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Obese Asthma Syndrome, Glucocorticoids, and Vitamin D: Mechanisms and Implications

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ABSTRACT

The obese asthma syndrome (OAS) is characterized by increased airway inflammation and impaired lung function. Obesity-induced inflammation, characterized by elevated pro-inflammatory cytokines and reduced anti-inflammatory adipokines, contributes to airway inflammation and asthma symptoms. Asthmatic patients with obesity often have a poor response to inhaled corticosteroids (ICS), which are the mainstay of asthma treatment. They achieve less asthma control, more hospitalizations, and experience a poorer quality of life. The detrimental effects of obesity on lung function and the additive or synergistic effects of systemic inflammation contribute to this reduced response to glucocorticoids. Additionally, studies have suggested a potential association between vitamin D deficiency, obesity, and asthma exacerbations. Low vitamin D levels have also been linked to glucocorticoid resistance, while in vitro evidence suggests that vitamin D can enhance the effectiveness of glucocorticoids. Weight loss through bariatric surgery shows promising results in improving asthma control and reducing airway inflammation.

Keywords: Airway. Asthma. Inflammation. Inflammosome. Obesity.

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INTRODUCTION

The association between obesity and asthma, referred to as "Obese Asthma Syndrome" (OAS) has been widely evaluated in recent years. Several clinical, epidemiological and experimental studies have identified pathways that could link the two processes, including systemic inflammation, lung function alterations, metabolic dysregulation, microbiome changes, and differences in epigenetic/genomic regulation[1].

Asthma and obesity are two widespread epidemics impacting the developed world. The connection between obesity and both asthma and severe asthma seems to depend on weight, indicating a causal and likely reciprocal relationship. In obesity, the increased expression of various mediators that intensify and spread inflammation is considered the culprit of obesity-related inflammation. The consequent regulatory effects of the immunomodulatory pathways involved in both conditions have been suggested as one of the mechanisms through which obesity increases the risk and severity of asthma[2].

In airway inflammatory disorders, inhaled corticosteroids (ICS) are the mainstay of therapy. However, up to 50% of asthmatics may not respond well to ICS, and up to 25% of patients with difficult-to-control asthma may not respond well to oral glucocorticoids[3]. This makes glucocorticoid hyporesponsiveness in asthma a challenging healthcare problem associated with significant morbidity and life-threatening disease progression. Specifically, in the asthma with obesity phenotype, a reduction in clinical response to inhaled glucocorticoids has been described[4,5].

Low serum vitamin D levels have been reported in obese individuals and have been found associated with asthma exacerbations[6]. Moreover, an inverse correlation between serum vitamin D concentrations with forced expiratory volume in one second (FEV_1) and body mass index (BMI) has been reported[7]. Vitamin D has been acknowledged to influence different functions with regard to the immune, nervous, cardiovascular and endocrine systems[8,9]. Vitamin D receptors (VDRs) are expressed in a plethora of tissues and cells, while the pleiotropic actions of vitamin D in non-skeletal outcomes have become increasingly recognized[10].

OBESE ASTHMA SYNDROME (OAS)

Asthma is a common chronic airway disease characterized by variable airflow limitation resulting from the combination of airway narrowing, airway hypersensitivity, airway wall thickening, and increased mucus hypersecretion. Airway narrowing results from both chronic inflammation and airway remodeling. Asthma is a heterogeneous disease with several distinct clinical presentations (phenotypes) and complex pathophysiological mechanisms (endotypes)[11].

Several studies have corroborated the existence of excess risk of developing asthma in obese subjects compared to subjects not overweight, regardless of gender or age[12-14]. Obesity is the consequence of excessive body fat accumulation due to an imbalance of energy intake and energy expenditure[15]. Diagnosis of obesity is usually established by assessing a BMI ≥ 30 kg/m^2.

The complexity of the OAS is exacerbated by the presence of more than one (or many) phenotypes. Two main sub-phenotypes of OAS have

been described according to age: 1. allergic asthma in children with obesity, which worsens pre-existing asthma, and 2. an often non-allergic, late-onset asthma developing as a consequence of obesity[16]. Asthma in the latter group is more difficult to control, it impairs lung function, requires more treatments with limited therapeutic effects, and leads to more frequent exacerbations than the non-obese asthma population[17-20].

Obesity has an impact on the ventilatory function of these patients. Among adults, elevated body weight is linked to a small decrease in FEV_1 and forced vital capacity (FVC), while the FEV_1/FVC ratio typically remains unchanged or slightly elevated. These changes are accompanied by reductions in lung volumes, such as functional residual capacity (FRC), alterations that characterize the so-called restrictive ventilatory defect. In addition, obesity is associated with increased airway hyperresponsiveness (AHR)[21].

Inflammation in OAS

Concerning inflammation, the excessive accumulation of adipose tissue in subjects with obesity results in an increased production of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, interferon- γ [IFN-γ], tumor necrosis factor [TNF]-α) and adipokines such as leptin, while there is a reduced release of adiponectin, a cytokine with anti-inflammatory properties[2]. There is a hypothesis suggesting that the persistent low-grade systemic inflammation observed in obesity leads to the release of pro-inflammatory substances from the inflamed adipose tissue. This phenomenon, via additive or synergistic mechanisms, is believed to increase the systemic and airway inflammation that underlies asthma[2].

Asthma has been classified, depending on the historical moment and the knowledge available, as allergic and non-allergic, eosinophilic, and non-eosinophilic, and type 2 (T2) high and T2 low or its equivalent non-T2, regarding the inflammatory profile[18,19,22] (Fig. 1). T2 asthma with eosinophilia is a common endotype in asthma, which can occur with and without any demonstrated allergies. T2 asthma with allergy is the most common asthma endotype with an early onset. Eosinophilic non-allergic asthma is in most cases a moderate to severe, late-onset disease frequently associated with chronic rhinosinusitis and nasal polyps. Type 2 immune responses involve T helper (Th)-2 cells, innate lymphoid cells (ILC)-2, immunoglobulin E-secreting B cells (IgE), natural killer T (NK-T) cells, mast cells, basophils, eosinophils, and their cytokines. Th2 cells produce various cytokines such as IL-4, IL-5, IL-9, and IL-13[23-25]. Non-eosinophilic asthma has been described mostly in adults and rarely in children and includes neutrophilic and paucigranulocytic asthma[26]. Th1 and Th17 are the subsets of cells that produce IL-17, IL-21, and IL-22, the dominant cytokines in non-T2 asthma[27,28].

Several studies have evaluated the cell-dominant pattern of airway inflammation in asthma patients with and without associated obesity. Data from these studies support that obesity is associated with a neutrophil-dominant rather than an eosinophil-dominant inflammatory pattern in the airway lumen[29,30]. There are, however, some discrepancies with respect to the type of airway inflammation associated with the obese phenotype. Some cluster analyses have shown that the association between

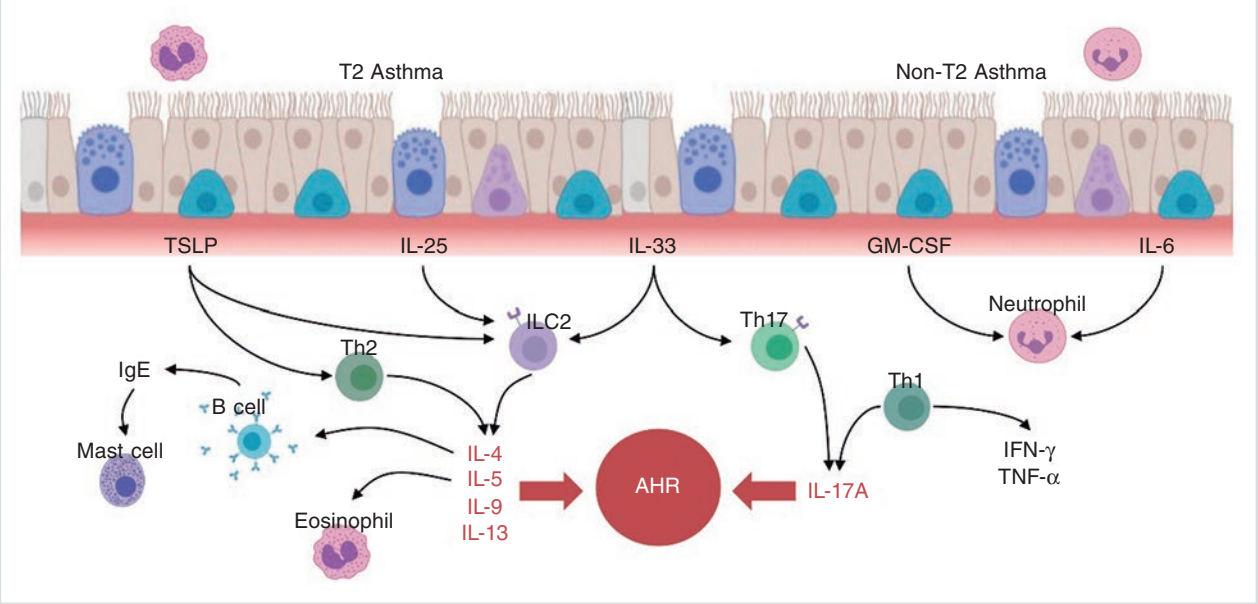

Figure 1. Asthma endotypes. T2 immune responses involves T helper (Th)-2 cells, innate lymphoid cells (ILC)-2, eosinophils, and their cytokines (IL-4, IL-5, IL-9 and IL-13). Cytokine production is controlled by alarmins, such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). T2 asthma could be allergic (when immunoglobulin E (IgE)-producing B secreting cells and mast cells are present) or non-allergic. Non-T2 asthma is mediated by type 1 inflammation where Th1 and Th17 release type 1 cytokines (IFN-γ, TNF-α, IL-17A) and neutrophils are present in the airway lumen. Pro-inflammatory cytokines in both T2 and non-T2 asthma trigger airway hyperresponsiveness (AHR).
Adapted from figure 1 in reference 2.

obesity and neutrophilic inflammation is more common in women[19]. However, other studies have not found such an association between obesity and neutrophilic airway inflammation in adults with asthma[31,32].

The abundant neutrophil concentration is associated with increased levels of IL-17A, a cytokine involved in neutrophil recruitment to the airways[29,30]. Data from animal models also support a link between IL-17A and OAS. Obese mice typically exhibit innate AHR, but this AHR is not observed when the animals are IL-17A deficient[33]. In the lungs of obese mice, increased IL-17A, producing chemokine receptor 6 (CCR6+) in ILC3, was found associated with AHR and neutrophilic inflammation[33]. Obese mice with a deletion of the TNF-α receptor (TNFR2) were protected against innate AHR and presented reduced levels of IL-17 in comparison with controls[34]. Interestingly, the relative reduction of eosinophil numbers with respect to neutrophils in the airway secretions of obese asthmatics (OA) contrasts with the higher eosinophil counts found in the airway submucosa in obese versus lean severe asthmatics[29,35]. Similar to IL-17, sputum IL-5 and IL-25 levels have been found to be significantly higher in OA compared to their lean counterparts. In contrast, neither IL-4 nor IL-13 sputum levels were found associated with BMI in asthma patients[29]. Two hypotheses have been suggested to explain the apparent paradox represented by

the reduced presence of eosinophils in sputum versus elevated eosinophilia in submucosa: 1. Survival of eosinophils in the airway is reduced in OAS, and 2. Eosinophils are retained in the submucosa and do not migrate to the airway lumen. The second hypothesis appears to be supported by studies reporting that more eosinophils are recruited to the lungs of obese patients with asthma compared with non-obese patients with asthma[36]. Furthermore, it is unlikely that eosinophils fail to survive within the airway lumens of OA because IL-5, a well-known eosinophil survival factor, is elevated in the sputum of obese versus lean severe asthmatics[29,35]. This observation is interesting because some severe OA may have an eosinophilic (in airway submucosa) non-T2 dominant type of asthma, and therefore may benefit from eosinophil-targeted therapeutics that might be excluded if attending only sputum results. The OAS is also associated with the presence of increased interleukin levels, such as TNF-α and IL-1β in the lung, even in the absence of an antigenic challenge[36]. TNF-α expression increased in peripheral blood mononuclear cells (PBMCs) in parallel with BMI increase in subjects with asthma[38].

Another mechanism that also accounts for neutrophilic airway inflammation in asthma is inflammasome activation in M1 macrophages. The nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome is an intracellular multiprotein complex that facilitates the autoactivation of the pro-inflammatory cysteine protease caspase-1. Then, the activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms[39]. IL-1β is found elevated in the blood of obese individuals[40] and was found to promote Th17 cell-dependent inflammation[39]. NLRP3 inflammasome can be activated by fatty acids via toll-like receptor 4 (TLR4) and increased sputum concentrations of IL-1β and increased NLRP3 and TLR4 expression in sputum cells have been reported in obese versus non-OA patients[41,42]. A recent paper reported that obesity induced by a high-fat diet in mice triggered the activation of an NLRP3 inflammasome in M1 macrophages resident on adipose tissue and in the lungs, resulting in an amplification of IL-1β production, the subsequent ILC3 activation, and IL-17 secretion, which in turn facilitates AHR in these patients[43]; this is a novel mechanism that has not been previously linked with airway disease[37] (Fig. 2).

Bariatric surgery and inflammation

Bariatric surgery is considered the most effective and sustained long-term treatment of severe obesity. Several studies have found significant improvements in asthma control, asthma severity, medications required, hospitalizations, sleep, exercise capacity and lung function tests[44,45].

A recent study sought to determine if adipose tissue inflammation was associated with increased inflammation in the airway of OA patients and whether weight loss after bariatric surgery would simultaneously improve metabolic and airway inflammation. In the asthmatic subjects with obesity, concentrations of the pro-inflammatory cytokines IL-6 and IL-8 decreased with weight loss. Changes in leptin and adiponectin protein levels in airways were similar to those found in adipose tissue: at baseline, leptin levels were higher,

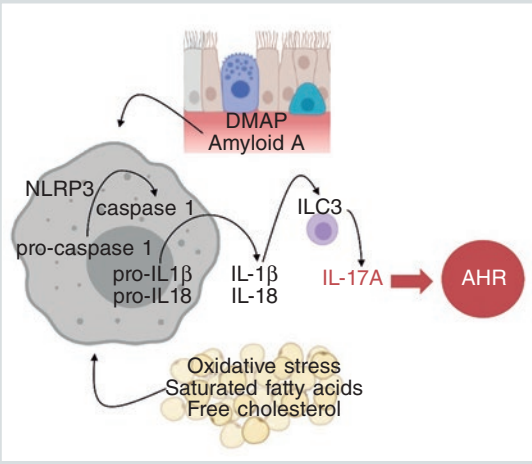

Figure 2. Inflammasome activation. In asthma, NLR family pyrin domain containing 3 (NLRP3) inflammasome is activated by danger-associated molecular patterns (DAMP) and serum amyloid A protein, produced by epithelial cells exposed to microbes. Moreover, NLRP3 is activated by saturated fatty acids, as well as free cholesterol, and oxidative stress, which are present in adipose tissue in obesity. The activation of NLRP3 in M1 macrophages resident on adipose tissue and in the lungs, resulting in an amplification in IL-1β and IL-18 production, the subsequent innate lymphoid cell (ILC)-3 activation, and IL-17A secretion, which in turn facilitates airway hyperresponsiveness (AHR) in patients.
Adapted from figure 1 in reference 2.

and adiponectin lower in bronchoalveolar lavage fluid (BALF) of participants with asthma compared with control subjects. AHR was more significantly related to visceral fat leptin than to BMI. The authors concluded that the high levels of adipokines produced in visceral adipose tissue in OAS are associated with airway reactivity but not with airway inflammation[46]. Other authors found no significant effect on serum cytokine levels in OA subjects after bariatric surgery. However, serum TNFR2, ezrin, MCP-1, and IL-18 levels significantly decreased at the six–twelve-month post-bariatric surgery follow-up in non-asthmatic obese subjects[47], but there was no effect on other cytokines such as IL-8, IL-9, TNF-α, TGF-β1, and GM-CSF[47,48].

Blood adiponectin concentration decrease in a negative relationship to increases in BMI[49,50]. Poor asthma control[51] and asthma severity[52,53] are both associated with lower adiponectin levels. Studies assessing the effects of bariatric surgery found that weight loss was associated with the recovery of serum adiponectin levels in obese[54] and OA patients[48,55]. Interestingly, the balance of the adiponectin/leptin inflammatory ratio leaned towards normal in asthmatic patients compared with OA and non-asthmatic subjects, in whom the ratio tended towards the pattern favouring inflammation. The adiponectin/leptin ratio negatively correlated with BMI. Weight loss was associated with a normalization of the ratio in obese subjects[47].

With respect to markers of allergic inflammation, no changes in submucosal cell counts of eosinophils, neutrophils, B cells, macrophages, $CD4^+$ T cells or $CD8^+$ T cells were found with weight loss following bariatric surgery. In contrast, mast cells decreased significantly in the same patients[56].

GLUCOCORTICOIDS

Glucocorticoids have anti-allergic, anti-inflammatory, and immunosuppressive properties, in addition to regulating the biosynthesis and metabolism of key nutrients such as sugars, fats, and proteins[57]. As one of the most effective medications to prevent and treat asthma, glucocorticoids primarily act on airway epithelium to inhibit airway inflammation[57,58]. At a cellular level, the anti-inflammatory effect of glucocorticoids is exerted through a reduction

in both the cell number and the function of inflammatory cells in the airways, including eosinophils, T-lymphocytes, mast cells, and dendritic cells[59].

Glucocorticoids diffuse across the cell membrane and bind to glucocorticoid receptors (GR) in the cytoplasm[59]. The widespread distribution of the GR within the body explains the efficacy of glucocorticoid treatment in most patients and in numerous inflammatory diseases[58,60]. In the nucleus, the GR binds to the glucocorticoid response elements (GRE) and activates (transactivation) or inhibits (transrepression) gene transcription depending on the type of GRE sequence[3]. Glucocorticoids induce anti-inflammatory genes such as IL-10, annexin 1, mitogen-activated protein kinase (MAPK) phosphatase-1 (MKP-1), inhibitor of nuclear factor kappa B (NFκB), lipocortin-1, IL-1 receptor antagonist, glucocorticoid-induced leucine zipper (GILZ), and the RNA-binding protein tristetraprolin (TTP)[61,62] (Fig. 3).

Apart from their classic genomic effects, glucocorticoids also have non-genomic actions, characterized by their rapid (i.e., lasting a few minutes) anti-inflammatory and immunosuppressive effects, and post-transcriptional actions regulating gene expression at the level of mRNA[62,63].

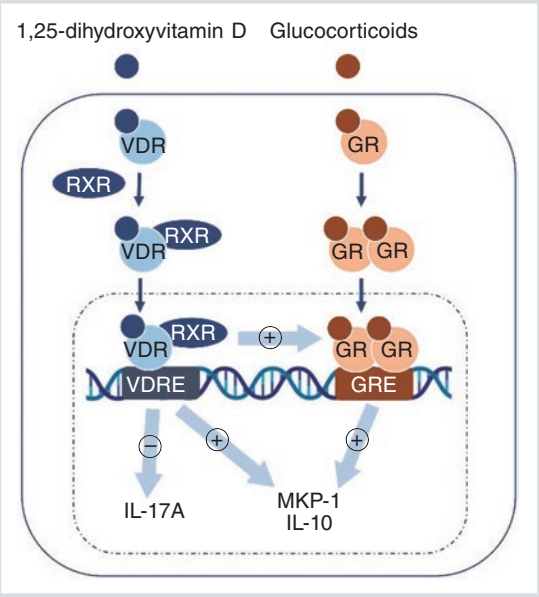

Figure 3. Cross-talk between vitamin D and glucocorticoids. 1,25-dihydroxyvitamin D, the active form of vitamin D, enhance the effects of glucocorticoids by promoting MKP-1 expression and by producing anti-inflammatory proteins such as IL-10. Moreover, 1,25-dihydroxyvitamin D may reduce the production of IL-17A via modulation of the VDR pathway.
GR: glucocorticoid receptor; GRE: glucocorticoid response elements; IL: interleukin; MKP-1: mitogen-activated protein kinase phosphatase 1; RXR: retinoic X receptor; VDR: vitamin D receptor; VDRE: vitamin D response elements.

Glucocorticoid hyporesponsiveness

ICS are considered the cornerstone of controller therapy for T2-high asthma, which contrasts with their poor therapeutic efficacy in T2-low asthma[11,64]. Obesity has been recognized as a risk factor for ICS hyporesponsiveness in asthma patients. Asthmatic patients with obesity have reduced odds of achieving asthma control, higher risk of asthma hospitalizations, and lower quality of life compared with asthmatics with a normal BMI[4,65,66]. A positive correlation has been found between high BMI with residual asthma symptoms that remained present in OA patients despite intensive treatment with high doses of ICS[66]. The mechanism(s) by which obesity negatively impacts asthma control by ICS remains to be fully elucidated. Detrimental effects of obesity on lung function and additive or synergistic effects of obese systemic inflammation on airways inflammation, have been proposed as potential

mechanisms to explain ICS hyporesponsiveness in obesity-related asthma[2,21].

Some studies analyse GR abnormalities[7,67,68]. Variants of GR formed by alternative splicing may modulate glucocorticoid sensitivity. Increased expression of GRβ isoform has been reported in patients with glucocorticoid-resistant asthma. It is induced by pro-inflammatory cytokines and competes with GRα to bind with GRE, thus acting as a dominant negative inhibitor[69,70]. Another group found that dysregulation of the GRα/GRβ isoform ratio may contribute to glucocorticoid hyporesponsiveness in OA[68]. A recent study showed that the GR nuclear translocation in $CD4^+$ T cells from healthy controls and patients with moderate asthma at the baseline was the same without significant difference while almost no GR translocation was detected in $CD4^+$ T cells of patients with uncontrolled severe asthma[71].

Other studies evaluate cytokine profiles in cultured cells under glucocorticoid treatment[72,73]. IL-10 is a potent anti-inflammatory and immune-regulatory cytokine which is secreted by Treg cells in response to glucocorticoids[74]. Th17 cells, which secrete IL-17, are increased in patients with severe asthma which is in turn associated with neutrophilic inflammation[75]. Th17 cells appear to be glucocorticoid resistant in mice studies[76].

Moreover, measuring dexamethasone-suppression of cell proliferation assays[67,77-79] and analysing expression of genes induced by glucocorticoids, such as MKP-1[7,31,79], are two of the most used methods to study glucocorticoid hyporesponsiveness. In proliferation assays, the glucocorticoid IC_{50} value can be used as an indirect marker of sensitivity because it represents the glucocorticoid dose that inhibits 50% of cell proliferation[79]. Bantulà et al.[79] found that dexamethasone IC_{50} values from obese subjects with or without asthma were lower compared with lean asthmatics and non-obese non-asthmatic participants, meaning obesity is characterized by a reduced response to glucocorticoid treatment, assessed by means of a PBMCs and $CD4^+$ T cells proliferation assay. Moreover, the reduced response negatively correlated with the serum adiponectin/leptin ratio, a marker associated with the level of inflammation in subjects with obesity[79].

One hypothesis is that obese subjects present an altered molecular response to glucocorticoids due to systemic inflammation. Glucocorticoids inhibit pro-inflammatory gene expression, in part through negative regulation of MAPK signalling pathways by molecules such as MKP-1[80]. Given that pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, are increased in many obese individuals, and given that these same cytokines are regulated by and potential regulators of p38 MAPK[80], it is possible that this pro-inflammatory environment might modify glucocorticoid function in asthmatic patients with obesity[31].

These data indicate that *in vitro* biomarkers of glucocorticoid hyporesponsiveness increase in both the lung and peripheral blood as body mass increases in individuals with asthma, but not in control subjects without asthma. This effect is manifested by a reduced induction of MKP-1 expression in response to dexamethasone in both PBMCs and BALF cells, and is related to enhanced expression of TNF-α in both peripheral and lung immune cells as body mass increases, suggesting a scenario in which one or more molecular pathways governing

glucocorticoid responses are modified in both the airway and peripheral blood in asthmatic subjects with overweight and obesity[31]. Interestingly, obesity in non-asthmatic subjects had no effect on MKP-1 expression, suggesting that, due to unclear reasons, the effect of obesity only impacts MKP-1 expression in asthma patients[31]. Other authors found no significant differences in dexamethasone-dependent induction of MKP-1 in OA compared with their lean counterparts[79]. Differences in patients' clinical characteristics, such as asthma severity or pulmonary function, may explain discrepancies between these studies[31,79]. Asthma severity has been shown to be closely related to the level of dexamethasone-induced MKP-1 expression[81].

Bariatric surgery and glucocorticoid sensitivity

In a large retrospective study, bariatric surgery led to the discontinuation of bronchodilators in 39.3% of patients within one year[82]. Similar results, with a 49% reduction in inhaled treatments at one year of bariatric surgery, improvement in asthma control assessed by the asthma control questionnaire (ACQ) score, and reduction of emergency room visits were found in other studies[48,83]. Bariatric surgery also improved lung function and reduced AHR[72,84]. However, in another study, the improved effect on AHR was only found in the group of OA with high serum IgE levels[48]. The effect on asthma control, therapeutic reduction and lung function seems to persist after five years of bariatric surgery[85]. In an *in vitro* study, PBMCs and $CD4^+$ T cells from obese subjects with or without asthma increased dexamethasone sensitivity six months after bariatric surgery. Weight loss after surgery was associated with a marked improvement in the reduced antiproliferative effects of glucocorticoids in subjects with obesity[79].

VITAMIN D

During the last decades, laboratory and observational studies have demonstrated that different nutrients, such as long-chain omega 3 fatty acids, curcumin, and vitamin D, among others, have therapeutical anti-oxidant and anti-inflammatory effects[86,87]. These studies showed that supplementation with these compounds may be associated with reduced exacerbations of inflammatory diseases including chronic obstructive lung disease or asthma[86].

Vitamin D is a hormone with pleiotropic effects and numerous regulatory mechanisms beyond bone health[88]. The active form of vitamin D, 1,25-dihydroxyvitamin D, binds the VDR, present in all tissues including T and B lymphocytes, dendritic cells, bronchial epithelial cells, and lung fibroblasts[88] (Fig. 3).

Vitamin D in obesity asthma syndrome

On the one hand, low serum vitamin D is correlated with impaired lung function, increased AHR, poor asthma control, reduced glucocorticoid response and increased number of asthma exacerbations[7,89,90]. Higher vitamin D serum levels have a positive effect on the prevention of exacerbation and better treatment of asthma symptoms[91], are associated with a higher rate of FEV_1 and FVC and with better asthma control[90,92]. Vitamin D may play a role in foetal lung development and in

the differentiation of type II pneumocytes and surfactant secretion[93].

On the other hand, low vitamin D levels have been extensively reported in obesity, with a prevalence ranging from 40-80%[94,95]. Low vitamin D levels inversely correlated with body weight, BMI, fat mass[9,96,97], and the risk of abdominal obesity[98]. It is well established that vitamin D levels in subjects with obesity are lower than people of normal weight[99], and some clinical studies support the role of obesity as a causal risk factor for the development of a low vitamin D status[100,101]. However, the exact mechanisms responsible for this association remain unclear. There is a hypothesis based on the potential of adipose tissue to store and retain vitamin D, preventing uncontrolled synthesis of vitamin D in the liver and protecting against potential toxicity[100]. When obese and non-obese adults were exposed to simulated sunlight or received an oral dose of 50,000 IU of vitamin D, they were able to raise their blood levels of vitamin D by no more than 50% compared with non-obese adults[102]. The study by Wortsman et al.[96] demonstrated that although skin biosynthesis of vitamin D did not differ between subjects with normal weight and obesity, serum vitamin D concentrations were lower in those with obesity. These findings suggest that vitamin D, as a fat-soluble vitamin, is possibly accumulated and sequestered into adipose tissue and is unable to enter the circulation to produce vitamin D in the liver. This can lead to lower plasma levels of vitamin D in subjects with excess accumulation of adipose tissue[10].

One of the few studies on the effect of vitamin D in asthmatic patients with obesity found that FEV_1 and FRC were lower among vitamin D deficient OA children than their sufficient counterparts, and total lung capacity was lower than their insufficient counterparts. Similar associations were not observed in normal-weight asthmatics and were not influenced by systemic inflammation[103].

Experimental evidence suggests an effect of the biological active form of vitamin D on multiple different processes and cell types. *In vitro* 1,25-dihydroxyvitamin D reduces the production of IgE from peripheral human B cells and increases expression of IL-10[104,105]. Moreover, serum vitamin D inversely correlates with sputum eosinophil count[91,106,107]. Interestingly, a recent study demonstrated that vitamin D exerts antiproliferative effects on PBMCs and $CD4^+$ T cells by itself, reducing cell proliferation in healthy participants as well as in obese subjects with or without asthma, and non-obese subjects[79].

Vitamin D can also prevent asthma by adjusting the effect of $CD4^+$ T cells such as Th1, Th2 and Treg cells. In the immune system, vitamin D has a complex role, high levels are associated to a decrease in the Th1 response, and it can modulate the Th2 response affecting cytokines such as IL-4, IL-5 and IL-13[93]. It also makes asthma control better by inhibiting Th17 lymphocytes related to asthma severity and low steroid responsiveness[108]. Interestingly, 1,25-dihydroxyvitamin D potently induced expression of the gene *SERPINA1*, encoding the anti-protease α-1-antitrypsin. α-1-antitrypsin promotes anti-inflammatory IL-10 synthesis in other immune cell populations[109]. Evidence exists that 1,25-dihydroxyvitamin D controls synthesis of the anti-inflammatory cytokine IL-10, with positive correlations seen *in vivo*[90.110]. Vitamin D has also been shown to induce

Treg cell differentiation and IL-10 secretion that helps attenuate the airway smooth muscle cell hypertrophy which underlies severe asthma pathophysiology[90].

Weight loss and vitamin D levels

Buscemi et al.[111] confirmed that patients with obesity have lower vitamin D levels that normalize after significant weight loss induced by a low-calorie ketogenic diet, supporting the hypothesis that vitamin D is stored in the adipose tissue and released following weight loss. Another study found that weight loss through bariatric surgery was also associated with an increase in vitamin D serum levels in both obese and OA subjects[79].

Furthermore, vitamin D deficiency was investigated in a meta-analysis of 12 prospective studies of 1285 subjects with obesity after bariatric surgery, who received vitamin D supplementation[112]. Vitamin D supplementation was associated with significant improvement in vitamin D levels one year after bariatric surgery, independently of study design, baseline levels, weight loss and vitamin D dosage. Also, vitamin D deficiency decreased from 54% preoperatively to 31% one year postoperatively[10]. The effect of bariatric surgery on vitamin D status is extremely difficult to be evaluated, due to the great variability in vitamin D supplementation strategy after surgery.

Vitamin D and glucocorticoids

Vitamin D alters the anti-inflammatory action of glucocorticoids. Both steroid hormone receptors and vitamin D receptors belong to the nuclear receptor superfamily. Given the structural similarities of steroid hormone molecules and their receptors, their co-localization in cells, and similar mechanisms on gene regulation and signalling, it is possible that cross-talk between these molecules affects glucocorticoid function and glucocorticoid response[3].

Several reports have shown that a low level of serum vitamin D can lead to a reduced glucocorticoid response and, consequently, a higher demand of daily doses of glucocorticoids[89,90,92]. Moreover, it has been suggested that receiving high doses of 1,25-dihydroxyvitamin D as an add-on therapy taken at monthly intervals may significantly decrease the requirement for glucocorticoid[113] and subsequently enhance the glucocorticoid response[114]. A small prospective study of children with asthma showed that vitamin D added on budesonide treatment reported less number of respiratory infections including asthma exacerbations than the steroid treatment alone[115]. Another epidemiological study in children showed that higher vitamin D levels were associated with lower use of ICS as well as leukotriene antagonists. Moreover, higher levels were also associated with low total IgE levels and blood eosinophil count[116]. A recent study found a negative correlation between the antiproliferative effects of glucocorticoids with vitamin D serum levels. Obese patients with vitamin D deficiency levels were those with the poorest antiproliferative response to glucocorticoids[79].

In addition to the *in vivo* clinical studies illustrating a glucocorticoid-sensitizing effect of vitamin D, evidence also exists *in vitro*

studies. The interaction of vitamin D with GR is not clearly understood, but studies show that vitamin D has steroid-sparing effects enhancing glucocorticoid responsiveness by increasing its anti-inflammatory activity[3,117]. A significantly lower concentration of glucocorticoids was required to suppress pro-inflammatory cytokine production by PBMCs in the presence of vitamin D[117]. Furthermore, vitamin D is capable of potentiating the anti-proliferative effects of glucocorticoids reducing the dexamethasone IC_{50} value and, subsequently, cells became more sensitive to glucocorticoid's action[79]. These suggest that vitamin D may enhance glucocorticoid responsiveness resulting in a lower dose of glucocorticoid required to reduce inflammation, thereby reducing glucocorticoid-mediated side effects[79,117].

In patients with glucocorticoid-resistant asthma, there appear to be defects in glucocorticoid-induced gene transcription of anti-inflammatory mediators such as IL-10 and MKP-1. In an *in vitro* study, PBMCs isolated from asthmatic subjects were treated with dexamethasone alone and dexamethasone with vitamin D. Enhanced induction of MKP-1 and IL-10 was seen in dexamethasone with vitamin D treatment group as compared to dexamethasone alone treatment group[118]. Moreover, the hormone increases the expression of MKP-1 with some differences between obese and non-obese subjects, a finding that suggests that the efficacy of vitamin D to increase dexamethasone-induction of anti-inflammatory genes is more pronounced in subjects with obesity[79].

Moreover, Xystrakis et al.[119] showed that adding 1,25-dihydroxyvitamin D to $CD4^+$ T cells culture or supplementing steroid refractory asthmatics with 1,25-dihydroxyvitamin D restored the dexamethasone induction of IL-10. A proposed mechanism for this is that vitamin D can overcome the downregulation of the glucocorticoid receptor by dexamethasone[120]. They concluded that supplementation of vitamin D may increase therapeutic response to glucocorticoid in glucocorticoid-resistant asthma[119].

Asthmatic patients synthesized much higher levels of IL-17A and IL-22 than non-asthmatic control subjects, with patients with steroid-resistant asthma expressing the highest levels of IL-17A. Glucocorticoids did not inhibit IL-17A cytokine expression in patients and, in contrast, enhanced its production in cell cultures from control subjects. Treatment with 1,25-dihydroxyvitamin D with or without dexamethasone significantly reduced both IL-17A and IL-22 levels[118,121,122]. Chambers et al.[123] found that oral vitamin D improved dexamethasone-induced IL-10 production *in vitro* and suppressed IL-17A production. Human studies reveal that 1,25-dihydroxyvitamin D diminished the production of IL-17A via modulation of the VDR pathway[120,122,124]. Cross-talk between vitamin D and glucocorticoids is represented in figure 3.

More research is needed to understand the OAS and its different phenotypes. Good clinical practice for respiratory physicians should include assessment of anthropometric and metabolic measurements in all patients with asthma, in order to accurately identify other phenotypes inside of the complexity of OAS. A multidisciplinary approach has a key role in the treatment of these patients (Fig. 4)[125].

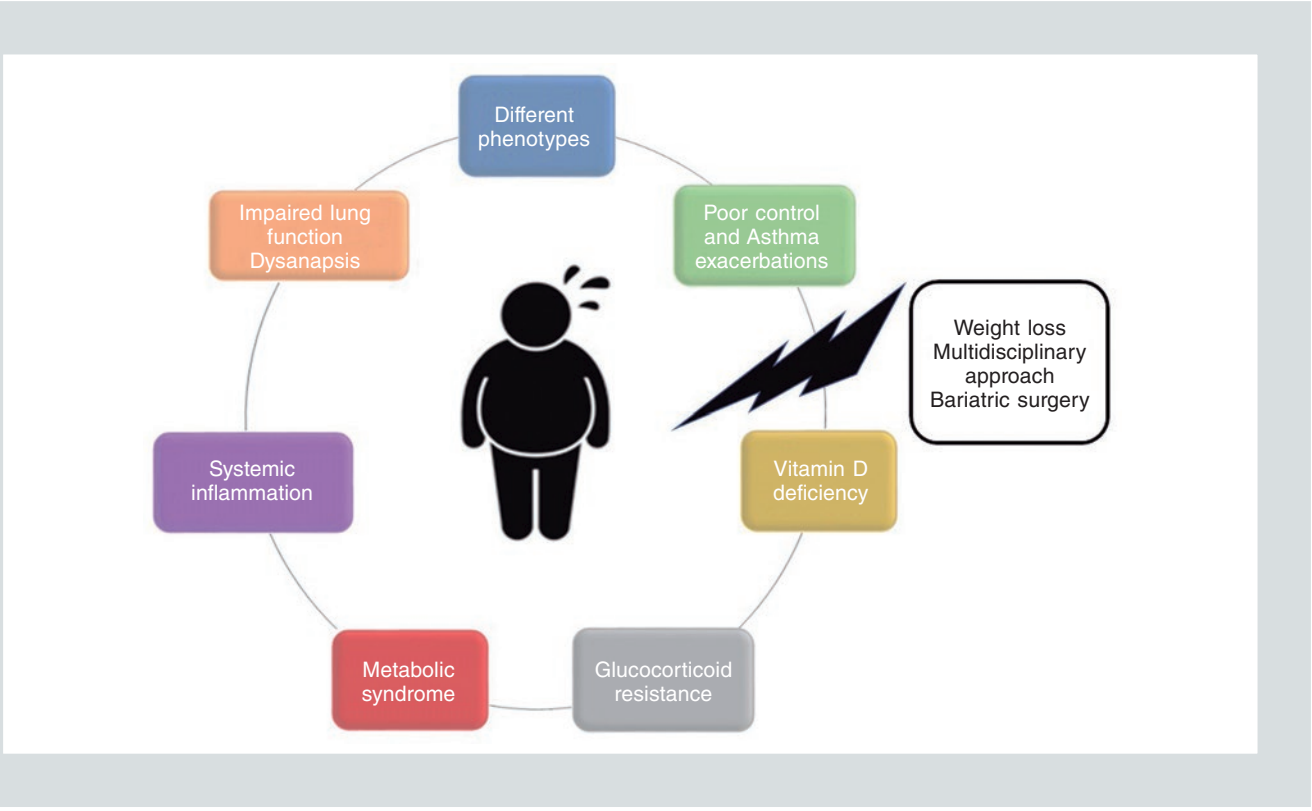

Figure 4. Complexity of the obese asthma syndrome (OAS). Multidisciplinary approach (respiratory physicians, endocrinologists, dieticians, etc.) is the key to break the pathological circle present in these patients.
Adapted from figure 1 in reference 125.

CONCLUSIONS

There has been much speculation and debate regarding the role of obese-related low-grade systemic inflammation as a potentiating factor for systemic and airway inflammation in patients with OAS in order to explain why patients with this association frequently present a severe disease, resistant to glucocorticoid treatment. However, the scientific evidence supporting this hypothesis is very scarce and inconsistent. In this review, we found evidence of partially differentiated systemic inflammation in asthma and obesity. We summarized contributions that may help to better understand the links between obesity and poor response to ICS in adults with obesity-associated asthma that support the role of obesity in ICS hyporesponsiveness and demonstrate the efficacy of weight loss to improve asthma symptoms and lung function. This effect can be, at least in part, due to the recovered anti-inflammatory response to glucocorticoids. Vitamin D supplementation in asthma patients with obesity and with vitamin D deficiency may contribute to achieve asthma control by improving ICS efficacy. Bariatric surgery is the most effective and sustained long-term treatment of severe obesity. Weight reduction significantly improves systemic and adipose tissue inflammatory activity levels and has been associated with a marked improvement in reducing antiproliferative effects of glucocorticoids in subjects with obesity.

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