Obesity and asthma. Key clinical questions

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SUMMARY

Obesity is an asthma common comorbidity and is associated not only with its development, but also with a poorer control and higher severity of it. Recent prospective evidence supports the idea that body weight gain precedes the development of asthma, but 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:

1. Obesity and asthma: the chicken or the egg? Clinical insights from epidemiological and phenotypes 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 obese asthma subjects respond to pharmacological treatments, and to biological drugs? Do we have effective specific interventions?.

Revised epidemiological, pathological and mechanistic evidence combined with data from the intervention clinical trials do not allow us to clearly state that obesity is an asthma-causative agent. However, the complexity and heterogeneity of these two illnesses make several clinical scenarios possible. Furthermore, the diagnosis of asthma in an obese patient represents an additional clinical challenge. Physicians need to be aware of the confounding effects created by the greater symptomatic perception, the alterations of lung function and the different comorbidities that the obese subjects present. A exhaustive phenotyping of the obese asthma patient should lead us to a rational therapeutic plan, including both, the pharmacological approach and anti-obesity specific therapies including a combined plan of diet and exercise and in extreme cases, bariatric surgery.

KEY WORDS: Asthma, Obesity, Diet, Exercise, Phenotypes, Comorbidity, Asthma treatment

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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:

1. La obesidad y asma: ¿el huevo o la gallina? Aspectos clínicos aprendidos de los estudios epidemiológicos y de fenotipos en el asmático obeso.
2. ¿Es la obesidad un factor de confusión en el diagnóstico y manejo del asma y especialmente en el asma grave o de difícil control?
3. ¿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 CLAVES: Asma, Obesidad, Dieta, Ejercicio, Fenotipos, Comorbilidad, Tratamiento del asma

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INTRODUCTION

WHO defines obesity as the excess or abnormal accumulation of body fat that affects health. Subjects with a body mass index (BMI) ≥ 30 Kg / m2 are considered obese and those with a BMI 25-29.9 Kg / m2, overweight. According to these criteria, it is accepted that 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 people is 47% and is currently stabilized. The prevalence of obesity in Spanish adults is 17%, and it is more prevalent between the fourth and seventh decades of life and generally in men (1). However, the highest prevalence rate by age and sex is 26% and it is observed in women aged between 65 and 74 (1).

In the case of children, the Aladino study (2), carried out by the Spanish Agency for Consumer Affairs, Food Safety and Nutrition, displayed overweight and obesity prevalence 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 that WHO recommends. When the Spanish standards, recommended by the Orbegozo Foundation, were used, prevalence dropped to 20% for overweight and 6% for obesity. This fact demonstrates a wide variability of figures according to the growth standards used.

Poverty and low educational level promote types of diet and lifestyle that increase obesity (3). In Spain, people with low educational level have 1.6 times for men and 2.4 times for women, more risk of obesity than their counterparts. In parallel, obesity as common asthma-related comorbidity, is associated with asthma development, 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, but 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, if patients first experience asthma and then possibly due to respiratory restrictions and reduced physical activity, become overweight or obese (4).

In order to carry out a systematic review on the key clinical aspects of asthma and obesity, we conducted a literature search of the last 12 years in PubMed databases

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and the complete bases of the Web of Science, focusing on epidemiology and phenotypes , diagnostic, monitoring and therapeutic interventions of asthma in the obese patient. The studies should have a precise methodology and clearly present the importance and limitations of their results in the management of the patients. In the case of therapeutic interventions, only randomized designs were considered. We also included systematic reviews and meta-analysis of studies conducted according to a robust methodology (5,6). The key words asthma, obesity, diagnosis, control, intervention, bronchial hyperresponsiveness, symptoms, perception of dyspnea, severe asthma and, bariatric surgery were used. The search was limited to papers written in English or Spanish.

The total number of records in the WOK for operators combining asthma and obesity with the mentioned limitations was 8968. Through the combination of operators and implementing the criteria described above, a total of 89 records were included, of which 73 are experimental studies, 11 systematic reviews 4 out of them with meta-analysis and, 5 methodological records. We grouped their discussion in the following 3 key clinical topics:

1. Obesity and asthma: the chicken or the egg? Clinical insights from epidemiological and phenotype based 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 obese asthma subjects respond to pharmacological treatments, and to biological drugs? Are effective specific interventions possible?.

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1. OBESITY AND ASTHMA: THE CHICKEN OR THE EGG?. CLINICAL INSIGHTS FROM EPIDEMIOLOGICAL AND PHENOTYPE SUDIES OF ASTHMA IN OBESE PEOPLE

The interrelationship between asthma and obesity is complex and subject to hard debate. The first prospective study on obesity and incidence of asthma was conducted in 1999 by Camargo and Weiss (7). In a population of 86,000 nurses, they recorded 1,600 cases of incident asthma. The risk of asthma increased in parallel to body mass index (BMI) between 1.5 and 3.8, and was especially associated with weight gain after 18 years-age. Subsequently, other prospective epidemiological studies and one meta-analysis have associated overweight and obesity with an increased risk of developing asthma (incident asthma). They report a dose-response relationship between them and the annual odds ratio (OR) of incident asthma of 1,38 (IC del 95%, 1,17 -1,62) and 1,92 (IC 95%, 1,43-2,95) respectively, for overweight and obese people when compared to normal BMI subjects (8). This risk slightly increased in females and in non-allergic asthma when compared to males and allergic asthma, respectively. Prospective epidemiological studies in childhood and adolescence showed a higher risk of incident asthma between obese or overweight subjects. In contrast with the above data regarding adults, the risk of incident asthma seemed to be higher among boys (9) and as usual in childhood, most asthma patients were allergic.

The results provided by these epidemiological studies are subject to criticisms. Firstly and although body mass index is an appropriate and widely accepted measure of adiposity, bearing in mind the great diversity of obesity appearance, it cannot be ruled out that BMI is not 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 has been recently described in other types of disorders such as Barrett's oesophagus (10) or insulin resistance (11), this former also associated to a sub-phenotype of asthma and obesity.

In addition, obesity can also induce respiratory symptoms among patients without concomitant obstructive pathology (12). Linked to this, the specificity of asthma diagnosis could dramatically drop when based upon epidemiological terms since the high frequency of non-specific respiratory symptoms that obese subjects

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present could be misdiagnosed as asthma. In general terms, misdiagnosis of asthma, due to either underdiagnosis or overdiagnosis occurs in about 30% patients, since many other diseases may mimic asthma symptoms (13,14).

The flip side of evaluation regards asthma as cause of or risk factor for obesity. In a recently published strong epidemiological study, Chen et al followed up to a cohort of more than 2000 children aged 5-8 years for 10 years until adolescence. They conclude 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 independent of asthma diagnosis. In addition to the excessive calories intake and the reduced physical activity which are the most frequent causes of obesity, this study also suggests that asthma plays a role in the development of obesity at childhood (15). Also, it has been reported that atopy facilitates the relationship between obesity, given by the rate between waist/hip perimeters, and the diagnosis of asthma (16).

In keeping with this, in Spain, Barranco et al (17) studied the prevalence of obesity in adult patients with incident asthma diagnosed by objective criteria, including methacholine challenge test. They studied more than 1400 patients and observed that obese and overweight subjects were diagnosed of asthma at a similar rate than normal BMI subjects. Moreover, asthma and obesity diagnosis was more frequent among males. Previously, a multicentre study also conducted in Spain, in patients with baseline FEV1 values above 70%, failed to find any association between obesity and asthma diagnosis (18).

Other important epidemiological studies, such as the European Community Respiratory Health Survey, neither found any clear causal associations 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 be crucial in the persistence of asthma in adults (20). On the contrary, the accelerated loss of lung function, that 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 non-eosinophilic asthma that begins in adulthood and predominates in females (22-23). Many patients included in these studies came from Primary Care Units, where asthma over-diagnosis is much more frequent (24,25). Overall,

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phenotypes contribute to better understand the heterogeneity of asthma and its therapeutic responses (26). As a sign of such phenotypic asthma heterogeneity, Heldin et al. (27) reported that the relationship between asthma and obesity is conditioned by the age at which asthma appears, and they distinguished two 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 by any *ad hoc* study. Instead, different studies corroborate the relationship between weight variation and asthma severity (7,28). However, as mentioned above, BMI is not an important factor in difficult-to-control asthma associated clusters, either in children or adults (29).

New approaches that use omics that is in all likelihood, a more appropriate methodology to asthma heterogeneity, do not consider that BMI (30) is a relevant actor. For sure, when dealing with complex and heterogeneous diseases as both, asthma and obesity are, our traditional reductionist approach should give way to other strategies that, based upon the biology of the systems, provide us with wider perspectives (31,32). In fact, Gómez-Llorente et al. (33) review the common pathophysiological mechanisms between obesity and asthma and suggest that the relationship between both of them would also imply other systemic inflammatory syndromes, insulin resistance or alterations in the microbiota. They propose that both, asthma and obesity, participate of a more complex syndrome, and represent a partial part of the total phenotype of this syndrome. In any case, association/correlation is not synonymous with causality and the relationship between asthma and its common comorbidities such as obesity is very complex and has many sides to decode (34)

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2. IS OBESITY A FACTOR TO BE TAKEN INTO ACCOUNT IN THE DIAGNOSIS AND FOLLOW-UP OF ASTHMA, ESPECIALLY IN SEVERE ASTHMA

When proceeding asthma diagnosis in an obese patient, several important considerations need to be taken into account. First, it is common that obese subjects have symptoms that simulate asthma (35). The low intensity systemic inflammation associated with obesity (neuroinflammation) is likely responsible for the greater proprioceptive sensitivity that obese patients present. It results in a corresponding more intense perception of dyspnea and a greater respiratory discomfort (36-38). All this determines that obese subjects in general and obese asthmatics in particular experience worse tolerance to exercise and consume more rescue medication, what is reflected in either, worse health related quality of life or poorer (pretended or real) asthma control (36-38). In contrast, obese or overweight asthmatics suffer from cough less frequently than patients with asthma and normal weight (36).

Second, it is crucial to determine whether 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, airways closure and gas exchange. The functional disorder most reliably described in obese patients is the decrease in lung volumes secondary to the reduced compliance of the respiratory system. Such reduced compliance can be attributed to any, compression of the rib cage by soft tissue, fatty chest wall infiltration or increase in 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 subjects who are overweight or obese (40). As immediate consequence of these changes in lung volumes, spirometry can fail in detecting airway obstruction from FEV1/ FVC ratio, since the decrease in FVC may lead to "normalizing" the quotient, resulting in a falsely restrictive or even in a pseudo-normal ventilatory alteration.

Early closure of the airways is also common in obese subjects. The diameter of the airways is reduced by both, breathing at low lung volumes and, fatty infiltration of the airway wall, which modifies the cycling speed of the crossed actin-myosin

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bridges of the bronchial smooth muscle (40). Airways resistance increases as consequence of the endobronchial lumen reduction and, this favours the early closure of the airways and, finally, 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 up to 60% in supine position (41). The early closing of the airways implies a limitation for the complete alveolar emptying during expiration and leads to air trapping. This justifies that obese patients usually maintain normal RV values unlike the remaining lung volumes.

During childhood, airway closure can be enhanced by airway disanapsis, which reflects the imbalance between lung parenchyma physiological growth and airway calibre. Gaps in this relationship tend to be larger in girls and are directly proportional to the body mass index (BMI) (42). They are manifested by reduction in FEV1 / FVC ratio, despite normal FEV1 and FVC. Therefore, obesity has different implications on spirometry values from adults and children. In obese adults, it is common to find reduced FVC values with a normal FEV1 / FVC ratio, suggesting restrictive ventilatory alteration. On the other hand, in obese children, spirometry usually shows decreases in FEV1 / FVC rate (obstructive ventilatory alteration) with either, normal or high FEV1 and FVC values. Furthermore, in obese asthma children, dysanapsis is associated to higher frequency and intensity of respiratory symptoms, more need for control and rescue medication, and greater number of exacerbations in the previous year (42).

We should also keep in mind that obesity can affect gas exchange. Although severe obesity does not usually alter blood arterial 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 lung bases and so, it alters the distribution of ventilation, giving rise to ventilation/perfusion imbalance (43). Such disorder can be partially responsible for the dyspnea and limitation to exercise experienced by morbid 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 and, cardiovascular diseases such as hypertension or ischemic heart disease (40). This association can lead to the wrong attribution to asthma of symptoms caused by comorbidities, leading to an unneeded and useless increase

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in asthma medication (38). In that way, the hyperinsulinemia that occurs in insulin-resistant asthmatic patients augments the symptomatic response to bronchoconstrictor agents, despite not enhancing airway limitation (44).

Notwithstanding these limiting factors, it has not already been demonstrated that obese patients are more frequently misdiagnosed of asthma (13). Moreover, some inconclusive data point towards a degree of asthma underdiagnosis between morbid obese subjects candidates for bariatric surgery (45). However, the above considerations suggest an overdiagnosis of asthma that would be primed by nowadays clinical practice (24). In fact, the inaccurate asthma diagnosis is specially frequent among obese asthma patients who frequently visit emergency services for respiratory symptoms (46).

In these circumstances, it is crucial to be especially careful when diagnosing asthma to some obese subject and, other causes of obesity-related dyspnea, such as cardiovascular disease, hypertension with left ventricle diastolic dysfunction, pulmonary hypertension associated with obstructive sleep apnea or hypoventilation-obesity syndrome, among others, should be considered. In addition, it is needed to confirm that 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 bronchial response to methacholine recorded by FEV1 values (24, 35), what makes methacholine challenge test especially useful in asthma diagnosis. However, during bronchoconstriction, obese patients without asthma develop more dyspnea (37,48, 49) and air trapping than non-obese subjects (50) what is likely secondary to both, their greater expiratory flow limitation and the premature closure of their airways. For this reason, when performing some bronchial challenge to any obese person, it would be helpful to record, besides FEV1 variation, the changes in FVC that will indirectly allow 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 bronchoconstrictor agent. In fact, up to 28% of non-asthmatic subjects who are candidates for bariatric surgery for morbid obesity have positive responses in bronchial challenge with mannitol and, this response disappears after bariatric surgery (51).

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When an obese patient has been diagnosed of asthma, our next challenge is to try to phenotype this asthma. In general, asthma associated with obesity may consist of either, 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 corticosteroid treatments, suffer from more expectoration and, have lower serum IgE levels and lower evidence of atopy (39). Higher degrees of oxidative stress and neutrophilic infiltration, apparently mediated by IL-17 occur in this phenotype of asthma (36-38). Commonly, these patients show little bronchial inflammation and their airways, due to the loss of lung elastic retraction, have greater sensitivity and are prone to collapse (53,54).

Instead, obesity-complicated asthma is usually early-onset asthma, with eosinophilic infiltration and high levels of IgE (52). In general, these patients have more severe obstruction and greater bronchial hyperresponsiveness than non-obese early-onset asthma patients (36-38). They also have a worse asthma control that increases the risks for both, hospitalization and admission in intensive care units in three and six times respectively (27).

Regardless of the evident differences in clinical presentation, exhaled nitric oxide could help to discriminate both groups of obese patients with asthma. Although the exhaled fraction of nitric oxide (FeNO) is usually lower in obese asthmatics, children or adults, than in asthmatics with normal weight (36), the identification of elevated FeNO in obese patients with asthma suggests obesity-complicated asthma. So, in a prospective cohort study, the Netherlands Epidemiology of Obesity, high FeNO levels were observed in 25% of the obese asthmatics. When compared to the remaining obese asthmatics, those with high FeNo levels had greater bronchoconstriction and more symptoms related to pollen, dust or animals exposure, suggesting predominance of a Th2 pattern (35).

To conclude, in every obese patient with asthma we always have to consider the effect that their metabolic disorder induces on asthma control. Several studies support the fact that obese patients often suffer from difficult-to-control asthma. In that way, the TENOR cohort of patients with difficult-to-control asthma, detected obesity in 31% and 69% of children and adults, respectively. The prevalence of

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obesity in the general infantile and adult American population is 20% and 35%, respectively (29). In Europe, the prevalence of obesity in difficult-to-control asthma cohorts ranges from 21% reported by Dutch series (55), 26% by Italian records (56), and 48% from the British Thoracic Society Difficult Asthma Registry cohort, almost the double than 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).

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

With regard to control and follow-up of obese asthmatics and in keeping with the above mentioned, the standard asthma control questionnaires such as ACT or ACQ can be certainly misleading. Obese asthma patients have higher perception of dyspnea and are more prone to use rescue medication than normal weight asthmatics. In these patients and mainly during inhaled corticosteroids-free periods, FeNO levels and sputum eosinophilia contribute greatly to determining the need and required dose of inhaled corticosteroids. They also help to ascertain what aspects of patient' symptoms are related to asthma, regardless of obesity (35). In addition, the management of these patients must consider besides asthma, the control of comorbidities suffered, each with its individual clinical weight what makes crucial to visit these patients in multidisciplinary asthma units (38).

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3. HOW OBESE ASTHMA PATIENTS RESPOND TO PHARMACOLOGICAL THERAPY AND TO BIOLOGICAL DRUGS? DO WE HAVE EFFECTIVE SPECIFIC INTERVENTIONS?

Several studies, generally *post hoc*, suggest that obese asthmatics respond worse to inhaled anti-asthma control drugs, including both, corticosteroids (CS) and, LABA-CS association. It has been attributed to the fact that frequently these patients, either adults (38,40,48,55,65-67) or children (68), have no eosinophilic airway inflammation. However, and as it occurs in normal-weight asthmatics, obese asthmatics display a better response to LABA-CS therapy than to montelukast (69). Moreover, a NHLBI-funded, combined *post hoc* analysis of 3 double-blind, placebo-controlled clinical trials in preschool asthmatics did not show lower response to pharmacological therapy, among obese subjects, either in symptom control or in number of exacerbations, compared to non-obese subjects (70).

New biological drugs, both anti-IgE: omalizumab (71) and anti-eosinophils: mepolizumab (72), reslizumab (73) and benralizumab (74), have demonstrated to be efficient in eosinophilic asthma. Since late-onset asthma obese patients usually have no relevant eosinophilia, and even more they display neutrophilic inflammatory phenotypes (65), it is reasonable to suppose a lack of clinical benefit to these drugs. Moreover, in the case of omalizumab and reslizumab, there is an important limitation for their use in obese patients since their doses are adjusted to weight (38). In keeping with it, a very recent retrospective real-life study suggests that obesity is a risk factor for the lack of response to omalizumab (75).

Obese asthmatics treatment response is altered as consequence of the obesity-associated comorbidities. Some of them, such as obstructive sleep apnea and gastroesophageal reflux, can simulate asthma symptoms that if misinterpreted, lead to an unnecessary increase in anti-asthmatic medication that does not results in clinical improvement. The treatment of asthma can also worsen the course of other comorbidities as oral corticosteroids over diabetes mellitus. Conversely, the treatment of comorbidities can also worsen asthma as happens with beta-blockers in the treatment of hypertension and ischemic heart disease over asthma (38-39).

Keeping all this in view, it is essential to overcome the traditional mono-organic approach of asthma in general, and of obesity-associated asthma in particular, and to manage globally and comprehensively all health problems derived. The

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multidimensional evaluation or treatable traits (32) is an emerging approach method to these patients, designed to identify and when possible treat, the health problems that occur simultaneously in asthma. These treatable traits are grouped into three domains: airway domain, extrapulmonary domain and risk factors domain. This management approach identifies treatable components of the obesity-asthma phenotype and addresses treatments to each of them. This may be a promising way to improve from a clinical perspective the heath care of obese asthmatics which again emphasized the need that these patients, suffering from complex disease, be attended at multidisciplinary asthma units.

The effectiveness of dietetic programs in obtaining a weight reduction and better control of the disease is generally low, according to the data obtained in a Cochrane review (76) and also supported by a subsequent systematic review of the Working Group on Asthma and Obesity of the European Academy of Allergy and Clinical Immunology (77). Recently, a systematic review of studies that quantify by objective means (accelerometry) the physical activity and the sedentary lifestyle of asthma patients has been published (78). Authors find no different engagement to sedentary lifestyle but they verify that females compared to males, and older people compared to their younger counterparts, perform less physical exercise, and that a higher level of exercise is associated with better lung function and asthma control (78).

In 2013 Scot et al. (79) published a randomized study evaluating the efficacy of a combined treatment of hypocaloric diet and exercise in improving patients' quality of life, asthma control and, inflammatory response. It was for the first time 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% out of them), and in asthma control (58% out of them). Physical training also reduced eosinophils by 50%. Moreover, recently, a randomized, blind-controlled trial shows for the first time, that when the effects of physical training coupled with hypocaloric diet are compared to those of isolated hypocaloric diet, the combined method induces significantly higher improvement in body composition and physical fitness. This approach has an additional beneficial effect in the modulation of inflammatory/anti-inflammatory balance and in lung function. It also contributes to improve asthma control and health-related quality of life in obese asthma adults (80). It is noteworthy that patients received regular

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psychological support to maintain their diet and exercise program. The weight loss recorded in the first 3 months of intervention was 7% of body weight in the combined approach group, and barely 2.5% in the group that performed isolated hypocaloric diet. With regard to the effect of this combined approach on patients receiving anti-obesity drugs such as sibutramine (inhibitor of serotonin reuptake) and orlistat (inhibitor of intestinal fat absorption), only one small, randomized and open clinical trial including 34 obese asthma subjects has been reported (81). Authors find positive results when implementing the hypocaloric diet and exercise program, but not as striking as those obtained in the above studies (79, 80).

In paediatric population, three randomized clinical trials have shown firstly, that by implementing combined dietary and exercise programs, it is possible to obtain significant BMI reductions in both, obese and overweight asthma children. Secondly, these changes are related to improvements in the patients' quality of life and in the indicators of disease control (82-84). In two out of these studies (82,84), significant changes were also observed in lung function, especially in FVC. Due to the characteristics of the intervention, these trials were controlled and randomized but not blind. Control children from the Willeboorse et al. trial (84), which was the longest one, with a total follow-up period of 18 months, started by 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 the reduction of the calories intake. However, it seems increasingly clear that there are certain patterns of food ingestion, mainly the exaggerated consumption of simple sugars and other carbohydrates, that are associated with the increase of chronic diseases such as diabetes, hypertension and asthma (85). The ingestion of such foods should be reduced and controlled although not drastically eliminated from the diet.

Bariatric surgery has also demonstrated effectiveness in both, asthma control and quality of life improvement in asthmatics suffering from morbid obesity (86). Although authors found no significant changes in the main variable representing bronchial obstruction: FEV1/FVC ratio (86), they showed an improvement in lung volumes related to restrictive ventilatory alteration: CRF and TLC. The beneficial effect in quality of life was maintained 5 years following surgery (87). Indications and contraindications of bariatric surgery are very specific in adults (Tables I A and C) (88) and even more in children and adolescents in whom it should only be

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performed in centres with extensive expertise in this kind of surgery in adults. These centres must also offer a real multidisciplinary approach involving the paediatric skills of surgery, nutritionist and psychological management (Table I B.) (88). The institutional requirements and the skills necessary for the bariatric surgery are also neatly defined. In keeping with that, surgeons implied should perform at least 50 bariatric surgeries per year (89)

CONCLUDING REMARKS AND RECOMMENDATIONS

Obesity is increasingly contemplated as a global world epidemic that has deleterious effects on patients' health and quality of life. Neither epidemiological, pathophysiological and mechanistic evidences nor data obtained from intervention clinical trials allow us to clearly state obesity as a causal agent of asthma. So, it should be mainly regarded as comorbidity of asthma. However the complexity and heterogeneity of these two pathologies make different clinical scenarios possible. In keeping with that, two different asthma phenotypes have been clearly described among obese subjects: early-onset asthma and late-onset asthma. From this perspective, it is likely that obesity appears progressively as comorbidity in early-onset asthma. Herein, asthma would be considered as a risk factor that would lead to obesity development. On the other hand, obesity would be some underlining layer for the development of non-eosinophilic 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 have greater symptom perception, show alterations in lung function and have obesity associated comorbidities. All of them are confounding factors in asthma diagnosis and, therefore, it is essential to turn to tests that allow the objective diagnosis of asthma mainly, lung static volumes measurement and methacholine bronchial challenge. Once the diagnosis of asthma is made, it is important to discriminate if this patient had previous asthma that worsened as a result of weight gain or if the onset of asthma followed obesity. In addition to this and other clinical features, in late-onset obese subjects, eosinophilic inflammation usually is low or absent, which makes FeNO measurement a particularly valuable test to identify them. Finally, obese asthma subjects commonly have poorer asthma control than non-obese asthmatics.

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Therefore, asthma control questionnaires should be interpreted carefully and completed with objective measures.

It is the careful phenotyping of the obese asthma patient that 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 those severe or difficult-to-treat obese asthma patients that receive either high doses of inhaled corticosteroids or biological treatments. These therapeutic modalities are only justified in the presence of active eosinophilic immunoinflammatory process, responsible for severe exacerbations that cannot be solved by traditional therapeutic plans. Many evidences recommend a diet combined with physical exercise as an effective intervention in the approach to these patients. For sure, it will not be a "bed of roses" for the patient and he will need on-going support to its implementation and maintenance. It must be the result of a multidisciplinary team that includes, in addition to doctors, dieticians, educators and physical trainers. Together with the former measurements, bariatric surgery could in some extreme cases of patients with morbid obesity be the cornerstone leading to therapeutic success.

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Table 1. Indications and contraindications for bariatric surgery (88):

A) Indications in age groups from 18 to 60 years:

1. BMI ≥40 kg/m2
2. BMI 35–40 kg/m2 with comorbidities that are expected to improve after surgically-induced weight loss (metabolic disorders, cardio-respiratory disease, severe joint disease, obesity-related severe psychological problems, etc.)
3. To be considered for surgery, patients should not lose weight or maintain long-term weight loss, despite adequate non-surgical comprehensive medical care.

B) Indications in Adolescents:

1. BMI >40 kg/m^2 (or 99.5th percentile for respective age) and at least one co-morbidity
2. Failure of at least 6 month-period of organized weight-loss treatment in a specialized center
3. Skeletal and developmental maturity
4. Able to commit to comprehensive medical and psychological evaluation before and after surgery
5. Will participate in a post-surgery 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. Non-stabilized 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 who guarantee their care.

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