Chapter 10

The Asthma Obese Phenotype

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Additional information is available at the end of the chapter

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Abstract

Asthma is a very heterogeneous disease, with two major asthma phenotypes, the allergic and the late onset asthma, differentiated by the triggers, the cellular dominance, the Th1/Th2 inflammation pattern and the local and serological markers. As there were many overlapping biological markers between these two phenotypes, different types of tentative classification followed. A clinical one makes a difference between the predominant eosinophilic one (with better response to glucocorticoid) and the predominant neutrophilic one with more severe evolution and low rate of therapeutical improvement. Another approach was based on cluster analysis of asthma characteristics (onset, atopic status, and body mass index (BMI)), sensitivity to methacholine test, peak flow variability, bronchodilatation response, postbronchodilator level of FEV1, sputum eosinophil and neutrophil count, FeNO test, clinical symptom scores, treatment scheme to control symptoms, exacerbations, and severity. Emerging data suggest a distinct late onset obese-asthma phenotype, with a specific pathophysiology, comorbidities, and clinical evolution. This chapter reviews the main characteristics of this phenotype: the specific lung function impairment, the underlying inflammation, the adipokine profile, the comorbidities and the therapeutical approach. The mutual influence between obesity and asthma will be illustrated, whenever scientific data are available.

Keywords: asthma-obese phenotype, metabolic changes in asthma, inflammation in asthma, asthma biomarkers

1. Introduction

Obesity became in recent years a recurrence and one of the major concerns in asthma research. This chapter presents the relation between obesity and asthma, underlining the influences

on pathological mechanisms, evolution, and treatment, in order to give an overview of the current knowledge about the asthma-obese phenotype (AOP). Inside the AOP, two distinct forms have been described: an early onset, atopic asthma with no gender differences in incidence and a late onset, non-atopic asthma predominantly in women [1]. We interpret the first as an atopic asthma aggravated by obesity and the second as a form of asthma favored by obesity. They have common characteristics related to the pathological consequences of obesity, the subject of our review.

2. Incidence

Worldwide, 15–20% of the population suffers from asthma [2, 3]. The prevalence have different slopes in different countries, with higher incidence in developing countries [4] and apparently constant rate in recent years or even with a tendency of reduction in current wheezing in countries with previous higher prevalence [2].

The trends of incidence of asthma and obesity are similar: a flat curve of high prevalence in developed countries and an increasing prevalence in less developed countries [2, 5]. However, the recently published analysis from the US national survey, comparing the 8.5% population attributable fraction for overweight/obesity between 1988 and 1994 with the 11.9% one, in 2011–2014, found this increase statistically non-significant [6]. Studies from developing countries, in prospective cohorts, confirmed the parallel increase in incidence of obesity and asthma, [7], particularly in obese women [8].

The AOP could be, in fact, related not to obesity but to the metabolic syndrome. A Norway study confirmed, but another large longitudinal study with 25 years of follow-up contradicted this assumption and found that independent factors to the metabolic syndrome play significant roles in the association of asthma with obesity [9]. Waist circumference was negatively associated with eosinophilia [10] and gave an odds ratio (OR) = 1.46 for asthma in females [11]. The relation between asthma and metabolic syndrome seems to be reciprocal, as asthma increases the risk for metabolic syndrome [12] and for obesity [13].

High BMI is also associated with the severity of asthma, particularly in women [14], with a reduced FEV1 %, a higher readmission rate and longer hospitalization stay [15]. In a large cross-sectional Israeli study, obesity was associated with mild and moderate to severe asthma in male, and to moderate to severe asthma in females [16]. Differences in severity between obese and non-obese were maintained after adjustment for demographics, smoking status, medication or gastroesophageal reflux [17].

Genomic studies also support this association. A twin-based research concluded that 8% of the genetic component of the obesity is shared with asthma [18]. A large case control sample of population with European origin revealed a protection for asthma-obesity co-occurrence with the 16p11.2 inversion [19]. Several gene polymorphisms (TNF-α, -β or leptin receptors) with interrelated physiopathological mechanisms for the AOP seem to be involved in risk and/or the therapeutical response [20–23].

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3. Pathogenic pathways

Impressive research data have been accumulated to explain the relationship between obesity and asthma. Among them, two pathogenic processes draw special attention: the lung function impairment and the specific airways inflammation.

3.1. Lung function impairment

3.1.1. Structural changes

In normal obese, forced vital capacity (FVC) is smaller than slow vital capacity (SVC), and this points to the possibility of even underdiagnosis obstruction, when using FEV1/FVC data [24]. Reduced SVC and total lung capacity (TLC), increased inspiratory reserve volume, decreased expiratory reserve volume (ERV) and maximal voluntary ventilation volume (MVV) was found in severe obesity [25]. The reduction in FVC%, FEV1%, MVV% was parallel with the BMI increase [26]. The reduction in the functional residual capacity (FRC) was more pronounced than of the TLC until BMI exceeded 35 kg/m^2, after which the decrease was proportionate [27]. While VC and TLC are markers of restriction, the MVV integrates the endurance and strength of the respiratory muscles with the airway diameter and resistance and is interpreted as an obstructive dysfunction. Another argument against a pure restrictive pattern in obesity is that the FRC reduction is due to the ERV reduction, with normal or even increased RV and reflects a lower airways caliber [28]. The volume of FRC is the expression of the equilibrium between the inward elastic recoil of the lung and outward elastic recoil of the chest wall. Obesity, particularly the abdominal one, reduces the expansion of the diaphragm and of the excursions of the thoracic cage, limiting the elastic recoil of the lung. Ventilation occurs at lower lung volumes, the transpulmonary pressure is lower. These changes affect the retractive forces of the lung parenchyma and the airways caliber and unload the airway smooth muscle (ASM); as consequence, the ASM shortens more in response to external stimuli. Even more, due to the decreased expansion of the airways, actin and myosin attach closer and are more difficult to detach during relaxation. A confirmation of these mechanisms is obtaining no difference in the fall of FEV1 after methacholine test with or without a previous avoidance of deep inspiration in nonasthmatic obese (NAO) persons [29].

3.1.2. Metabolic changes

Obesity increases the respiratory demand, with greater energy expenditure for breathing. Obesity-related inflammatory cytokines (such as TNF-α or leptin) and hormones (insulin) increase the ASM contractility. The insulin growth factor 1 stimulates the proliferation of the ASM. Insulin raises the expression of β1-containing laminins, promoting contractility [30].

Successful weight loss programs reverse the lung function changes and have an important role in asthma management in these patients. Weight loss reduces airway resistance, airways obstruction, improves peak expiratory flow (PEF) variability, and increases FRC and ERV [31].

Weight loss in obese asthmatics (OA) with high IgE and dominant Th2 inflammation improved the resting respiratory system mechanics, assessed by oscillometry, but had no effect on the

sensitivity of air closure during the methacholine test, reflected by FVC % reduction. Certain differences in response, according to the underlying inflammation of the AOP subtypes, have been noticed [32] serving as argument that weight loss cumulates the benefit of the structural, the metabolic, and of the inflammatory improvement in OA.

3.2. Influences of the obesity inflammation pattern on asthma

Obesity generates a low-grade inflammation, switches blood monocytes and tissue macrophages to the M1 activation pathway, and impairs the ratio between regulatory T-lymphocytes (Treg) and Th17. Changes from the lean to obese pattern involve the switch of macrophages from M2 to M1 domination, switch from Th2 to Th1 cells, and switch from the Treg cells and NKT to B cells, mast cells and neutrophils. Together with the adipokine profile modification, a pro-inflammatory pattern develops (**Figure 1**).

3.2.1. Polarization of the macrophages

Macrophages are polarized to the M1 state by interferon-γ and by inducers of TNF-α, such as lipopolysaccharides (LPS). M1 macrophages upregulate pro-inflammatory cytokines as TNF-α, interleukin IL-1β, IL-6, IL-12, IL-15, and IL-23 and oxidative stress.

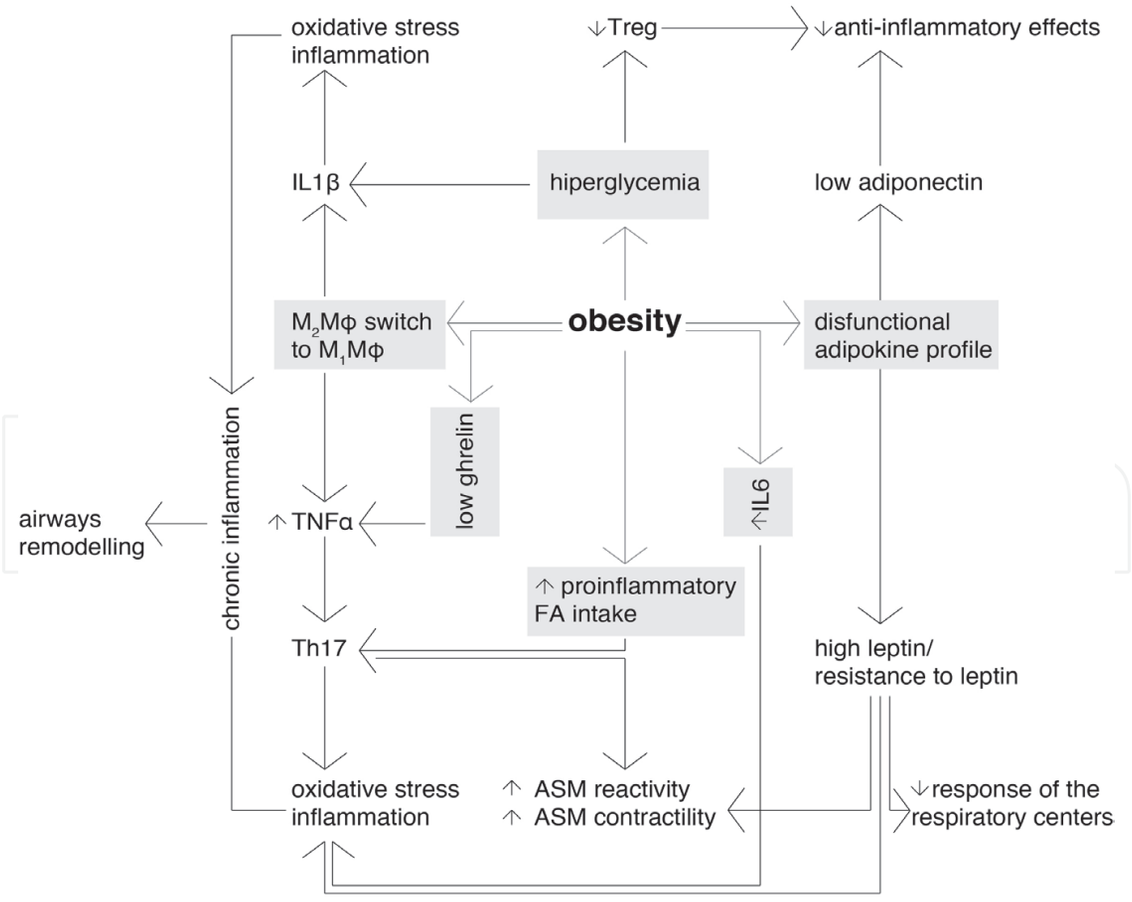

Figure 1. Obesity-related inflammation in asthma. ASM = airway smooth muscle; FA = fatty acids; IL1β = interleukin 1β, IL6 = interleukin 6; M1Mϕ = M1 macrophage; M2Mϕ = M2 macrophage; Th17 = T helper 17 cells; TNFα = tumor necrosis factor α; Treg = regulatory T cells.

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Lung macrophages are a heterogeneous population divided into alveolar and interstitial macrophages. In non-allergic asthma, M1 macrophages are increased and pathogenic, while in allergic forms, they seem to be protective. Due to their defense capacity against pathogens, they have a role in preventing the asthma exacerbation. The most extensively investigated negative effects of the M1 polarization specific cytokine signature are TNF-α and IL-1β in asthma. Exogenous administration of recombinant TNF-α shifts to the left the curve of responsiveness to methacholine in normal subjects [33]. In asthma patients, high levels of TNF-α in bronchoalveolar lavage or bronchial biopsies are associated with severity [34]. How TNF-α induces airways hypersensitivity is not completely understood, but experimental research showed that TNF-α increases ASM contractility by intracellular calcium increase. The intimate process involves a variety of G-protein coupled agonists (methacholine, histamine and serotonine). After binding to TNF receptor 2, TNF-α increases the Th17 differentiation and induces vascular modifications through endothelin and neurotrophic tyrosine kinase receptor type 2. Of interest for obesity, a condition associated with low ghrelin levels is that the raise of TNF-α level in the bronchoalveolar lavage after ovalbumin challenge is attenuated by this orexigenic factor [35].

The IL-1β is a pro-inflammatory cytokine with special interest for bronchoconstriction, particularly if primed by IL-5. IL-1β is a result of activation of numerous lung cells, including lymphocytes, macrophages, mastocytes and even ASM. IL-1β could be the link between toll-like receptors (TLR) and nucleotide-binding oligomerization domain-like receptors (NLR), the NLRP3 inflammasome and the activation of the TH17 cells, as both TLR and NLR that sense the external signals promote IL-1β secretion [36]. From macrophages cytoplasm, IL-1 is secreted through lipid pores requiring the presence of gasdermin D (GSDMD), a protein identified from genomic-wide studies as a possible asthma marker [37]. Experimental data showed that GSDMD expression regulates cell growth of ASM and promotes fibrosis with remodeling of airways [38]. Cellular stress-related inflammation, with high extracellular release of adenosine triphosphate (ATP), uric acid crystals, and cholesterol also involve the IL-1β signal [39]. The expression of IL-1β is upregulated by prolonged hyperglycemic state [40], with possible impact on AOP.

3.2.2. The predominant Th1/Th17 activation

The level of Th17 increases in obese, if a certain threshold of the BMI is achieved, in absence of an acute or chronic inflammation [41]. An inhibition effect on adipogenesis in mesenchymal cells and on the adipocyte differentiation raised the hypothesis that IL-17 could be a regulatory cytokine of obesity itself, providing a negative feedback on the adipose tissue expansion [42]. Several mechanisms have been proposed to explain how Th17 increases in obesity. The higher metabolic activity related to nutrients intake raises the ATP level and the release of ATP molecules to the extracellular space; ATP binds to P2X7, a purinergic receptor, capable of driving Th17 responses during inflammation and secretion of pro-inflammatory cytokines [43]. Unhealthy diet, with high pro-inflammatory, long chain, saturated free fatty acid (FFA), and low anti-inflammatory ω3- polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFA) activates the TLR in adipocytes and macrophages, and the Th1/Th17 pathways in dendritic cells [44]. Micronutrient deficiencies, such as low levels of vitamin D, are also frequent in obese persons. The enhanced infection susceptibility is due to the decreased levels of cathelicidin in the primary defense cells, aggravating the clinical evolution.

In obesity, the adipocytes have a significant contribution to the circulating IL-6, promoting the differentiation of TH17 and naive CD4 T-cells. Leptin, another cytokine of the IL-6 family, is also increased, with many pathological implications for asthma. Among these, leptin modulates Th17 response by conditioning the signal transducer and activator of transcription 3 (STAT3) expression and phosphorylation in CD4 cells [45]. Th1 and Th17 differentiation require mammalian Target of Rapamycin 1 (mTORC1) signals [46], which are known to be activated by growth factors, amino acids or insulin, all being raised at obesity.

Through IL-17 secretion, Th17 cells recruit and activate neutrophils to produce pro-inflammatory cytokines (IL-6, IL-8) [41], chemokines, and adhesion molecules. IL-17 upregulates IL-8 secretion in airway epithelial cells and initiates airway remodeling, increasing the levels of fibroblast-derived inflammatory mediators, such as the α-chemokines, IL-8, and growth-related oncogene-α [41]. Pathogenic Th17 cells express IL-1R1, a type of IL-1β receptor, with bronchoconstriction effect [47].

Epigenetic markers, such as promoter methylation of transcription factors associated with increased Th1 differentiation, were found in OA preadolescent compared to non obese asthmatic patients (NOA) [48].

3.2.3. Reduction of Treg

Tregs have a significant role in suppression of allergy and asthma, as they are sources of anti-inflammatory cytokines (IL-10, TGFβ1 and IL-35) and have suppressor function on a variety of immune cells (B cells, NK cells, CD4+, CD8+) and dendritic cells. Tregs are even able to kill effector lymphocytes in a perforin-dependent manner. The number of studies related to the Treg number and function in asthma is increasing but are far from being conclusive: in allergic inflammation, Tregs are generally low and less able to control the inflammation process. An increased number of Tregs were found in more severe asthma, an effect that could be also due to the inhaled corticoids [49].

Concerning AOP, a reduction of Treg is present in insulin resistance OA [50]. Particularly with high amount of abdominal fat, Treg is reduced, contributing to the low-grade inflammation and insulin resistance development. Leptin has similar inhibitory effect on Treg [51]. Treg expresses the insulin receptor, and hyperinsulinemia affects their IL-10 production and the suppressor functionality [52]. As insulin levels are frequently elevated in obese subjects, the insulin effect on Treg could be a part of the explanation of the severity of asthma of the AOP.

3.2.4. The adipokine profile

The inflammation pattern in obesity is closely related to the adipokine profile. A meta-analysis of 13 studies with 3642 patients concluded that the high leptin and low adiponectin are associated with the diagnosis of asthma [53].

The leptin receptor is constitutively expressed in epithelial lung cells but also on immune cells. **Leptin** directly stimulates respiratory centers, increases frequency, minute and tidal volume. These positive effects on the respiratory function are lost in obesity, a state of leptin

resistance, but high dose of leptin administered to obese mice was able to restore the breathing pattern and the arterial CO_2 [54].

Compared to obese non-asthmatic, leptin levels are increased in OA [55]. The difference is higher in women [56] and in patients with lung neutrophilia [57]. High leptin level upregulates the expression of inflammatory proteins, such as cPLA2-α [58] or phospholipase D1 [59], raises leukotrienes (LT) production [60] and bronchial responsiveness. Again, the effect was manifest particularly in obese women [61]. LT synthesis in neutrophils depends on circulatory arachidonic acid, on nuclear localization of the 5-lipooxigenase [62], and on the level of extracellular signal regulated kinases (ERK) activity, significantly influenced by androgens. This might contribute to the gender differences in AOP.

Attenuation of the constitutive muscarinic activation of the ASM cells via the central nervous system (a normal dilatator effect and leptin) has been proposed as part of leptin resistance [63]. Leptin resistance seems to be selective, as the pro-inflammatory effects are maintained in obesity. Leptin effects on airway remodeling could be related to reduction in α1-antitripsin expression, enhanced intercellular adhesion molecule 1 (ICAM-1) expression and increase in the CCL11, G-CSF, VEGF, and IL-6 production [64].

The circadian secretion of leptin is the highest at midnight; in obese subjects, the basal and the evening increase is higher than in lean subjects [65]. This could be an influencer of the nocturnal asthma attacks and of the overall severity of asthma.

In contrast with leptin increase, plasma adiponectin is decreased in asthma [66], independent of the BMI [67]. The adiponectin is correlated with the FEV1 decline, and with the high serum and sputum IgE [68]. Adiponectin is able to polarize the macrophages to an M2 state [69], switches the balance by inhibition of pro-inflammatory cytokines (TNFα), stimulates the anti-inflammatory ones (IL10), diminishes Nf-Kb activation, and negatively correlates with protein C and IL6. Despite experimental data to confirm these actions, adiponectin's role in predicting asthma severity remains controversial.

Adiponectin circulates as trimer (the low molecular weight form) or hexamers (the high molecular weight form), and the inconsistent findings of these studies could be explained by different serum adiponectin components that were measured, as only high low-molecular-weight isoform was strongly associated with the asthma risk and lung function decrease [70].

4. Clinical and therapeutic particularities of OA

4.1. Biomarkers

The specific physiopathology of the AOP was translated in different attempts to define biomarkers. Particular biomarkers or different cut points for predicting airway inflammation were proposed. Classification and relevant examples of proposed biomarkers are summarized in **Table 1**. Most of these studies were not reproduced on larger scales, and currently there are no guidelines on their clinical utilization.

Category	Biological sample	Type	Comments
Inflammatory biomarkers	Sputum	High MMP1, MMP2, and MMP8	Study design primarily for asthma severity: these MMP not found in other clusters [71]
		IL-5	Comparison between OA and LA inside the group of severe asthma [72]
		14 differentially expressed genes encoding proteins related to the cell cycle and growth factor regulating pathways (MAPK1, E2F1, and SPRY2) and to the interferon signaling pathway (OASL, OAS3 and TRIM14)	Study design for cluster identification; the results selected refer to the comparison between late onset asthma, severe, high proportion of atopic, nonsmokers and obese female asthmatics, high frequency of exacerbations despite near normal lung function, 73.6% atopy. [73]
		Gene expression of calcium signal transmission (*S100P, S100A16),* lymphocyte differentiation (*MAL),* and mucin (*MUC1)* increase	Comparison of diet (high fat meal)-induced metabolism in asthma and healthy controls. No specific analysis related to BMI, but mean BMI was in the obesity range in asthma and in overweight range in controls [74]
	Exhaled breath condensate	Increase in glucose, n-valerate, acetoin, isovalerate, and 1,2-propanediol levels and a decrease in formate, ethanol, methanol, acetone, propionate, acetate, lactate, and saturated fatty acid levels	Relatively small cross-sectional study, well designed to differentiate AOP from obese-non asthma and lean-asthma, strong statistical power of correlation [75]
	Bronchial submucosa	Increased eosinophil count	In a severe asthma population, eosinophil number in submucosa correlated with BMI [72]
	Bronchial submucosa	No increase in eosinophil count	In mild to moderate OA, eosinophil number in submucosa not different from obese without asthma [76]
	Blood	Low periostin l	Study design primarily for asthma severity: low levels found also in other clusters, no difference between OAP and other cluster presented [71]
	Blood	CCL17, IL-4, IL-13	Cross-sectional study. Comparison of lean asthma and obese asthma [77]
	Expired air	FeNO test	Large cross-sectional study; low FeNO associated with adiposity indicators; in high FeNO group, adiposity indicators associated with worse asthma severity or control [78]
Adipokine profile	Blood	Leptin	Cross-sectional study, comparison to lean asthma AO, leptin mediates asthma control [77]

Category	Biological sample	Type	Comments
	Blood	Adiponectin	Review of the controversial epidemiological results in human studies mainly to heterogeneity of the design of these studies [79]
	Blood	Resistin	Post-weight management intervention Δ resistin negatively associated to Δ FRC and Δ RV [80]
Functional test (bronchial reactivity)		Challenge test with ozone	Comparison between obese and non-obese; post-exposure decrease of FVC in obese, similar bronchial reactivity and IL-6 increase [81]
		Challenge test with mannitol	Airway hyper-responsiveness to mannitol in obese non-asthmatic without asthma comparative to non-obese subjects [82]

Table 1. Asthma-obese phenotype biomarkers.

4.2. Comorbidities

The clinical manifestations and the treatment response appear to be influenced by comorbidities. They can be summarized as allergic (rhinitis, eczema), smoking-related, psychogenic (hyperventilation, depression, and anxiety disorders), metabolic syndrome, gastroesophageal reflux disease and obstructive sleep apnea [83]. Comorbidities become significant when there is reciprocal impact. As a disease is the expression of a certain number of dysregulated functional mechanisms, comorbidities, by cumulating more abnormalities, will always have a potential negative impact. Comorbidities might share co-determination factors or potentiate mechanisms for the related comorbidity. The asthma-obesity relation suits very well in these last categories.

In terms of co-determination factors, the chronic asthma inflammation is influenced by the metabolic inflammation, as previously described. Certain comorbidities, such as the gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA) have an independent high prevalence in asthma and in obesity but aggravate each other when they coexist.

4.2.1. Gastroesophageal reflux disease

To evaluate prevalence, different definitions of Gastroesophageal reflux disease (GERD) are used in the epidemiological studies: the presence of the reflux symptoms, the pH measurement, the endoscopic findings of the gastroesophageal mucosal disease or presence of the hiatal hernia. Despite the variation in methodology, the incidence was significantly higher than in the non-asthmatic population no matter what criteria were used. On the obesity side, a meta-analysis showed that the risk for GERD progressively increases with the increase in BMI

[84]. The asthma-GERD relation is bilateral. GERD is the cause for the abnormal acid reflux that leads to microaspiration into the airways, initiating reflex cough and bronchoconstriction via vago-vagal reflexes. Asthma bronchoconstriction triggers acid reflux, as happens in some patients during the methacholine test. Theophylline increases gastric acid secretion and lowers low esophagus sphincter tone [85]. Both obesity and asthma increase the transdiaphragmatic and intragastric pressures and favor hiatal hernia.

Despite common agreement that GERD was associated with more severe asthma symptoms, apparently, no association between GERD and the severity of asthma was found in a subpopulation of OA [86]. This emphasizes the need for dedicated studies to this particular phenotype.

Indirect arguments that asthma control might have positive influence on GERD are the presence of the silent reflux in asthma patients and the relative risk of development of GERD [87], but there are no published data to confirm this hypothesis.

GERD influences also obesity, by changing type and frequency of meals. Reduction in weight has favorable effects on GERD-related symptoms.

Due to the presence of the increased cholinergic tone in both asthma and GERD, the use of anticholinergic medication might be of interest.

4.2.2. Obstructive sleep apnea

Obstructive sleep apnea (OSA) has a higher prevalence in men, while OA is more prevalent in women. Due to the high association rate between OSA and asthma [86] and the worse asthma control in the presence of OSA, an overlap asthma-OSA syndrome was proposed [88]. As with the GERD, asthma increases the risk of the new-onset OSA [89]. Obesity is the major risk factor for OSA, but OSA also leads to obesity: impaired sleep architecture changes leptin signal with a reduction in satiety along with craving for high energy foods [90], modifies transcriptional networks in visceral fat, and reduces secretion of growth hormone. The excessive daytime sleepiness reduces physical activity, increases the proportion of the fat mass compared to the free fat mass and makes weight loss programs more difficult to succeed.

OSA has negative impact on asthma. During apnea episodes, the upper way vibration and suction collapse, activate vagal tone, and induce reflex bronchoconstriction. The more negative intrathoracic pressure developed during apnea increases the pulmonary capillary volume. These pathological processes trigger asthma attacks. Repeated mechanical trauma is associated with upper and lower airway inflammation [91]. OSA aggravates nocturnal asthma, lowers the quality of life, and leads to more frequent exacerbations.

Asthma has negative effects on OSA. In asthma patients, OSA is more severe, with lower apnea-hypopnea index (AHI). Sleep efficiency and arousal index were higher in severe asthma compared to moderate asthma, but apparently no correlation have been found between OSA severity and measures of the asthma severity evaluated by FEV1 or with the asthma quality of life score [92]. High dose, long-term corticosteroid treatment, particularly in poorly controlled asthma could be a contributing factor to obesity and OSA [93].

Nocturnal GERD links asthma, GERD, and OSA under a common aggravating factor. The increase of the respiratory effort exacerbates asthma and OSA symptoms and is associated with higher AHI and inflammation in the exhaled breath condensate [94].

4.2.3. Metabolic syndrome-related comorbidities

Increased incidence of type 2 diabetes and cardiovascular events (hypertension, ischemic heart disease, cerebrovascular disease) is also expected to happen, as directly influenced by obesity. In a very large adult study, elevated waist circumference and triglyceride (TG) and low high-density lipoprotein (HDL) were significantly associated with wheezing [95]. In this respect, statins represent a potential treatment modality in severe asthma; their anti-inflammatory effects and the enhancement of the corticosteroid sensitivity make them good candidates for AO treatment, particularly in cases with metabolic syndrome [96].

4.3. Therapeutical challenges

Current guidelines do not differentiate pharmacotherapy between OA and NOA, but studies have confirmed that AO is more severe and more difficult to control, with the regular medication [83, 97].

AOP benefits from **lifestyle** changes: weight reduction is a priority goal, but all other general asthma interventions should be addressed: smoking cessation, allergen exposure avoidance, occupational risk assessment, and so on. Diet and/or bariatric surgery is correlated with reduction of exacerbations and improvements in the lung function, clinical manifestations, and quality of life [98, 99]. Successful interventions increase in efficacy of the inhaled corticosteroids (ICS) after smoking cessation [100] and after losing weight [98].

Treatment of **comorbidities** related to overweight directly impacting asthma. Positive effects on asthma control have been reported from continuous positive airway pressure (CPAP) therapy of OSA [92]. There is also a benefit on the pulmonary function in OA with diabetes treated with dipeptydil-peptidase4 inhibitors related to the correction of the oxidative/antioxidative imbalances [101].

Proton pomp inhibitors and histamine H2 receptor improve GERD-related symptoms and quality of life but does not influence asthma control [102]. However, improvement of symptoms in severe, selected cases was obtained from different surgical procedures [103, 104]. However, the common high cholinergic tone in GERD and asthma raised the hypothesis that anticholinergic therapy could be a common solution [104]. A Cochrane systematic review provided some evidence that long-acting muscarinic antagonists added to ICS show some benefits on FEV1 [105], but prospective studies should confirm if there is also benefit in the AOP, and if this effect is higher in asthma-GERD association. The anti-inflammatory effect of statins in asthma is not consistent across studies [106]. Whether their effect on asthma evolution is increased in those OA with dyslipidemia remains to be demonstrated.

If standard step-increase asthma medication is not efficient, specific endotype treatment (precision medicine approach) would be desirable.

OA is associated with some specific inflammatory pathways activation, one of which is 5-lipoxygenase pathway inflammation; leukotriene antagonists have similar efficacy with ICS in the presence of obesity [107]. Some biological therapies for severe forms of asthma were proven beneficial also in OA. For example, in OA patients with raised eosinophils and high airways reversibility, Mepolizumab was more efficient in the reduction of exacerbations [108]. Nevertheless, the ones that targeted commonly upregulated pathways were not successful. For example, a 12 weeks treatment with Brodalumab (a human anti-IL-17 receptor) had no clinically meaningful effects [109]. Golimumab, an anti-THF-α humanized antibody, provided some improvements, but limited use due to the risks associated with this therapy: infections, congestive heart failure, malignancies, and demyelinating disorders [110]. However, in a small selected group of overweight and obese severe asthma patients this treatment reduced the oral steroid dose and hospitalizations [111].

5. Conclusions

To conclude, the AOP is supported by epidemiological, pathophysiological, and clinical data. There are still many uncertainties about the OAP and even more about the two subtypes, described until now only from the epidemiological perspective; further research is needed to elucidate common and specific mechanisms and to improve our knowledge about the specific biomarkers and the therapeutical approaches for the subtypes of AOP.

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References

[1] Ather JL, Poynter ME, Dixon AE. Immunological characteristics and management considerations in obese patients with asthma. Expert Review of Clinical Immunology. 2015;**11**:793-803

[2] Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet. 2006;**368**(9537):733-743

[3] Gershon AS, Wang C, Guan J, To T. Burden of comorbidity in individuals with asthma. Thorax. 2010;**65**:612-618

[4] Huang C, Liu W, Hu Y, et al. Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in shanghai, China. PLoS One. 2015;**10**:e0121577

[5] Abarca-Gómez L et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. The Lancet. 2017, pii: S0140-6736;(17):32129-32123

[6] Akinbami LJ, Rossen LM, Fakhouri THI, Fryar CD. Asthma prevalence trends by weight status among US children aged 2-19 years. Pediatric Obesity. 2017:1988-2014

[7] Forno E, Acosta-Pérez E, Brehm JM, et al. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. The Journal of Allergy and Clinical Immunology. 2014;**133**:1308-1314

[8] Mishra V. Effect of obesity and asthma among adult Indian women. International Journal of Obesity and Related Metabolic Disorders. 2004;**28**:1048-1058

[9] Assad N, Qualls C, Smith LJ, et al. Body mass index is a stronger predictor than the metabolic syndrome for future asthma in women. The longitudinal CARDIA study. American Journal of Respiratory and Critical Care Medicine. 2013;**188**:319-326

[10] Lessard A, Turkotte H, Cornier Y, Boulet LP. Obesity and asthma. A specific phenotype? Chest. 2008;**134**:317-323

[11] Brumpton B, Langhammer A, Romundstad P, et al. General and abdominal obesity and incident asthma in adults: The HUNT study. The European Respiratory Journal. 2013;**41**:323-329

[12] Del-Rio-Navarro BE, Castro-Rodriguez JA, Garibay Nieto N, et al. Higher metabolic syndrome in obese asthmatic compared to obese nonasthmatic adolescent males. The Journal of Asthma. 2010;**47**:501-506

[13] Renosto LC, Acatauassu C, Andrade I, et al. Growth velocity and weight gain in prepubertal asthmatic children. Revista da Associação Médica Brasileira. 2017;**63**:236-241

[14] The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. The European Respiratory Journal. 2003;**22**:470-477

[15] Okubo Y, Michihata N, Yoshida K, et al. Impact of pediatric obesity on acute asthma exacerbation in Japan. Pediatric Allergy and Immunology. 2017;**00**:1-5

[16] Machluf Y, Farkash R, Fink D, Chaiter Y. Asthma severity and heterogeneity: Insights from prevalence trends and associated demographic variables and anthropometric indices among Israeli adolescents. The Journal of Asthma. 2017;**5**:1-11

[17] Schatz DM, Magid DJ, Camargo CA. The relationship between obesity and asthma severity and control in adults. The Journal of Allergy and Clinical Immunology. 2008;**122**:507-511

[18] Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. The Journal of Allergy and Clinical Immunology. 2005;**116**:1235-1241

[19] González JR, Cáceres A, Esko T, et al. A common 16p11.2 inversion underlies the joint susceptibility to asthma and obesity. American Journal of Human Genetics. 2014;**94**:361-372

[20] Yang Y-H, Liu Y-Q, Zhang L, et al. Genetic polymorphisms of the TNF-α-308G/a are associated with metabolic syndrome in asthmatic patients from Hebei province, China. International Journal of Clinical and Experimental Pathology. 2015;**8**:13739-13746

[21] Rosmond R. Association studies of genetic polymorphisms in central obesity: A critical review. International Journal of Obesity. 2003;**27**:1141-1151

[22] Kaya Z, Caglayan S, Akkiprik M, et al. Impact of glucocorticoid receptor gene (NR3C1) polymorphisms in Turkish patients with metabolic syndrome. Journal of Endocrinological Investigation. 2016;**39**:557-566

[23] Ishiyama-Shigemoto S, Yamada K, Yuan X, et al. Association of polymorphisms in the beta2-adrenergic receptor gene with obesity, hypertriglyceridaemia, and diabetes mellitus. Diabetologia. 1999;**42**:98e101

[24] Fortis S, Corazalla E, Wang Q, Kim HJ. The difference between slow and forced vital capacity increases with increasing body mass index: A paradoxical difference in low and normal body mass indices. Respiratory Care. 2015;**60**:113-118

[25] Costa D, Barbalho MC, Miguel GPS, Forti EMP, Azevedo JLMC. The impact of obesity on pulmonary function in adult women. Clinics. 2008;**63**:719-724

[26] Ladosky W, Botelho MA, Albuquerque JP Jr. Chest mechanics in morbidly obese nonhypoventilated patients. Respiratory Medicine. 2001;**95**:281-286

[27] Jones RL, Nzekwu MMU. The effects of body mass index on lung volumes. Chest. 2006;**130**:827-833

[28] King GG, Brown NJ, Diba C, et al. The effects of body weight on airway caliber. The European Respiratory Journal. 2005;**25**:896-901

[29] Boulet LP, Turcotte H, Boulet G, Simard B, Robichaud P. Deep inspiration avoidance and airway response to methacholine: Influence of body mass index. Canadian Respiratory Journal. 2005;**12**:371-376

[30] Dekkers BGJ, Schaafsma D, Tran T, Zaagsma J, Meurs H. Insulin- induced laminin expression promotes a hypercontractile airway smooth muscle phenotype. American Journal of Respiratory Cell and Molecular Biology. 2009;**41**:494-504

[31] Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest. 2000;**118**:1315-1321

[32] Chapman DG, Irvin CG, Kaminsky DA, et al. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. Respirology. 2014;**19**:1170-1177

[33] Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor-alpha increases airway responsiveness and sputum neutrophilia in normal human subjects. American Journal of Respiratory and Critical Care Medicine. 1995;**152**:76-80

[34] Yang T, Li Y, Lyu Z, et al. Characteristics of proinflammatory cytokines and chemokines in airways of asthmatics: Relationships with disease severity and infiltration of inflammatory cells. Chinese Medical Journal. 2017;**130**:2033-2204

[35] Fu T, Wang L, Zeng Q, Zhang Y, Sheng B, Han L. Ghrelin ameliorates asthma by inhibiting endoplasmic reticulum stress. The American Journal of the Medical Sciences. 2017;**354**:617-625

[36] Besnard AG, Togbe D, Couillin I, et al. Inflammasome–IL-1–Th17 response in allergic lung inflammation. Journal of Molecular Cell Biology. 2012;**4**:3-10

[37] Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. The New England Journal of Medicine. 2010;**363**:1211-1221

[38] Das S, Miller M, Beppu AK, et al. GSDMB induces an asthma phenotype characterized by increased airway responsiveness and remodeling without lung inflammation. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**:13132-13137

[39] Gasse P, Riteau N, Charron S, et al. Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. American Journal of Respiratory and Critical Care Medicine. 2009;**179**:903-913

[40] Schroder K, Zhou R, Tschopp J. The NLRP3 inflammasome: A sensor for metabolic danger? Science. 2010:296-300

[41] Schindler TI, Wagner J-J, Goedicke-Fritz S, et al. TH17 cell frequency in peripheral blood is elevated in overweight children without chronic inflammatory diseases. Frontiers in Immunology. 2017;**8**:1543

[42] Ahmed M, Gaffen SL. IL-17 in obesity and adipogenesis. Cytokine & Growth Factor Reviews. 2010;**21**(6):449-453

[43] Pandolfi JB, Ferraro AA, Sananez I, et al. ATP-induced inflammation drives tissue-resident Th17 cells in metabolically unhealthy obesity. Journal of Immunology. 2016;**196**:3287-3296

[44] Stelzner K, Herbert D, Popkova Y, et al. Free fatty acids sensitize dendritic cells to amplify TH1/TH17-immune responses. European Journal of Immunology. 2016;**46**:2043-2053

[45] Reis BS, Lee K, Fanok MH, et al. Leptin receptor signaling in T cells is required for Th17 differentiation. Journal of Immunology. 2015;**194**:5253-5260

[46] Delgoffe GM, Pollizzi KN, Waickman AT, et al. The mammalian target of Rapamycin (mTOR) regulates T helper cell differentiation through the selective activation of mTORC1 and mTORC2 signaling. Nature Immunology. 2011;**12**:295-303

[47] Chehimi M, Vidal H, Eljaafari A. Pathogenic role of IL-17-producing immune cells in obesity, and related inflammatory diseases. Journal of Clinical Medicine. 2017;**6**:68

[48] Rastogi D, Siuzuki M, Greally JM. Differential epigenome-wide DNA methylation patterns in childhood obesity-associated asthma. Scientific Reports. 2013;**3**:2164

[49] Yang Y, Zang HL, Wu J. Role of T regulatory cells in the pathogenesis of asthma. Chest. 2010;**138**:1282-1283

[50] Eller K, Kirsch A, Wolf AM, et al. Potential role of regulatory T cells in reversing obesity-linked insulin resistance and diabetic nephropathy. Diabetes. 2011;**60**:2954-2962

[51] Cipolletta D. Adipose tissue-resident regulatory T cells: Phenotypic specialization, functions and therapeutic potential. Immunology. 2014;**142**:517-525

[52] Han JM, Patterson SJ, Speck M, Ehses JA, Levings MK. Insulin Inhibits IL-10–mediated regulatory T cell function: Implications for obesity. Journal of Immunology. 2013:1302181

[53] Zhang L, Yin Y, Zhang H, Zhong W, Zhang J. Association of asthma diagnosis with leptin and adiponectin: A systematic review and meta-analysis. Journal of Investigative Medicine. 2017;**65**:57-64

[54] O"Donnell CP, Schaub CD, Haines AS, et al. Leptin prevents respiratory depression in obesity. American Journal of Respiratory and Critical Care Medicine. 1999;**159**:1477-1484

[55] Mai X-M, Böttcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. Pediatric Allergy and Immunology. 2004;**15**:523-530

[56] Muc M, Todo-Bom A, Mota-Pinto A, Vale-Pereira S, Loureiro C. Leptin and resistin in overweight patients with and without asthma. Allergol Immunopathol (Madr). 2014;**42**:415-421

[57] Ubags ND, Vernooy JH, Burg E, et al. The role of leptin in the development of pulmonary neutrophilia in infection and acute lung injury. Critical Care Medicine. 2014;**42**:e143-e151

[58] Hsu P-S, Wu C-S, Chang J-F, Lin W-N. Leptin promotes $cPLA_2$ gene expression through activation of the MAPK/NF-κB/p300 Cascade. International Journal of Molecular Sciences. 2015;**16**:27640-27658

[59] Lee S-M, Choi H-J, Oh C-H, Oh J-W, Han J-S. Leptin increases TNF-α expression and production through phospholipase D1 in raw 264.7 cells. PLoS One. 2014;**9**:e102373

[60] Giouleka P, Papatheodorou G, Lyberopoulos P, et al. Body mass index is associated with leukotriene inflammation in asthmatics. European Journal of Clinical Investigation. 2011;**41**:30-38

[61] Coffey MJ, Torretti B, Mancuso P. Adipokines and cysteinyl leukotrienes in the pathogenesis of asthma. Journal of Allergy (Cairo). 2014;**42**:415-421

[62] Luo M, Jones SM, Peters-Golden M, Brock TG. Nuclear localization of 5-lipoxygenase as a determinant of leukotriene B_4 synthetic capacity. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**:12165-12170

[63] Arteaga-Solis E, Zee T, Emala CW, Vinson C, Wess J, Karsenty G. Inhibition of leptin regulation of parasympathetic signaling as a cause of extreme body weight-associated asthma. Cell Metabolism. 2013;**17**:35-48

[64] Suzukawa M, Koketsu R, Baba S, Igarashi S, et al. Leptin enhances ICAM-1 expression, induces migration and cytokine synthesis, and prolongs survival of human airway epithelial cells. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2015;**309**:L801-L811

[65] Radić R, Nikolić V, Karner I, et al. Circadian rhythm of blood Leptin level in obese and non-obese people. Collegium Antropologicum. 2003;**27**:555-561

[66] Assad NA, Sood A. Leptin, adiponectin and pulmonary diseases. Biochimie. 2012;**94**: 2180-2189

[67] Sood A, Qualls C, Schuyler M, et al. Low serum adiponectin predicts future risk for asthma in women. American Journal of Respiratory and Critical Care Medicine. 2012;**186**(1):41-47

[68] Kim KW, Shin HY, Lee KE, Kim ES, Kim KE. Relationship between adipokines and manifestations of childhood asthma. Pediatric Allergy and Immunology. 2008;**19**:535-540

[69] Ohashi K, Parker JL, Ouchi N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. The Journal of Biological Chemistry. 2010;**285**:6153-6160

[70] Hayashikawa Y, Iwata M, Inomata M, et al. Association of serum adiponectin with asthma and pulmonary function in the Japanese population. Endocrine Journal. 2015;**62**:695-709

[71] Hinks TSC, Brown T, Lau LCK, et al. Multidimensional endotyping in patients with severe asthma reveals inflammatory heterogeneity in matrix metalloproteinases and chitinase 3-like protein 1. The Journal of Allergy and Clinical Immunology. 2016;**138**(1):61-75

[72] Desai D, Newby C, Symon FA, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. American Journal of Respiratory and Critical Care Medicine. 2013;**188**(6):657-663

[73] Lefaudeux D, De Meulder B, Loza MJ, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum-omics. The Journal of Allergy and Clinical Immunology. 2016. DOI: 10.1016/j.jaci.2016.08.048

[74] Li Q, Baines KJ, Gibson PG, Wood LG. Changes in expression of genes regulating airway inflammation following a high-fat mixed meal in asthmatics. Nutrients. 2016;**8**(1):30

[75] Maniscalco M, Paris D, Melck DJ, et al. Coexistence of obesity and asthma determines a distinct respiratory metabolic phenotype. The Journal of Allergy and Clinical Immunology. 2017;**139**(5):1536-1547

[76] van Huisstede A, Rudolphus A, van Schadewijk A, et al. Bronchial and systemic inflammation in morbidly obese subjects with asthma: A biopsy study. American Journal of Respiratory and Critical Care Medicine. 2014;**190**:951-954

[77] Zhang X, Zheng J, Zhang L, et al. Systemic inflammation mediates the detrimental effects of obesity on asthma control. Allergy and Asthma Proceedings. 2018;**39**(1):43-50

[78] Han Y-Y, Forno E, Celedón JC. Adiposity, fractional exhaled nitric oxide, and asthma in U.S. children. American Journal of Respiratory and Critical Care Medicine. 2014;**190**(1): 32-39

[79] Nigro E, Daniele A, Scudiero O, et al. Adiponectin in asthma: Implications for Phenotyping. Current Protein & Peptide Science. 2015;**16**:182-187

[80] Ballantyne D, Scott H, MacDonald-Wicks L, et al. Resistin is a predictor of asthma risk and resistin: Adiponectin ratio is a negative predictor of lung function in asthma. Clinical and Experimental Allergy. 2016;**46**:1056-1065

[81] Bennett WD, Ivins S, Alexis NE, et al. Effect of obesity on acute ozone-induced changes in airway function, reactivity, and inflammation in adult females. PLoS One. 2016;**11**(8):e0160030

[82] Arismendi E, Rivas E, Vidal J, et al. Airway hyperresponsiveness to mannitol in obesity before and after bariatric surgery. Obesity Surgery. 2015;**25**(9):1666-1671

[83] Boulet LP, Boulay ME. Asthma-related comorbidities. Expert Review of Respiratory Medicine. 2011;**5**:377-393

[84] Hampel H, Abraham NS, El-Serag HB. Meta-analysis: Obesity and the risk for gastroesophageal reflux disease and its complications. Annals of Internal Medicine. 2005;**143**(3):199-211

[85] Ekström T, Tibbling L. Influence of theophylline on gastro-oesophageal reflux and asthma. European Journal of Clinical Pharmacology. 1988;**35**:353-365

[86] Bruno A, Pace E, Cibella F, Chanez P. Body mass index and comorbidities in adult severe asthmatics. BioMed Research International. 2014, Article ID 607192:7

[87] Ruigómez A, Rodriguez LA, Wallander MA, et al. Gastroesophageal reflux disease and asthma. Chest. 2005;**128**(1):85-93

[88] Madama D, Silva A, Matos MJ. Overlap syndrome – Asthma and obstructive sleep apnea. Revista Portuguesa de Pneumologia. 2016;**22**(1):6-10

[89] Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Pep- pard PE. Association between asthma and risk of developing obstructive sleep apnea. Journal of the American Medical Association. 2015;**313**:156-164

[90] Ong CW, O'Driscoll DM, Truby H, et al. The reciprocal interaction between obesity and obstructive sleep apnoea. Sleep Medicine Reviews. 2013;**17**:123-131

[91] Devouassoux G, Levi P, Rossini E, et al. Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure–induced airway hyperresponsiveness. The Journal of Allergy and Clinical Immunology. 2007;**119**:597-603

[92] Julien JY, Martin JG, Ernst P, et al. Prevalence of obstructive sleep apnea–hypopnea in severe versus moderate asthma. The Journal of Allergy and Clinical Immunology. 2009;**124**:371-376

[93] Rașcu A, Popa DE, Arghir OC, Otelea MR. Effects of corticosteroid treatment on respiratory muscles function in patients with severe obstructive lung disease. Farmácia. 2016;**64**(6):819-822

[94] Emilsson ÖI, Benediktsdóttir B, Ólafsson Í, et al. Respiratory symptoms, sleep-disordered breathing and biomarkers in nocturnal gastroesophageal reflux. Respiratory Research. 2016;**17**:115

[95] Fenger RV, Gonzalez-Quintela A, Linneberg A, et al. The relationship of serum triglycerides, serum HDL, and obesity to the risk of wheezing in 85,555 adult. Respiratory Medicine. 2013;**107**(6):816-824

[96] Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. Respirology. 2017;**22**:651-661

[97] Akerman MJ, Calacanis CM, Madsen MK. Relationship between asthma severity and obesity. The Journal of Asthma. 2004;**41**:521-526

[98] Ulrik CS. Asthma and obesity: Is weight reduction the key to achieve asthma control? Current Opinion in Pulmonary Medicine. 2016;**22**:69-73

[99] Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. The Journal of Allergy and Clinical Immunology. 2011;**128**:508-515

[100] Livingston E, Chaudhuri R, McMahon AD, et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. American Journal of Respiratory and Critical Care Medicine. 2003;**168**:1308-1311

[101] Tai H, Wang M-Y, Zhao Y-P, et al. The effect of alogliptin on pulmonary function in obese patients with type 2 diabetes inadequately controlled by metformin monotherapy. Medicine (Baltimore). 2016;**95**(33):e4541

[102] Mattos ÂZ, Marchese GM, Fonseca BB, et al. Antisecretory treatment for pediatric gastroesophageal reflux disease - A systematic review. Arquivos de Gastroenterologia. 2017;**54**:271-280

[103] Hu Z, Wu J, Wang Z, et al. Outcome of Stretta radiofrequency and fundoplication for GERD-related severe asthmatic symptoms. Frontiers in Medicine. 2015;**9**:437

[104] Sriratanaviriyakul N, Kivler C, Vidovszky TJ, Yoneda KY. Journal of medical case reports: LINX®, a novel treatment for patients with refractory asthma complicated by gastroesophageal reflux disease: A case report. BioMed Central. 2016;**10**

[105] Kew KM, Evans DJ, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting

beta2-agonists (LABA) for adults with asthma. Cochrane Database of Systematic Reviews. 2015;**6**:CD011438

[106] Yuan C, Zhou L, Cheng J, et al. Statins as potential therapeutic drug for asthma? Respiratory Research. 2012;**13**(1):108. DOI: 10.1186/1465-9921-13-108

[107] Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. The European Respiratory Journal. 2006;**27**:495-503

[108] Ortega H, Li H, Suruki R, Albers F, et al. Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. Annals of the American Thoracic Society. 2014;**11**(7):1011-1017

[109] Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti–IL-17 receptor monoclonal antibody, in moderate to severe asthma. American Journal of Respiratory and Critical Care Medicine. 2013;**188**:1294-1302

[110] Durham AL, Caramori G, Chung KF, Adcock IM. Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. Transgenic Research. 2016;**167**:192-203

[111] Taillé C, Poulet C, Marchand-Adam S, et al. Monoclonal anti-TNF-α antibodies for severe steroid-dependent asthma: A case series. Open Respiratory Medicine Journal. 2013;**7**:21-25