Obesity and Asthma: Key Clinical Questions

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Abstract

Obesity is a common comorbidity of asthma that is associated not only with development of the disease, but also with poorer disease control and greater severity. Recent prospective evidence supports the idea that body weight gain precedes the development of asthma, although the debate is far from over. The objective of this document is to conduct a systematic review of 3 clinical questions related to asthma and obesity: (*a*) Obesity and asthma: the chicken or the egg? Clinical insights from epidemiological and phenotyping studies. (*b*) Is obesity a confounding factor in the diagnosis and management of asthma, especially in severe or difficult-to-control asthma? (*c*) How do obese asthma patients respond to pharmacological treatments and to biological drugs? Do we have effective specific interventions? Revised epidemiological, pathological, and mechanistic evidence combined with data from interventional clinical trials prevent us from clearly stating that obesity causes asthma. However, the complexity and heterogeneity of both illnesses make several clinical scenarios possible. Furthermore, asthma represents an additional clinical challenge in the obese patient. Physicians need to be aware of the confounding effects created by the more marked perception of symptoms, alterations in lung function, and the various comorbidities that obese persons present. Exhaustive phenotyping of the obese asthma patient should enable us to develop a rational therapeutic plan, including both the pharmacological approach and specific antiobesity therapies such as combining diet and exercise and, in extreme cases, bariatric surgery.

Key words: Asthma. Obesity. Diet. Exercise. Phenotypes. Comorbidity. Asthma treatment.

Resumen

La obesidad es una comorbilidad común al asma y se ha asociado no solo con el desarrollo del asma, sino también con un peor control de la misma y con el asma grave. La evidencia prospectiva reciente respalda la idea de que el aumento del peso corporal precede al desarrollo del asma, pero el debate no está ni mucho menos cerrado. El objetivo de este documento es efectuar una revisión sistemática sobre los aspectos clínicos claves del asma y la obesidad: (*a*) La obesidad y asma: ¿el huevo o la gallina? Aspectos clínicos aprendidos de los estudios epidemiológicos y de fenotipos en el asmático obeso. (*b*) ¿Es la obesidad un factor de confusión en el diagnóstico y manejo del asma y especialmente en el asma grave o de difícil control? (*c*) ¿Cuál es la respuesta del asmático obeso al tratamiento farmacológico, y a los fármacos biológicos? ¿Disponemos de intervenciones específicas eficaces?

Nuestra revisión de la evidencia epidemiológica, fisiopatológica y mecanística combinada con los datos obtenidos de los ensayos de intervención no permite afirmar claramente que la obesidad sea un agente causal del asma, por lo que debe ser considerada en muchos casos una comorbilidad. No obstante, la complejidad y heterogeneidad de estas dos patologías hacen muy posible diversos escenarios clínicos. Por otra parte, el diagnóstico de asma en un paciente obeso supone un reto clínico adicional, en el que se debe tener presente el efecto de confusión originado por la mayor percepción sintomática, las alteraciones de la función pulmonar y las distintas comorbilidades que presenta el sujeto obeso. Un minucioso fenotipado del paciente asmático obeso, es el que nos debe conducir a un plan terapéutico racional, que contemple el ajuste farmacológico y la puesta en marcha de medidas específicas contra la obesidad con un plan combinado de dieta y ejercicio y en los casos indicados, la cirugía bariátrica.

Palabras clave: Asma. Obesidad. Dieta. Ejercicio. Fenotipos. Comorbilidad. Tratamiento del asma.

Introduction

The World Health Organization defines obesity as an excess or abnormal accumulation of body fat that affects health. Persons with a body mass index (BMI) ≥30 kg/m^2 are considered obese, and those with a BMI of 25-29.9 kg/m^2 are considered overweight. According to these criteria, the prevalence of overweight and obesity has increased significantly in recent decades, especially in Western countries, where almost half of the population is overweight. In Spain, the prevalence of overweight is now stable at 47%. The prevalence of obesity in Spanish adults is 17%; the condition is more prevalent between the fourth and seventh decades of life and generally in men [1]. However, the highest prevalence by age and sex is 26%, which is observed in women aged between 65 and 74 years [1].

In the case of children, the Aladino study [2], which was carried out by the Spanish Agency for Consumer Affairs, Food Safety, and Nutrition, revealed a prevalence of overweight and obesity of 23.2% (22.4% in boys and 23.9% in girls) and 18.1% (20.4% in boys and 15.8% in girls), respectively. This study used the growth standards recommended by the World Health Organization. When Spanish standards (as recommended by the Orbegozo Foundation) were applied, prevalence dropped to 20% for overweight and 6% for obesity. Therefore, figures vary widely according to the growth standards used.

Poverty and low educational level promote diets and lifestyles that increase the frequency of obesity [3]. In Spain, the risk of obesity is 1.6 times greater for men and 2.4 times greater for women with a low educational level than for people with a higher educational level. In parallel, obesity as a common asthma-related comorbidity is associated with development of asthma, poorer control of asthma symptoms, and increased risk of hospitalization. Recent prospective evidence supports the idea that body weight gain precedes the development of asthma, although the debate is far from over. Most of these studies have serious limitations, and it is unclear whether obesity directly increases the risk of asthma or, conversely, whether patients first experience asthma and then become overweight or obese, possibly owing to respiratory restrictions and reduced physical activity [4].

In order to carry out a systematic review of the key clinical aspects of asthma and obesity, we conducted a literature search covering the last 12 years in PubMed and the complete databases of the Web of Science, focusing on epidemiology, phenotypes, diagnosis, monitoring, and therapeutic interventions. To be included in the review, studies had to have a precise methodology and clearly present the importance and limitations of their results for patient management. In the case of therapeutic interventions, only randomized designs were considered. We also included systematic reviews and meta-analyses of studies conducted based on a robust methodology [5,6]. The key words used were asthma, obesity, diagnosis, control, intervention, bronchial hyperresponsiveness, symptoms, perception of dyspnea, severe asthma, and bariatric surgery. The search was limited to papers written in English or Spanish.

The total number of records in the Web of Knowledge for operators combining asthma and obesity with the abovementioned limitations was 8968. After combining operators and implementing the criteria set out above, a total of 89 records were included. Of these, 73 were experimental studies, 11 systematic reviews (4 with a meta-analysis), and 5 methodological records. We organized our discussion around the following 3 key clinical topics:

1. Obesity and asthma: the chicken or the egg? Clinical insights from epidemiological and phenotyping studies.
2. Is obesity a confounding factor in the diagnosis and management of asthma and especially in severe or difficult-to-control asthma?
3. How do obese asthma patients respond to pharmacological treatments and to biological drugs? Are specific effective interventions possible?

Obesity and Asthma: The Chicken or The Egg? Clinical Insights From Epidemiological and Phenotyping Studies

The interrelationship between asthma and obesity is complex and controversial. The first prospective study on obesity and the incidence of asthma was conducted in 1999 by Camargo and Weiss [7], who recorded 1600 cases of incident asthma in a population of 86 000 nurses. The risk of asthma increased in parallel to BMI by between 1.5- and 3.8-fold and was especially associated with weight gain after age 18 years. Subsequently, other prospective epidemiological studies and 1 meta-analysis associated overweight and obesity with an increased risk of developing asthma (incident asthma). The authors reported a dose-response relationship and an annual odds ratio (OR) of incident asthma of 1.38 (95%CI, 1.17-1.62) and 1.92 (95%CI, 1.43-2.95), respectively, for overweight and obese people when compared with persons with a normal BMI [8]. This risk increased slightly in females and in nonallergic asthmatics when compared with males and allergic asthmatics, respectively. Prospective epidemiological studies in childhood and adolescence showed a higher risk of incident asthma in obese and overweight persons. In contrast with the above data for adults, the risk of incident asthma seemed to be higher among boys [9], and, as is usual in childhood, most asthma patients were allergic.

The results provided by these epidemiological studies are subject to criticism. First, and although BMI is an appropriate and widely accepted measure of adiposity, given the very nature of obesity, BMI may not be the best measurement of the effect of obesity on the lung. As an example, it is known that the mechanical effect of obesity on lung function is strongly associated with the central distribution of body fat. This fact is well known in cardiovascular diseases and was recently discussed in other types of disorders such as Barrett esophagus [10] and insulin resistance [11]. Barret esophagus was also associated with a subphenotype of asthma and obesity.

In addition, obesity can induce respiratory symptoms in patients with no concomitant obstructive disease [12]. Similarly, the specificity of a diagnosis of asthma could drop dramatically when based upon epidemiological data, since the high frequency of nonspecific respiratory symptoms that

obese patients present could be misdiagnosed as asthma. In general terms, asthma is misdiagnosed (underdiagnosis or overdiagnosis) in about 30% patients, since many other diseases may mimic asthma symptoms [13,14].

Conversely, asthma can be regarded as a cause of or risk factor for obesity. In a recently published epidemiological study, Chen et al [15] followed a cohort of more than 2000 children aged 5-8 years for 10 years until adolescence. They concluded that children with asthma are at higher risk for developing obesity during childhood and adolescence. Moreover, the use of rescue medication seems to prevent the risk of obesity independently of a diagnosis of asthma. In addition to the excessive calorie intake and the reduced physical activity that are the most frequent causes of obesity, the authors also suggested that asthma plays a role in the development of obesity during childhood. In addition, atopy is thought to facilitate the relationship between obesity (waist/hip perimeters) and the diagnosis of asthma [16].

In Spain, Barranco et al [17] studied the prevalence of obesity in adult patients with incident asthma diagnosed based on objective criteria, including the methacholine challenge test. The authors studied more than 1400 patients and observed that obese and overweight patients were diagnosed with asthma at a rate similar to that of persons with a normal BMI. Moreover, asthma and obesity were more frequently diagnosed among males. A Spanish multicenter study of patients with baseline FEV_1 values above 70% failed to find any association between obesity and asthma [18].

Other important epidemiological studies, such as the European Community Respiratory Health Survey did not find a clear causal association between obesity and asthma [19]. Finally, according to the results of a recent European prospective study on the factors associated with the remission or persistence of adult-onset asthma, obesity does not seem to play a crucial role in the persistence of asthma in adults [20]. On the contrary, the accelerated loss of lung function, which is an important element in the persistence and severity of asthma, is associated with a low BMI [21].

Preliminary studies on asthma phenotypes by cluster analysis described a phenotype of noneosinophilic asthma that begins in adulthood and predominates in females [22-23]. Many patients included in these studies came from primary care units, where asthma is more frequently overdiagnosed [24,25]. Overall, phenotypes improve our understanding of the heterogeneity of asthma and the response to therapy [26]. The role of phenotypic heterogeneity in asthma can be seen in the study by Heldin et al [27], who reported that the relationship between asthma and obesity is conditioned by the age at which asthma appears and distinguished 2 different clinical patterns. In patients with early-onset asthma, obesity developed progressively in children with severe asthma. On the other hand, in adults with late-onset asthma, obesity could be a risk factor for or a cause of severe asthma. Although these data suggest a causal relationship between asthma and obesity, this has not been demonstrated in ad hoc studies. Instead, some studies corroborate the relationship between variation in weight and severity of asthma [7,28].

However, as mentioned above, BMI is not an important factor in difficult-to-control asthma in children or in adults [29].

New omics-based approaches seem to be more appropriate for assessing the heterogeneity of asthma; however, they do not consider BMI to be a relevant factor [30]. When dealing with complex and heterogeneous diseases such as asthma and obesity, our traditional reductionist approach should give way to other strategies that, based upon systems biology, provide us with wider perspectives [31,32]. In fact, Gómez-Llorente et al [33] review the pathophysiological mechanisms shared by obesity and asthma and suggest that the relationship between both conditions would also imply other systemic inflammatory syndromes, insulin resistance, and alterations in microbiota. The authors propose that both asthma and obesity participate in a more complex syndrome and represent part of the total phenotype of this syndrome. In any case, association/correlation is not synonymous with causality, and the relationship between asthma and common comorbidities such as obesity is very complex and has many facets to decode [34].

Should Obesity Be Taken Into Account in the Diagnosis and Follow-up of Asthma, Especially Severe Asthma?

Several important considerations must be taken into account when diagnosing asthma in an obese patient. First, obese patients commonly have symptoms that simulate asthma [35]. The low-intensity systemic inflammation associated with obesity (neuroinflammation) is likely responsible for the greater proprioceptive sensitivity of obese patients. This results in a correspondingly more intense perception of dyspnea and greater respiratory discomfort [36-38]. Consequently, obese persons in general and obese asthmatics in particular tolerate exercise worse and consume more rescue medication, as reflected in poorer health-related quality of life and poorer (perceived or real) asthma control]36-38]. In contrast, obese or overweight asthmatics experience cough less frequently than normal-weight patients with asthma [36].

Second, it is crucial to determine whether the symptoms that obese subjects present are due to asthma, to obesity-induced lung function alterations, or to obesity-related comorbidities. In adults, obesity mainly affects lung volumes, airway closure, and gas exchange. The functional disorder most reliably reported in obese patients is the decrease in lung volumes secondary to reduced compliance of the respiratory system. Reduced compliance can be attributed to compression of the rib cage by soft tissue, fatty infiltration of the chest wall, or increased lung blood volume [39]. The lung volumes that undergo the greatest reduction are the expiratory reserve volume and the functional residual capacity (FRC), while the effects on total lung capacity (TLC) and forced vital capacity (FVC) are less evident, except in severe obesity. On the other hand, the residual volume (RV) is usually maintained in overweight and obese persons [40]. As an immediate consequence of these changes in lung volumes, spirometry can fail to detect airway obstruction from the FEV_1/FVC ratio, since the decrease in FVC may "normalize" the quotient, resulting in a falsely restrictive or even pseudonormal ventilatory alteration.

Early closure of the airways is also common in obese persons. The diameter of the airways is reduced by breathing

at low lung volumes and fatty infiltration of the airway wall, which modifies the cycling speed of the crossed actin-myosin bridges of the bronchial smooth muscle [40]. Airway resistance increases as a consequence of the reduction in endobronchial lumen, and this favors early closure of the airways and causes bronchoconstriction [40]. In fact, negative expiratory pressure techniques have proved that up to 20% of obese patients have evident limitation to expiratory flow while sitting and that these figures increase to 60% in the supine position [41]. Early closure of the airways implies a limitation for complete alveolar emptying during expiration and leads to air trapping. Consequently, obese patients usually maintain normal RV values despite altered values for the remaining lung volumes.

During childhood, airway closure can be enhanced by airway desynapsis, which reflects the imbalance between the physiological growth of lung parenchyma and airway caliber. Gaps in this relationship tend to be larger in girls and are directly proportional to BMI [42]. They manifest as a reduction in the FEV_1/FVC ratio, despite normal FEV_1 and FVC values. Therefore, obesity has different implications with respect to spirometry values depending on whether these are from adults or children. In obese adults, it is common to find reduced FVC values with a normal FEV_1/FVC ratio, suggesting restrictive alteration of ventilation. On the other hand, in obese children, spirometry usually reveals decreases in the FEV_1/FVC ratio (obstruction of ventilation) with either normal or high FEV_1 and FVC values. Furthermore, in obese asthmatic children, desynapsis is associated with higher frequency and intensity of respiratory symptoms, greater need for control and rescue medication, and more exacerbations in the previous year [42].

We should also bear in mind that obesity can affect gas exchange. Although severe obesity does not usually alter partial pressure of oxygen, it may slightly increase the alveolar-arterial oxygen gradient. This is secondary to the closure of small airways that reduces ventilation in the lung bases; therefore, it alters the distribution of ventilation, giving rise to a ventilation/perfusion imbalance [43]. Such a disorder may be partially responsible for the dyspnea and exercise limitation experienced by morbidly obese people.

Finally, obesity is frequently associated with a variety of comorbid diseases such as gastroesophageal reflux, obstructive sleep apnea, diabetes mellitus, and metabolic syndrome, as well as with cardiovascular diseases such as hypertension and ischemic heart disease [40]. This association can lead to the erroneous attribution to asthma of symptoms caused by comorbidities, thus leading to an unnecessary and useless increase in asthma medication [38]. Therefore, the hyperinsulinemia observed in insulin-resistant asthmatic patients augments the symptomatic response to bronchoconstrictor agents, even though these do not improve airway limitation [44].

Notwithstanding these limiting factors, it has not been demonstrated that obese patients are more frequently misdiagnosed with asthma [13]. Moreover, inconclusive data point to a degree of underdiagnosis among morbidly obese patients who are candidates for bariatric surgery [45]. However, the above considerations point to overdiagnosis of asthma resulting from current clinical practice [24]. In fact, inaccurate diagnosis of asthma is especially frequent among obese asthma patients who frequently visit the emergency department with respiratory symptoms [46].

In these circumstances, we must be particularly careful when diagnosing asthma in obese persons and attentive to other causes of obesity-related dyspnea, such as cardiovascular disease, hypertension with left ventricle diastolic dysfunction, pulmonary hypertension associated with obstructive sleep apnea, and hypoventilation-obesity syndrome. In addition, we must confirm that the patient's symptoms are related to the objective presence of reversible airflow limitation, together with changes in lung volumes and bronchial hyperresponsiveness [43,47]. Obesity itself does not alter the bronchial response to methacholine in terms of FEV_1 values [24,35], thus making the methacholine challenge test especially useful in the diagnosis of asthma. However, during bronchoconstriction, obese patients without asthma develop more dyspnea [37,48,49] and air trapping than nonobese patients [50], probably as a result of greater limitation of expiratory flow and premature closure of the airways. For this reason, when performing bronchial challenge in obese persons, it would be helpful to record, in addition to the variation in FEV_1, the changes in FVC that will indirectly enable us to monitor air trapping and hence the perception of dyspnea [50]. However, the possibility of false-positive results in bronchial hyperresponsiveness tests among obese patients should also be considered, mainly when mannitol is used as a bronchoconstrictor agent. In fact, up to 28% of nonasthmatic morbidly obese candidates for bariatric surgery have positive responses in bronchial challenge with mannitol, and this response disappears after bariatric surgery [51].

When an obese patient has been diagnosed with asthma, our next challenge is to try to phenotype the asthma. In general, asthma associated with obesity may consist of a form of late-onset asthma induced by obesity or a form of early-onset asthma in which pre-existing symptoms are aggravated by weight gain [52].

The most specific clinical characteristics of obesity-induced asthma are late onset, female predominance, higher prevalence of severe asthma, and greater use of medication. These patients are also more likely to be refractory to corticosteroids, expectorate more frequently, and have lower serum IgE levels and less evidence of atopy [39]. Higher degrees of oxidative stress and neutrophilic infiltration, apparently mediated by IL-17, are detected in this phenotype [36-38]. Bronchial inflammation is uncommon in these patients, and their airways are more sensitive and prone to collapse owing to the loss of lung elasticity (retraction) [53,54].

Obesity-complicated asthma is usually early-onset asthma, with eosinophilic infiltration and high levels of IgE [52]. In general, obstruction is more severe and bronchial hyperresponsiveness more pronounced in these patients than in nonobese early-onset asthma patients [36-38]. They also have worse asthma control, which increases the risks for hospitalization 3-fold and admission to intensive care units 6-fold [27].

Regardless of the evident differences in clinical presentation, exhaled nitric oxide could help to discriminate

between these groups of obese asthmatic patients. Although the exhaled fraction of nitric oxide (FeNO) is usually lower in obese asthmatics (children and adults) than in asthmatics with normal weight [36], the identification of elevated FeNO in obese patients with asthma suggests obesity-complicated asthma. Thus, in the prospective Netherlands Epidemiology of Obesity cohort study, high FeNO levels were observed in 25% of obese asthmatics. When compared with the remaining obese asthmatics, those with high FeNO levels had greater bronchoconstriction and more symptoms related to pollen, dust, or animal exposure, suggesting the predominance of a T_H2 pattern [35].

To conclude, in obese patients with asthma, we always have to consider the effect of their metabolic disorder on asthma control. Several studies show that obese patients often have difficult-to-control asthma. Data from the TENOR cohort of patients with difficult-to-control asthma revealed obesity in 31% and 69% of children and adults, respectively. The prevalence of obesity in the general American population is 20% for children and 35% for adults [29]. In Europe, the prevalence of obesity in difficult-to-control asthma ranges from 21% in The Netherlands [55] to 26% in Italy [56] and 48% in Britain, almost the double that observed in the British general population (25%) [57]. In addition, when patients with asthma and obesity manage to reduce their weight, there is a decrease in both symptoms and airway hyperresponsiveness, along with an improvement in asthma control [58,59].

Various biological and nonbiological mechanisms have been proposed to explain the relationship between obesity and poor asthma control. These include decreased response to corticosteroids, the effect of some immunomodulatory adipokines, the change in pulmonary dynamics, low levels of vitamin D, and obesity-related comorbidities such as gastroesophageal reflux and depression [46,60,61]. Gastroesophageal reflux is also a common comorbidity in obese children and is responsible for worse asthma control [36]. Strikingly, obesity is less frequent in aspirin-exacerbated asthma with polyposis, which is a phenotype usually associated with severe asthma [62]. However, it is also necessary to emphasize that some studies fail to show an association between obesity and poor asthma control in children [63] or in adults [64,65]. However, interestingly, these studies also report a particularly low prevalence of obesity-associated comorbidities.

With regard to control and follow-up of obese asthmatics, and in keeping with the data presented above, the standard questionnaires such as the Asthma Control Test and Asthma Control Questionnaire can certainly be misleading. Obese asthma patients have a more marked perception of dyspnea and are more prone to use rescue medication than normal-weight asthmatics. In these patients, and mainly during inhaled corticosteroid–free periods, the dose of inhaled corticosteroids depends to a large extent on FeNO levels and sputum eosinophilia. These also help to ascertain those aspects of patients' symptoms that are related to asthma, regardless of obesity [35]. In addition to asthma, management must also take into account control of comorbidities, each of which carries its individual clinical weight, thus making care in multidisciplinary asthma units essential [38].

How Obese Asthma Patients Respond to Pharmacological Therapy and to Biological Drugs? Do We Have Effective Specific Interventions?

Several studies, mainly post hoc studies, suggest that obese asthmatics respond worse to inhaled antiasthma control drugs, including both corticosteroids and the combination of long-acting ß$_2$-agonists (LABA) and corticosteroids. This finding has been attributed to the fact that these patients—both adults [38,40,48,55,65-67] and children [68]—frequently have no eosinophilic airway inflammation. However, and as occurs in normal-weight asthmatics, obese asthmatics display a better response to LABA-corticosteroid therapy than to montelukast [69]. Moreover, a National Heart, Lung, and Blood Institute–funded, combined post hoc analysis of 3 double-blind, placebo-controlled clinical trials in preschool asthmatics did not show a lower response to pharmacological therapy in obese patients in terms of symptom control or number of exacerbations, compared with nonobese patients [70].

New biological drugs, including anti-IgE agents such as omalizumab [71] and antieosinophilic agents such as mepolizumab [72], reslizumab [73], and benralizumab [74], have proven to be efficient in eosinophilic asthma. Since obese patients with late-onset asthma usually have no relevant eosinophilia and display neutrophilic inflammatory phenotypes [65], it seems reasonable to assume that these drugs lack any clinical benefit. Moreover, use of omalizumab and reslizumab is limited with respect to obese patients, since their doses are adjusted for weight [38]. In this sense, a very recent retrospective real-life study suggests that obesity is a risk factor for the lack of response to omalizumab [75].

Response to treatment in obese asthmatics is altered as a consequence of obesity-associated comorbidities. Some, such as obstructive sleep apnea and gastroesophageal reflux, can simulate asthma symptoms and, if misinterpreted, lead to an unnecessary increase in antiasthmatic medication that does not result in clinical improvement. The treatment of asthma can also worsen the course of other comorbidities, as occurs with oral corticosteroids in patients with diabetes mellitus. Conversely, the treatment of comorbidities can also worsen asthma, as is the case with ß-blockers in the treatment of hypertension and ischemic heart disease [38-39].

Consequently, it is essential to overcome the traditional single-organ approach to asthma in general and to obesity-associated asthma in particular and to manage associated health problems holistically and comprehensively. Multidimensional evaluation and treatable traits [32] comprise an emerging approach in obese patients that is designed to identify and, when possible, treat the health problems that co-occur with asthma. Treatable traits are grouped into 3 domains: the airway domain, the extrapulmonary domain, and the risk factor domain. This promising management approach identifies treatable components of the obesity-asthma phenotype and provides treatments for each of them. It could also ensure clinical improvement in obese asthmatics, again emphasizing the need for obese patients to be treated on a multidisciplinary basis.

The effectiveness of dietary programs for weight reduction and better disease control is generally low according to data from a Cochrane review [76] and a subsequent systematic review of the Working Group on Asthma and Obesity of the European Academy of Allergy and Clinical Immunology [77]. A recent systematic review of studies that quantify the physical activity and the sedentary lifestyle of asthma patients by objective means (accelerometry) [78] revealed no differences with respect to a sedentary lifestyle, although it did show that females and older persons were less likely to engage in physical exercise and that a higher level of exercise is associated with better lung function and asthma control [78].

In 2013, Scott et al [79] reported the result of a randomized study evaluating the efficacy of combining a hypocaloric diet and exercise in improving patients' quality of life, asthma control, and inflammatory response. For the first time, the authors verified that in both overweight and obese asthma patients, a weight loss of 5%-10% was associated with clinically significant improvements in asthma-related quality of life (83%) and in asthma control (58%). Physical training also reduced the eosinophil count by 50%. Moreover, a recent randomized, blinded, controlled trial showed for the first time that when the effects of physical training coupled with a hypocaloric diet are compared with those of a hypocaloric diet alone, the combined method induces a significantly greater improvement in body composition and physical fitness. This approach has an additional beneficial effect on the modulation of inflammatory/anti-inflammatory balance and on lung function. It also helps to improve asthma control and health-related quality of life in obese adults with asthma [80]. It is noteworthy that patients received regular psychological support to maintain their diet and exercise program. The weight loss recorded in the first 3 months was 7% in the combined approach group and barely 2.5% in the hypocaloric diet group. With regard to the effect of this combined approach on patients receiving antiobesity drugs such as sibutramine (serotonin reuptake inhibitor) and orlistat (intestinal fat absorption inhibitor), only 1 small, randomized, open-label clinical trial including 34 obese asthma patients has been reported [81]. Authors find positive results when implementing the hypocaloric diet and exercise program, although not as striking as those obtained in the abovementioned studies [79,80].

In the pediatric population, 3 randomized clinical trials have shown that by implementing combined dietary and exercise programs, it is possible to obtain significant BMI reductions in both obese and overweight asthmatic children. In addition, these changes are related to improvements in patients' quality of life and in indicators of disease control [82-84]. Two of the studies [82,84] also revealed significant changes in lung function, especially in FVC. However, the characteristics of the intervention meant that these trials were controlled and randomized but not blind. Control children from the trial performed by Willeboorse et al [84], which was the longest to date (total follow-up of 18 months), started their own exercise and dietary programs, which also led to significant weight losses and reduced the comparative effect of the intervention in the active group. The diets used in these trials focused on reducing calorie intake. However, it seems increasingly clear that certain patterns of food ingestion, mainly the exaggerated consumption of simple sugars and other carbohydrates, are associated with an increased frequency of chronic diseases such as diabetes, hypertension, and asthma [85]. The ingestion

Table. Indications and Contraindications for Bariatric Surgery [88]

A. Indications in age groups from 18 to 60 years
1. Body mass index ≥40 kg/m^2
2. Body mass index 35-40 kg/m^2 with comorbidities that are expected to improve after surgically induced weight loss (eg, metabolic disorders, cardiorespiratory disease, severe joint disease, obesity-related severe psychological problems).
3. To be considered for surgery, patients should not lose weight or maintain long-term weight loss, despite adequate comprehensive nonsurgical medical care.
B. Indications in adolescents
1. Body mass index >40 kg/m^2 (or 99.5th percentile for respective age) and at least 1 comorbidity.
2. Failure of at least 6 months of organized weight-loss treatment in a specialized center.
3. Skeletal and developmental maturity.
4. Able to commit to a comprehensive medical and psychological evaluation before and after surgery.
5. Will participate in a postsurgery multidisciplinary treatment program in a unit with specialized pediatrics support (physicians, nursing, anesthesia, psychology, postoperative care).
C. Contraindications
1. Absence of a recorded period of specialized medical management.
2. Inability to participate in prolonged medical follow-up.
3. Nonstabilized psychotic disorders, severe depression, personality and food-related disorders, unless specifically advised by a psychiatrist experienced in obesity.
4. Alcohol abuse and/or drug dependencies.
5. Diseases threatening life in the short term.
6. Patients who are unable to care for themselves and have no long-term family or social support that guarantees their care.

of such foods should be reduced and controlled, although not drastically eliminated from the diet.

Van Huisstede et al [86] showed that bariatric surgery was effective in controlling asthma and improving quality of life in asthmatics with morbid obesity [86]. Although the authors found no significant changes in the main variable representing bronchial obstruction, ie, the FEV_1/FVC ratio, they did report an improvement in lung volumes related to restrictive ventilatory alteration (FRC and TLC). The beneficial effect on quality of life was maintained 5 years after surgery [87]. Indications and contraindications of bariatric surgery are very specific in adults (Table, A and C) [88], and even more in children and adolescents in whom it should only be performed in centers with extensive expertise in this kind of surgery in adults. These centers must also offer a real multidisciplinary approach led by pediatric surgeons, nutritionists, and psychologists (Table, B) [88]. The institutional requirements and the skills necessary for bariatric surgery are also neatly defined. Consequently, the surgeons involved should perform at least 50 bariatric surgeries per year [89].

Concluding Remarks and Recommendations

Obesity is increasingly considered a global epidemic that has deleterious effects on patients' health and quality of life. Current epidemiological, pathophysiological, and mechanistic data and data obtained from interventional clinical trials prevent us from clearly stating that obesity is a causal agent of asthma. Therefore, obesity should be considered a comorbidity of asthma. However, the complexity and heterogeneity of both conditions make different clinical scenarios possible. Two clear asthma phenotypes have been described among obese individuals, namely, early-onset asthma and late-onset asthma. From this perspective, obesity is likely to appear progressively as a comorbidity in early-onset asthma. Thus, asthma could be considered a risk factor that leads to development of obesity. On the other hand, obesity could be a type of underlying condition for the development of noneosinophilic asthma in a number of obese patients with late-onset asthma.

The diagnosis of asthma in an obese patient represents an additional clinical challenge. Obese patients are more aware of their symptoms, have altered lung function, and have obesity-associated comorbidities. All of these factors confound the diagnosis of asthma, with the result that it is essential to turn to tests that enable the objective diagnosis of asthma, mainly measurement of static lung volumes and methacholine bronchial challenge. Once the diagnosis of asthma is made, it is important to determine whether the patient had previous asthma that worsened as a result of weight gain or whether the onset of asthma followed obesity. In addition to this and other clinical features, in individuals with late-onset obesity, eosinophilic inflammation is usually infrequent or absent, thus making measurement of FeNO particularly valuable for identifying patients at risk. Finally, control of asthma is commonly poorer in obese asthmatics than in nonobese asthmatics. Therefore, asthma control questionnaires should be interpreted carefully and completed with objective measures.

Careful phenotyping of the obese asthma patient will help us to establish a rational therapeutic plan based on the physiological mechanisms underlying clinical expression. First, we must consider pharmacological treatment, paying special attention to severe or difficult-to-treat obese asthma patients who receive either high doses of inhaled corticosteroids or biological treatments. These therapeutic modalities are only justified in the presence of active eosinophilic immunoinflammatory process, which are responsible for severe exacerbations that cannot be solved by traditional therapeutic plans. Second, there is considerable evidence in favor of diet combined with physical exercise as an effective intervention in the approach to these patients. Undoubtedly, a certain degree of effort will be required on the part of the patient, who will need continuous support with respect to implementation and maintenance. The approach must be multidisciplinary and involve doctors, dieticians, educators, and physical trainers. Finally, bariatric surgery could prove necessary in extreme cases of morbid obesity.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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