been found between asthma and obesity and it has been shown that obesity increases the risk of asthma⁽¹⁾. The large and pathologically specific group of obese patients with asthma has attracted the attention of scientists and medical doctors worldwide. The present review explores the complex association between the two conditions, with focus on their epidemiology, but also involving the pathophysiology and clinical aspects, which can serve for the creation of the personalised, tailor-made intervention and prevention initiatives for severely affected patients.

Overweight and obesity

Overweight and obesity are defined by the WHO as excess fat accumulation that presents a risk to health⁽²⁾. Obesity has become an acute focal point of research, as it is a strong risk factor for various diseases. These include CVD, diabetes, asthma, orthopaedic diseases and some forms of cancers^(3–7),

not to mention the social stigma and low self-esteem that obese individuals may suffer⁽³⁾.

The rapid urbanisation and Westernisation of countries has led to consumption of larger amounts of energy with a decline in daily activity, which has resulted in rising epidemics of obesity^(8,9). According to the WHO, in 2008, over 1.4 billion adults older than 20 years of age were overweight; among them, approximately 200 million men and 300 million women were obese⁽²⁾.

We are now aware that adipose tissue is not merely for storage of spare energy consumed but not used. Adipose tissue is a physiologically complex and highly active metabolic and endocrine organ that secretes various hormones (adipokines). These regulate the appetite in the central nervous system, as well as insulin, fatty acid levels and sex hormone precursors^(10,11).

Asthma

Similarly, an increase in the prevalence of asthma and allergies has been observed in recent decades^(12,13). This rapid increase, with clearly observable social and demographic patterns, again suggests changes in lifestyle to be a possible explanation⁽¹⁴⁾.

Abbreviation: Th, T helper.

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Since more than 300 million individuals suffer from this disease and its prevalence is increasing, the importance of studies in this field has also increased. It is often reported in children but affects all age groups⁽¹⁵⁾.

Asthma has a very strong genetic component, and new genes contributing to its development and severity continue to be found^(16–18). Nevertheless, environmental, behavioural and socio-economic risk factors significantly modulate the development and course of the disease^(19,20).

Epidemiologists, after close and detailed analyses of the asthmatic spectrum, have pointed out the necessity of distinguishing not only different asthma phenotypes (different observable characteristics of the same disease) but also endotypes (different pathophysiological origins of the same disease)^(21,22). One of the phenotypes is obesity-induced asthma⁽²³⁾.

Association between asthma and obesity

The parallel increase in the prevalence of obesity and asthma in childhood suggests a link between the two.

In 1986, Seidel *et al.*⁽²⁴⁾, through a large study in Holland, showed for the first time that asthma was associated with severe obesity in women. However, it was not until 1999 when Camargo *et al.*⁽²⁵⁾ performed a prospective cohort study of 85 911 women from the US Nurses' Health Study II that evidence suggested that BMI has a strong, independent and positive association with risk of adult-onset asthma. After this, a number of publications on this topic increased and remained of strong interest to researchers and physicians.

Indeed, numerous cross-sectional^(26,27) and longitudinal studies^(28,29) confirmed this association. A study of 12 388 children and adolescents from the USA showed double the risk of having asthma for children with a BMI greater than or equal to the 85th percentile⁽³⁰⁾. Another study, including 4- to 17-year-olds from the Third National Health and Nutrition Examination Survey (NHANES-III), showed an increased prevalence of asthma with increased quartile of BMI, significant for the lowest and the highest quartile. These results show a dose-dependent and U-shaped association between BMI and asthma prevalence in children⁽³¹⁾. A similar U-shaped correlation was found for adult men in a cross-sectional study of 5524 subjects included in the New York State Behavioral Risk Factor Surveillance System. In this study, women had a monotonic association, with only the higher BMI values being associated with asthma⁽³²⁾. Not all studies confirm this association. A comparative study of children performed by Guler *et al.* found no significant difference between asthmatic and healthy children, even when atopy was taken into account⁽³³⁾. A recent study on allergies and asthma involving eight European birth cohorts of 12 050 children found an association between the sex- and age-specific BMI trajectories during the first 6 years of life and the incidence of asthma. The rapid increase in body mass in the first 2 years of life appeared to be the strongest predictor of asthma incidence later in childhood⁽³⁴⁾.

Although BMI is the most common and easiest measure of adiposity, it assesses total body mass without clarifying the real contribution of fat tissue in the total mass or its distribution. There is strong evidence demonstrating that not only total body mass but also fat distribution can modify the effect of adiposity on health.

Abdominal obesity is the clinical name for accumulation of fat tissue in the abdominal area, also known as central obesity; it seems to be an additional strong risk factor for co-morbidity in relation to obesity for diseases including asthma⁽³⁵⁾.

Although the association appears at all ages, its relationship with regard to sex changes in proportion as individuals age, being stronger in males in childhood⁽³⁶⁾ and skewing towards females in adulthood⁽³⁷⁾. The results of studies on the obesity-induced asthma phenotype are much more consistent when investigating adults rather than children. There is strong evidence in the literature that the phenotype of obese asthmatic is more prevalent among adult women, especially at the postmenopausal age^(38,39). Hormonal changes related to menopause could be one factor which could explain this dimorphism, suggesting that postmenopausal oestrogen-based therapy increases the development of asthma symptoms in women⁽⁴⁰⁾. The answer could also lie in fat distribution and composition. Adipokines have been shown to be more strongly associated with asthma symptoms in women than in men⁽⁴¹⁾. This once again points toward the endocrine function of adipose tissue. Not every type of fat has the same physiological activity; ectopic fat (deposition of TAG within cells of non-adipose tissue) is more physiologically active within the viscera and skeletal muscle and produces more adipokines, which can promote asthmatic inflammation. This fat, although it exists in lower quantities in women, is more physiologically active⁽³⁹⁾. This could partly be the reason for the higher prevalence of obesity-induced asthma in adult women than in men.

The situation is less clear and more difficult to explain in children. There are many inconsistencies in the reports on obesity-induced asthma amongst children^(36,42). Discrepancies may reflect differences in methodology, as there are not only various markers of obesity used but also different definitions of asthma. The mechanism justifying the higher prevalence of obesity related to asthma amongst boys is fairly unclear, but those sources reporting a stronger association amongst girls suggest similar explanations to those in adults, pointing at adipokine production⁽³⁹⁾ and early menarche; this is caused by increased body mass associated with higher risk for asthma⁽⁴³⁾. The genetic predisposition of girls toward this asthma phenotype has also been mentioned in the literature⁽⁴⁴⁾.

What comes first?

One of the many questions frequently posed in discussions on this topic is what appears first in this specific group of patients, asthma or obesity? Although the association may be bi-directional, prospective studies suggest that obesity precedes and is a risk factor for the development of asthma⁽⁴⁵⁾. However, this chicken-or-egg question is much harder to answer than it might seem, due to the difficulty of determining the exact moment when the two situations set in. What we usually treat as the onset of asthma is the moment when the first symptoms occur and when the diagnosis is made. This, however, does not mean that the pathological state leading to these symptoms or to other physiological alterations did not appear earlier. Prospective studies show that children who are diagnosed with asthma already have altered respiratory function in their infancy, which suggests that the disease might originate in the prenatal state⁽⁴⁶⁾.

A similar situation exists with regard to obesity. We know by now that prenatal and perinatal factors such as birth weight, maternal weight gain, and diet considerably alter the risk of developing obesity later in the child's life^(47,48). Moreover, the impact of the increased neonatal size on the development of asthma at the age of 7 years has been observed in a Danish cohort from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC). Children developing asthma by the age of 7 years already as neonates had expressed lung function deficit and increased bronchial responsiveness⁽⁴⁹⁾. As both asthma and obesity often begin before the moment of birth, claiming a causal relationship is difficult.

Lately there has been a focus on the effect of weight loss in asthmatic patients. In a study run in a private out-patients centre in Finland, two groups of obese patients with asthma participated in an 8-week, supervised weight-reduction programme, which included a very low-energy diet. Over the course of the programme, weight reduction in the intervention group of obese patients with asthma improved lung function, asthma symptoms, morbidity and health status⁽⁵⁰⁾. Studies performing a weight-loss intervention for asthmatic obese children also found that with decreased weight there is a significant improvement in asthma control, lung function and asthma-related quality of life^(51,52). Some authors report a decrease in systemic and airway inflammation⁽⁵³⁾, while others did not find this association⁽⁵⁴⁾.

Possible links

In the literature there are several links concerning the association between asthma with obesity⁽⁵⁵⁾. Epidemiological studies have shown and highlighted that the risk of developing asthma is significantly higher with a positive family history of atopic diseases, with a very significantly increased risk when there is a history of maternal atopy^(56–58). Likewise, a family history of obesity is a strong risk factor for this condition⁽⁵⁹⁾. This highlights the need to research the genetic contribution to obesity and related problems of asthma patients. Indeed, investigating the putative genetic background for both asthma and obesity highlighted some genes as candidates⁽⁶⁰⁾. This does not, however, explain the full variation of the disease and further hypotheses had to be tested to reach a deeper understanding of the phenomenon. A reverse causation was proposed as a putative mechanism contributing to increased weight amongst asthmatic children. It has been shown that inhaled steroids, a commonly prescribed medication for asthma, might have a positive dose effect on children's weight and therefore increased medication use would cause obesity, rather than the other way around⁽⁶¹⁾. It seems more plausible, however, that obesity precedes asthma or at least its manifestation, a hypothesis which is supported by growing evidence⁽⁶²⁾.

Asthma-like symptoms such as shortness of breath and wheezing could appear as the result of excess of thoracic and abdominal fat mass that mechanically restricts respiration⁽⁶³⁾. This would stiffen the movement of the lungs and diaphragm and cause shortness of breath, oxidative stress and, as a result, reduction of resting lung volumes such as functional residual capacity⁽⁶⁴⁾. It has been suggested that increased obesity is more related to non-specific (self-reported and not specific to

one disease only) asthma symptoms such as dyspnoea or nocturnal awakenings and could lead to the impression of lower asthma control, unrelated to severity of inflammation⁽⁶⁵⁾.

There are researchers who claim that there might be an overdiagnosis of asthma amongst obese patients due to the dyspnoea resulting in mechanical restriction⁽⁶⁵⁾ and indeed this has been shown to be true in some cases, with a substantial amount of underdiagnoses observed as well⁽⁶⁶⁾. Another study, however, showed that overdiagnosis is no more likely in cases of obesity than it is for non-obese individuals⁽⁶⁷⁾.

Both obesity and asthma, as described above, are conditions of affluence, and their prevalence has increased significantly over the past few decades. It has been suggested that the Westernised lifestyle played a significant role in these epidemics⁽⁶⁸⁾. Patterns of prevalence have increased, seeming to prove this hypothesis, since they follow the countries' development and Westernisation^(69,70). As a natural consequence of this analysis, the question arose whether the association between asthma and obesity could be explained by the existence of common risk factors due to changing environment and lifestyle. The risk factors related to the Westernised lifestyle that led to an increase in cases of obesity and asthma could also have led to the increase in the number of obese asthmatics. There are a number of common factors observed to be promoting both conditions, such as sedentary lifestyle^(71,72), dietary changes^(73–77), vitamin D insufficiency due to lower exposure to sunlight^(78–81) and tobacco exposure^(82–84), amongst others. Westernised lifestyle increased exposure to risk factors common to these conditions and contributed to the increase in obese children's development of asthma symptoms, as well as their experiencing them more severely and finding less success in treatment^(85–90). Studies have been conducted worldwide examining the role of these factors in childhood obesity, related especially to asthma. Early-life exposures play a crucial role in the development of asthma and obesity. Some of the most important factors linking asthma with obesity are birth weight, both low and high⁽⁴⁹⁾, and breast-feeding⁽⁶²⁾. In addition, poor maternal diet, low in micronutrients such as vitamins D, E and C, and maternal weight gain during pregnancy were shown to increase the chances of the offspring having asthma and/or obesity later in life^(91–95). These factors could contribute to the coexistence of these two conditions⁽⁸⁶⁾; however, the evidence is rather ambiguous.

There might also be a pharmacological contribution to the increased body mass in asthmatic individuals. Evidence exists indicating that treatment with steroids, very commonly used for asthma, is associated with a higher annual body mass gain and the association might be dose-dependent⁽⁶¹⁾.

Although these factors might indeed contribute to the association between these two conditions, one of the strongest pieces of evidence points to the physiological activity of the fat tissue. Adipokines regulate energy homeostasis through hunger and satiety control^(96,97). Some adipokines such as leptin or resistin are produced in excess in obesity⁽⁹⁸⁾, while others, such as adiponectin and ghrelin are reduced. This imbalance promotes pro-inflammatory responses and leads to inflammation^(99–101). A link between these adipokines was found in paediatric⁽¹⁰²⁾ and adult populations, with a stronger relationship observed in female, rather than male, individuals^(41,103). Receptors for leptin have been

found in lung tissue⁽¹⁰⁴⁾ and various studies have observed increased concentrations of adipokines in asthmatic and allergic patients^(102,103).

Most likely, the association between increased obesity amongst children with asthma is multifactorial. Surely, some part of the link can be explained by overestimation due to fat mass on the thoracic chest mimicking asthma symptoms⁽⁶⁵⁾; part of the weight increase may also be due to medication or decreased activity caused by exercise-induced wheezing attacks, resulting in reverse causation⁽⁶¹⁾. There is no doubt that the endocrine role of adipose tissue (adipokines) is a strong physiological link and very plausibly could be a mechanism in causing a chain of disruption leading to inflammation and narrowing of airways^(98,105–107). Despite existing evidence indicating that adipokines may be a plausible link between obesity and asthma, clinical studies bring inconclusive results. A case–control study, by Holguin *et al.*⁽¹⁰⁸⁾, compared the markers of inflammation and oxidation in bronchoalveolar lavage between asthmatic and healthy individuals. Despite increasing BMI being associated with the levels of airway leptin and adiponectin both in asthmatics and healthy controls, these associations were not associated with biomarkers of oxidation or inflammation.

Similarly, in a large prospective cohort study, asthma was linked with obesity only in adults, not in children, and they did not find evidence of a role for leptin or adiponectin in this association⁽¹⁰⁹⁾. No difference in leptin and adiponectin concentrations was found between asthmatics and controls in the study by Jang *et al.*⁽¹¹⁰⁾; however, the leptin:adiponectin ratio was correlated with BMI in asthmatics.

Leptin plays an additional role; it not only works as a hormone, as described above, it also works⁽¹⁰¹⁾ as a neurotransmitter in the hypothalamus⁽¹¹¹⁾. It was recently shown that leptin acts on the parasympathetic nervous system, which is responsible for the regulation of homeostasis, through the inhibition of the action of acetylcholine on the muscarinic acetylcholine receptor M3R. These receptors mediate the bronchoconstriction in response to acetylcholine and its other antagonists and control the dilation of the airways⁽¹¹²⁾. Moreover, leptin-mediated acetylcholine imbalance can cause an increase in the T helper (Th) 2 cells and a decrease of Th1, which can cause the state of allergic inflammation⁽¹¹³⁾.

Many neuropeptides which regulate appetite and satiety play an important role in asthmatic and allergic inflammation and are in metabolic interaction with leptin⁽¹¹⁴⁾. Human and animal studies suggest that adiposity-induced leptin increase and subsequent leptin resistance would affect these transmitters, causing or worsening asthma symptoms. This relates both to orexigenic neuropeptides such as neuropeptide Y^(114–120), endocannabinoids^(121,122), endogenous opioids^(123–126); and anorexigenic neuropeptides such as tachykinins and its most studied members substance P^(127–132), α -melanocyte-stimulating hormone^(133–135), corticotropin-releasing factor^(136–141) and serotonin^(142–150). Altogether, it suggests that these peptides can modulate asthmatic inflammation among obese patients. Despite clinical discrepancies, leptin seems to play an important role in this neuro-immune crosstalk between adipose tissue and pathogenesis of asthma. It might be a potential target for treatment and a key element for understanding the complex problem of obesity-induced asthma.

Obesity-induced asthma phenotype

Obesity-induced asthma has been proposed as one of many distinctive asthma phenotypes^(23,151–153). Classification of obesity-induced asthma as a distinct phenotype means that this group of asthmatics have a distinct clinical and immunological profile that differs from other phenotypes. As mentioned above, this particular type of asthma seems to be more common amongst adult women, is more likely to be non-atopic and is characterised by a later onset⁽²³⁾. A childhood obesity-induced asthma phenotype has also been proposed⁽¹⁵¹⁾. It is generally characterised by primary and predominantly atopic asthma and the severity of asthma in this phenotype is increased by the presence of obesity⁽⁸⁵⁾. It has also been suggested that obesity has even more effect on lung function for children than it does for adults⁽¹⁵³⁾. As in the case of adults, amongst children too, obesity is more closely related to non-atopic asthma⁽¹⁵⁴⁾. Similarly, it has also been observed that obese children have a lower response to treatment with inhaled steroids and are at a higher risk of emergency hospitalisations than asthmatics with normal weight⁽¹⁵⁵⁾. Obese children also tend to have lower disease control, higher severity of symptoms and more exacerbations⁽¹⁵⁶⁾. Moreover, obese asthmatic children were shown to have a Th1 polarisation rather than the typical atopic Th2 immunological profile⁽¹⁵⁷⁾. Interestingly, it has been shown that obese children might respond differently to environmental triggers, and traffic exposure to polycyclic aromatic hydrocarbons is more likely to cause asthma in obese children than those with normal weight⁽¹⁵⁸⁾.

Nevertheless, even within the obesity-induced asthma phenotype, heterogeneity can be observed in the clinical characteristics of patients and corresponding differences in their treatment approach⁽¹⁵²⁾. A strong focus was placed on describing the clinical profile of these individuals.

Conclusion

Despite the growing evidence for the asthma–obesity association, there is no consensus on causality and mechanism. Regardless of what the links of mechanism and causality are between the two conditions, the fact is that obesity is related to higher hospitalisation rates for asthma as well as higher doses of medications required for control of the disease; it seems to be a dose-dependent association⁽¹⁵⁶⁾. Increasing numbers of obese individuals will result in an increased prevalence of obesity-induced asthma in adult and paediatric populations. For obese patients with asthma and their families this equals higher medication costs and a more difficult and less effective treatment, which constitutes a heavy burden and results in the lowering of their quality of life. Moreover, this problem is related to increased economic costs for public health systems as well. To avoid these issues, prevention and lifestyle secondary and primary weight-loss interventions are of great importance. As the phenotype of asthma, associated with obesity, seems to be a specific condition, it is necessary to study it independently. This distinct phenotype may be characterised by different environmental, socio-economic and family risk factors than for non-obese asthmatics and non-asthmatic obese children. An in-depth knowledge of the risk factors for the development of obesity-induced asthma is essential in order to design effective, evidence-based prevention and intervention programmes.

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