REVIEW ARTICLE

Asthma and comorbidities: recent advances

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ABSTRACT

Asthma is usually associated with pulmonary and extrapulmonary comorbidities that are more common in patients with severe asthma than in those with mild-to-moderate illness or in the general population. These comorbidities may affect the clinical intensity and severity of asthma and, as a result, increase health care costs related to its therapy. On the other hand, their recognition and appropriate treatment appear to improve asthma outcomes while optimizing therapy by preventing overtreatment. Comorbid conditions such as gastroesophageal reflux disease, allergic rhinitis, obesity, depression, diabetes mellitus, and cardiovascular disease are commonly known, though their prevalence varies significantly between studies; however, many more comorbidities may remain undiagnosed and only be discovered in an experienced specialized environment. Unfortunately, the pathogenetic pathways linking asthma and many comorbidities are still unknown, which explains why they may often be misdiagnosed as diseases related to asthma treatment. Nevertheless, asthma and comorbid conditions often have common risk factors, and some evidence suggests that they share inflammatory pathways which exacerbate asthma. Inflammation was shown to play an essential role in the onset and development of various comorbidities. The role of systemic inflammation in asthma, on the other hand, remains unknown. Understanding the mechanism(s) that link(s) asthma and its concomitant disorders is critical for developing an effective treatment strategy. This review examines the epidemiology, pathophysiology, treatment suggestions, and significant knowledge gaps of these comorbidities.

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Introduction The term "comorbidities" can refer to diseases that develop coincidentally, although it is mainly used to denote 2 illnesses that impact one another.[1] Asthma is frequently accompanied by various comorbidities that influence its clinical intensity, severity, or care.[2] Each additional comorbidity is associated with a clinically significant decrement in quality of life (QoL).[3] However, it can be challenging to distinguish a comorbidity from a coexisting condition. The difference between these 2 entities is that the former contributes to the pathophysiology of asthma and leads to its exacerbations, while the latter does not. In any case, both must be appropriately identified and treated.[2]

Several population-based retrospective studies using health administrative data found that asthmatic patients had considerably higher rates of comorbidities.[4-7] They can be either pulmonary[4,5] or extrapulmonary[4,5] in nature, and are more common in severe asthma patients than in those with mild-to-moderate disease or in the general population.[4,7] The prevalence of comorbidities in asthmatic patients varies between studies but it is high mainly in asthmatic women of older age, former smokers, and patients with asthma who are prednisone-dependent.[8]

These findings highlight the need for more extensive research into the origins of the problem, actual influence of comorbidities on the natural history and severity of asthma, mechanisms by which they may affect asthma, and implications for asthma therapy.[9]

Respiratory tract/pulmonary comorbidities Respiratory tract/pulmonary comorbidities specifically affect the upper and middle/lower respiratory tract. Obstructive sleep apnea (OSA), allergic rhinitis, chronic rhinosinusitis, nasal polyposis, and vocal cord dysfunction (VCD)/inducible

laryngeal obstruction are upper respiratory tract disorders associated with asthma.[4] Dysfunctional breathing, chronic obstructive pulmonary disease (COPD), and bronchiectasis are comorbidities that specifically affect the middle/lower respiratory tract.[5]

Upper respiratory tract comorbidities **Obstructive sleep apnea** OSA is common in obese individuals with severe asthma and leads to more severe disease and poor asthma control.[7,10] The prevalence of OSA can reach up to 90% in severe asthma.[4] However, the interplay of the 2 entities is still not fully understood. Increased vagal tone leading to airway hyperresponsiveness (AHR) and recurrent oxidative stress at the bronchial level via hypoxia and hyperoxygenation are 2 mechanisms that may contribute to bronchoconstriction.[4] There is compelling evidence that continuous positive airway pressure and adenotonsillectomy, the first-line treatments for OSA in adults and children, improve asthma control.[10] However, it is unknown how asthma medication affects OSA in people with both disorders.

Allergic rhinitis Most patients with asthma have symptoms of seasonal or perennial allergic rhinitis.[4,9] Therefore, some consider the simultaneous presence of allergic rhinitis and asthma as a single disorder referred to as combined asthma and allergic rhinitis syndrome, which predominantly manifests as a type 2 (T2) immune response.[11]

Asthma and allergic rhinitis share similar triggers and pathophysiology, characterized by similar inflammatory cell infiltrates.[12] The upper and lower respiratory tracts have the same anatomical, functional, pathogenic, clinical, and immunological features, including the same lymphoid network, thus reacting to airborne allergens by activating similar effector cells. Asthma and allergic rhinitis are both immunoglobulin (Ig) E–mediated allergies that are induced by comparable allergens and share some inflammatory and pathophysiological pathways. Other mechanisms of the nose--lung interaction have been proposed, including autonomic imbalance via changes in neural tone to effector tissues.[12] For example, neuronal stimulation in the nose can result in the release of cholinergic neurotransmitters and contraction of the airway smooth muscle (ASM).[12] Also, neuropeptide release, interaction with cellular recruitment, increased lower airway exposure to airborne contaminants from mouth breathing, and increased demand for conditioning of the inspired air could play a role in the pathogenesis of both disorders.[12] In any case, examination of IgE polysensitization to multiple aeroallergen components revealed common IgE sensitivity to pollen and indoor allergens in asthma and rhinitis rather than to pollen allergens in rhinitis alone.[13]

The prevalence of allergic rhinitis in asthmatics is similar regardless of asthma severity. For example, in the U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes) cohort, allergic rhinitis was present in 55% of severe asthma patients and 60% of those with non-severe asthma.[14] The SAPALDIA study showed similarities in the inflammatory pattern of asthma and allergic rhinitis, in which eosinophils and T-lymphocytes are the predominant cells.[15] However, rhinitis is also common in nonallergic asthma.[16] Individuals with allergic rhinitis who are sensitized to perennial allergens are significantly more likely to develop asthma than individuals who are sensitized to seasonal allergens.[17]

Adequate therapy with inhaled corticosteroids and/or second-generation antihistamines in patients with asthma and allergic rhinitis is critical for lowering the risk for occurrence of acute asthma exacerbations.[16]

Chronic rhinosinusitis and nasal polyposis The incidence of chronic rhinosinusitis among asthma patients is believed to be between 22% and 45%.[16] Approximately 20% of patients with chronic rhinosinusitis have nasal polyposis.[18] Chronic rhinosinusitis with nasal polyposis (CRSwNP) is frequently associated with asthma and allergic rhinitis but the cellular and molecular mechanisms that contribute to the clinical symptoms are not fully understood.[19] The presence of chronic rhinosinusitis increases the incidence of exacerbations and reduces symptom control and QoL in asthmatic patients.[20]

Bronchoconstriction often accompanies sinusitis, presumably due to reflexes controlled at the pharyngeal level through extra-thoracic receptors.[4] Chronic rhinosinusitis with and without nasal polyps may be related to allergic and nonallergic causes and may increase the risk of aspirin-induced asthma in individuals with late--onset asthma.[4] Furthermore, patients with severe asthma and CRSwNP are given oral corticosteroids (OCS) on a regular basis, which puts them at a significant risk of OCS-related side effects.[21] CRSwNP may also be associated with other comorbidities of asthma, such as depression, obesity, and cardiovascular disease.[20,22]

In severe asthma, surgery or medical treatment of chronic rhinosinusitis improves asthma management and QoL by decreasing airway obstruction.[4] In addition, current biological therapy with anti–interleukin (IL)-4, IL-5, and IL-13 monoclonal antibodies should also be used.[23]

Vocal cord dysfunction/inducible laryngeal obstruction VCD, now referred to as inducible laryngeal obstruction,[24] is a syndrome characterized by aberrant adduction of the vocal cords during inspiration, resulting in variable blockage of the extra--thoracic airway. It is a confounder of asthma and may erroneously lead to the diagnosis of hard-to--treat asthma.[25]

The prevalence of inducible laryngeal obstruction can vary from 19% to 50%.[4] VCD can be caused by occupational, chemical, and physical irritants and postnasal drip, gastroesophageal reflux disease (GERD), and viral upper respiratory

tract infections.[4] In addition, patients with VCD are more likely to have GERD, rhinitis, and experience anxiety and sadness.[4] Exercise can often induce a laryngeal obstruction.[5]

Patients with VCD often complain of attacks of dyspnea with a defined onset and end point that do not respond to bronchodilators used to prevent or relieve symptoms.[5] Inspiratory stridor or a sense of air hunger are also frequently observed. Individuals with exercise-induced laryngeal obstruction often experience symptoms at the highest level of exertion. Outside the abovementioned episodes, basic physiological tests, such as spirometry and bronchodilator tests, are usually normal.[5] Flow volume loops often demonstrate flattening of the inspiratory curve after a methacholine challenge test. However, the specificity of this finding for VCD is limited. Laryngoscopy is the usual diagnostic method for VCD, although it may show false negative results when conducted during an interval without exacerbations.[4] Although VCD is difficult to diagnose, it should be considered when patients have chronic wheezing at rest after utilizing inhaled bronchodilators.

Since some symptoms of VCD overlap with those of asthma, its detection and treatment may reduce the risk of hospitalization, overmedication, and unnecessary health care costs.[26] Many athletes with confirmed exercise-induced laryngeal obstruction utilize asthma medication, often despite negative asthma testing, and few claim that the therapy relieves their respiratory problems during high-intensity exercise.[27] Therefore, exertional respiratory issues that do not respond to asthma medication should prompt diagnostics for exercise-induced laryngeal obstruction in athletes.

Antimuscarinic agents were shown to be beneficial in small case series and are being studied in randomized trials.[5] In addition, supraglottoplasty, a surgical procedure used to treat laryngomalacia that involves removing or modifying obstructive tissue to promote greater airway stability and patency, is sometimes suggested for obstructions limited to the supraglottic structures.[5] Speech therapy is considered the cornerstone of VCD treatment. Finally, several behavioral treatment techniques are mentioned, including visual biofeedback during the VCD episodes, inspiratory muscle training, and behavioral health / performance psychology intervention.[5]

Middle/lower respiratory tract comorbidities

Dysfunctional breathing The term "dysfunctional breathing" refers to a group of disorders in which there is a persistent shift in the biomechanical respiratory rhythm that causes pulmonary and extrapulmonary symptoms[5] which can lead to mental discomfort.[28] In patients with asthma, the incidence of dysfunctional breathing is about 30%[5] but in the population with severe asthma, it is 44%.[4] The most common symptoms are dyspnea (at rest and during exercise), chest tightness, chest pain, excessive yawning, deep sighing, and hyperventilation.[5] They occur in the absence of an organic abnormality and often despite normal lung function. As these symptoms can mimic or be mistaken for those of asthma, they can lead to misdiagnosis of asthma and even overtreatment.[5] However, dysfunctional breathing does not respond to asthma therapy.[5] Nevertheless, AHR may result from dysfunctional breathing because hyperventilation, promoting hypocapnia, can lead to increased airway resistance in asthmatics.[4] In addition, stress may cause bronchoconstriction directly via vagal stimulation or increase airway caliber sensitivity in susceptible individuals.[28]

Asthmatics with coexisting dysfunctional breathing have poorer asthma control and lower QoL than people with asthma alone.[4] Women are at a higher risk, and asthmatic patients with dysfunctional breathing are also more likely to have other comorbid conditions such as sinonasal symptoms, anxiety, depression, obesity, and frequent acute asthma episodes.[5,29]

Chronic obstructive pulmonary disease There is a large group of asthmatic patients, commonly smokers with severe asthma, who have fixed airway obstruction, primarily because of airway remodeling in addition to a neutrophilic pattern, and in this manner resemble those with COPD. On the other hand, there are many COPD patients with good reversibility of airway obstruction and increased eosinophil counts who, as a consequence, can be confused with asthmatic patients.[30] Furthermore, it is widely recognized that there are patients, especially elderly, who present with features of both illnesses. The presentations of asthma and COPD can converge and mimic each other, making it difficult to diagnose these patients with either condition.[31]

The interactions between the cellular and molecular pathways of the 2 disorders are complicated and appear to go beyond the primary additive impact. Therefore, the coexistence of asthma and COPD in the same patient was recognized as a separate entity labelled as asthma-COPD overlap (ACO).[32] The prevalence of ACO among patients with asthma ranges from 3.2% to 51.4%, with a pooled prevalence of 26.5%.[33] T2 inflammation is elevated in people with ACO, which is related to higher reversibility of airflow obstruction and improved responsiveness to inhaled corticosteroids.[32] On the other hand, individuals with ACO have worse diffusion capacity and higher neutrophil and IL-6 concentrations as compared with nonsmokers. However, the 2021 strategy report of the Global Initiative for Chronic Obstructive Lung Disease stated that "we no longer refer to asthma-COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders, although they may (...) coexist in an individual patient. If a concurrent diagnosis of asthma is suspected, pharmacotherapy should primarily follow asthma guidelines, but pharmacological and nonpharmacological approaches may also be needed for their COPD."[34]

Bronchiectasis Bronchiectasis, which is usually thought to be the result of uncontrolled long-term asthma,[35] is more common in older people and may be related to smoking history.[36] The mean prevalence of bronchiectasis in asthma patients is 36.6%.[36] These patients have a lower ratio of forced expiratory volume in 1 second to forced vital capacity and more frequent exacerbations than those with asthma alone, with no significant difference in sex, asthma duration, or serum IgE levels between asthmatic patients with and without bronchiectasis.

Uncontrolled bronchial inflammation likely causes increases in mucus production and local mucosal damage, culminating in anatomical abnormalities typical of bronchiectasis.[35] There is evidence that neutrophilic airway inflammation in asthmatic patients can cause epithelial damage[37] and that imbalances between proteases (particularly neutrophil elastase) and antiproteases can even induce lung tissue damage.[38] This pathological scenario is exacerbated by altered mucociliary clearance, leading to further injury and airway remodeling.[39] In addition, recurrent airway infections and increased bronchial secretions can lead to airway limitation which can exacerbate or worsen underlying asthma symptoms.[40]

Bronchiectasis associated with asthma has at least 2 phenotypes: eosinophilic bronchiectasis and chronic infectious bronchiolitis / bronchiectasis.[41] A direct link between T2 inflammation and bronchiectasis cannot often be ruled out or confirmed.[42] Certainly, eosinophils can cause damage to the bronchial tissue through degranulation and the production of enzymes such as eosinophil-derived neurotoxin, eosinophil cationic protein, eosinophil peroxidase, and major basic protein. It has been suggested that this damage induces the production of alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin, by bronchial epithelial cells.[42] The alarmins, in turn, activate type 2 innate lymphoid cells to produce IL-5, IL-4, and IL-13, resulting in a vicious cycle with further recruitment and activation of eosinophils, mucus production, and the development of subepithelial fibrosis with airway remodeling. On the other hand, IL-17 and tumor necrosis factor-α (TNF-α), which are major mediators in neutrophilic airway inflammation, enhance ASM hyperresponsiveness to contractile agonists,[41] which may contribute to airway constriction. Furthermore, when activated with lipopolysaccharide, neutrophil-derived exosomes increase ASM cell proliferation.[41] Bronchiectasis has also been documented as a long-term consequence in asthma patients who had bronchial thermoplasty.[5]

Long-term macrolide therapy is well tolerated and successful in the treatment of exacerbation-prone noneosinophilic asthma, and it should be considered when both conditions overlap.[4] In addition, biologics that target T2 inflammation may be considered in patients with bronchiectasis and severe asthma.[43]

Extrapulmonary comorbidities GERD, cardiovascular disease, obesity, diabetes mellitus, and anxiety / depression are the most frequent extrapulmonary comorbidities of asthma.[9]

Gastroesophageal reflux disease The abnormal respiratory physiology of patients with asthma facilitates the occurrence of GERD.[9,14] The respiratory obstruction may cause negative pleural pressures which increase the pressure gradient between the chest and abdominal cavity and promote reflux. On the other hand, GERD can cause asthma symptoms directly through its effects on AHR, and indirectly through aspiration-induced inflammation.

Indeed, the microaspiration of stomach acid can cause airway constriction either directly by activating a vagal response that promotes bronchoconstriction, or indirectly by inducing chronic inflammatory changes that ultimately contribute to increased airway responsiveness. Exposure of the bronchial epithelial cells to a mixture of pepsin, acid pH, and bile acids was found to induce structural disruption, increased permeability, IL-33 production, inflammatory mediator release, and alterations in the gene expression for a variety of biological processes.[44] These results imply that GERD may play a role in increasing the exposure of the subepithelial airway mucosa to allergens and pathogenic microorganisms, increasing the likelihood of inflammation and exacerbations. However, it was suggested that a shared component, including emotional disorders, rather than a causal relationships may be significant.[45] Therefore, 2 possible mechanisms of action have been proposed: mediation, in which having an atopic disease increases the risk of depression, anxiety, or neuroticism which then trigger and exacerbate GERD; or a common cause, in which having depression, anxiety, or neuroticism increases vulnerability to developing or reporting both atopic diseases and GERD.

In patients with mild-to-moderate asthma, the prevalence of GERD is 21%, while in patients with severe asthma, it ranges from 46% to 63%.[4] GERD has been linked to poor symptom management and is a risk factor for severe asthma exacerbations.[4]

The Global Initiative for Asthma strategy indicates that symptomatic reflux should be treated.[46] Antisecretory drug treatment is based on proton pump inhibitors (PPIs). Studies analyzing the impact of PPI treatment on asthma show conflicting results. A meta-analysis documented little impact on morning peak expiratory flow in asthmatic patients with symptomatic GERD.[47] In the case of uncontrolled asthma and in the absence of clinical symptoms of GERD, there is no reason to administer systematic treatment with PPIs.[46]

Bronchodilators, including β-agonists and methylxanthine, may reduce the lower esophageal sphincter tone, thereby promoting acid reflux and creating a potentially vicious circle.[48] Anticholinergic drugs not only impair lower esophageal

sphincter function, but also other gastrointestinal processes implicated in the etiology of reflux.[48]

Evidence supporting the efficacy of surgery for adults with asthma and GERD, as well as evidence in the pediatric population, is currently insufficient.[49]

Cardiovascular disease Clinical evidence suggests a strong link between cardiovascular disease (CVD) and asthma morbidity.[9] Asthmatics have a 42% higher risk of CVD than individuals without asthma.[50] However, CVD is more frequent in patients with difficult-to-control asthma than in those with more treatable disease.[51] We were unable to identify a clear association of asthma with acute or previous myocardial infarction;[9] however, a higher risk of ischemic heart disease appears to be present only in those over 53 years of age.[52] Furthermore, only people with asthma who report allergies have an elevated risk of coronary heart disease.[53] Asthma and CVD appear to have stronger links in women than in men.[9] Although the strength of association is low, hypertension is the most common cardiovascular comorbidity found in patients with severe asthma.[9] CVD has been shown to affect outcomes in patients with asthma, with heart failure playing a prominent role in the development of edema-induced bronchoconstriction.[54]

Experimental data indicate that systemic inflammation associated with asthma may impair cardiovascular function.[9] The specific biological mechanisms that may facilitate the development of cardiovascular comorbidity remain to be fully determined. Dysregulation of cytokines, mainly IL-4, IL-6, IL-9, IL-17A, and IL-33 but also interferon-γ and TNF-α, has notable effects in both diseases, although inflammatory regulation in asthma differs from that of atherosclerosis.[55] Actually, other inflammatory cells including macrophages, monocytes, lymphocytes, neutrophils, and mast cells also participate to a great extent in the pathogenesis of both diseases, sharing similar activities.[56] The finding that only asthma with allergy is strongly related to the risk of coronary heart disease may be due to biological mechanisms such as mast cell release that connect allergy in asthma to coronary heart disease.[57] Histamine, cysteinyl leukotrienes, and platelet-activating factor, released by immunologically activated human heart mast cells, strongly influence the left ventricular function, cardiac rhythm, and coronary artery tone, exerting negative inotropic effects and inducing myocardial depression. Furthermore, cardiac mast cells produce chymase and renin which stimulate the angiotensin system locally and cause arteriolar vasoconstriction.[57] In any case, ASM proliferation is common in both AHR and atherosclerotic lesions.[56]

Asthma medications have been implicated in most cardiovascular problems in asthmatic patients.[9] Surprisingly, the UK General Practice Research Database showed that the patterns of risks of myocardial infarction were identical when short-acting β_2-agonists, long-acting β_2-agonists, and inhaled corticosteroids were used.[58] For each of these medicines, the risk of myocardial infarction increased shortly after initiation of therapy and subsequently decreased. Hazard rates were similarly higher in heavy, long-term users. The Framingham myocardial infarction risk score was strongly related to myocardial infarction incidence in persons using asthma medication. These data imply that the first presentation with symptoms like asthma (probably dyspnea) represents the occurrence of ischemic heart disease in a high proportion of cases.[9]

According to emerging evidence, a single medicine may have the same target in both disorders. Statins are the basis of CVD prevention.[6] However, a Cochrane analysis published in 2020 found that statin treatment was ineffective for asthma.[59] Nevertheless, a very recent meta-analysis of 11 RCTs and 8 observational asthma studies suggests that statins can improve asthma control and minimize exacerbations.[60] Canakinumab, an anti–IL-1β monoclonal antibody, was found to be more effective in reducing the incidence of recurrent cardiovascular events than placebo, regardless of the lipid-level reduction.[61] However, it has not been studied in RCTs on asthma.

Obesity Numerous investigations reported an important link between obesity and asthma, although the route of causality remains unknown.[9] The prevalence of asthma in overweight/obese people surpasses 50%, with a good association with the body mass index.[62] Obesity has been shown to increase the risk of asthma in women but not in men.[63] Female sex hormones may play a role in the etiology of asthma, with obesity impacting estrogen levels, which may influence the transition from a T1 to T2 response.[63]

Since obesity is a component of the metabolic syndrome, a link between the metabolic syndrome and asthma is speculated to exist.[9] Systemic inflammatory markers are higher in obesity, and adipokines generated by adipose cells, albeit marginally, are associated with asthma symptoms.[9] Proinflammatory adipokines in the circulation might cause or worsen airway inflammation and modify inflammatory pathways associated with corticosteroid-resistant asthma, contributing to AHR or asthma[9] and better responsiveness to leukotrienes modifiers.[64] Obesity may influence airway inflammation via mechanisms other than typical IgE-mediated allergy processes.[9] Classically activated (M1) and alternatively activated (M2) macrophages, which parallel T1 and T2 polarization of T cells, may coexist in different organs and have different effects on asthma and obesity. Therefore, it is plausible that M1-mediated inflammation in the adipose tissue of obese patients exacerbates the M2-mediated asthmatic inflammation of the lungs.[65] Furthermore, obesity may affect genes that regulate the production of β_2-adrenoceptors, IL-1α, insulin-like growth factor, and glucocorticoid receptors.[4] In any case, the increased tissue

mass in the chest wall and abdomen, which has direct mechanical effects on the lungs, might affect AHR or directly aggravate the symptoms of asthma.[9] Also, the relationship between obesity and asthma symptoms might be an epiphenomenon, with the underlying association attributable to comorbidities or obesity-related lifestyle factors.[9] However, regardless of all these possible links between asthma and obesity, weight loss programs and bariatric surgery should be explored in obese individuals with asthma, particularly those with poor disease management.[4]

Diabetes mellitus There are strong connections between asthma and type 2 diabetes mellitus (T2DM), at least in women, with a nearly doubled incidence of asthma in those with T2DM.[9] Over a mean of 11 years of follow-up, individuals with hyperglycemia or T2DM had a 43% increased risk of incident asthma.[66] Furthermore, there is a negative relationship between diabetes severity (as characterized by illness duration and type of antidiabetic drugs) and lung function, suggesting that the lung is a target organ of diabetic harm.[67] High levels of glycated hemoglobin A_{1c} are linked to asthma-related hospitalizations and small decrements in lung function.[68] These last findings are not surprising given that high glucose concentrations cause hyperresponsiveness of human isolated bronchi and increased intracellular calcium release in cultured ASM cells via a Rho/Rho-associated kinase and myosin phosphatase targeting subunit 1-dependent pathway, implying that these critical pathways may contribute to the reduced lung function seen in diabetic patients.[69]

The molecular basis for the association between diabetes and asthma is yet to be thoroughly investigated and understood. There is growing evidence that the systemic inflammatory pathway is the common connection between airway diseases and T2DM, and several molecular mechanisms involving proinflammatory pathways and vascular inflammation have been suggested.[70] Nevertheless, the systemic component's processes remain unknown. According to scientific evidence, asthma and T2DM are linked to low-grade systemic inflammation, which may be dependent or independent of adiposity.[6,71]

As already mentioned, systemic inflammatory markers are elevated in obesity.[9] TNF-α and IL-6 promote T2 cell development and the production of cytokines such as IL-4 and IL-5, which are implicated in the usual inflammation seen in eosinophilic asthma.[6,71] These cytokines can also induce T2 cell development into T17 cells, and an obese target population with T2DM and severe neutrophilic asthma has a milieu rich in T17 cells and increased levels of IL-17. Furthermore, when TNF-α interacts synergistically with IL-6, it causes an increase in leptin and resistin circulation levels, favoring higher peripheral insulin resistance by blocking signaling through the insulin receptor, thereby increasing the risk of T2DM.[6,70,71]

The relationship between T2DM and poor lung function may also be related to insulin resistance,[70] which is more strongly associated with the risk of asthma in adults than obesity.[72] However, it is unclear whether insulin resistance is a cause of asthma or just the outcome of the activity of inflammatory mediators implicated in the pathophysiology of the disease.[71] In any case, by blocking neuronal M_2 muscarinic receptors and boosting acetylcholine release from airway parasympathetic neurons, hyperinsulinemia enhances vagally mediated bronchoconstriction.[73]

T2DM as a comorbidity may be managed using corticosteroids, which may result in a dose-dependent increase in serum glucose concentration.[74]

Currently, most pharmaceutical approaches to asthma and T2DM therapy are symptomatic and do not address the underlying causes of these disorders. However, it is reasonable to consider the treatment of systemic inflammation as a viable way of treating asthma and T2DM concurrently if they present as comorbidities. Exendin-4, a glucagon-like peptide (GLP)-1 agonist, stimulates GLP-1 receptor (GLP-1R) in human isolated bronchi and causes bronchorelaxation via the cAMP–protein kinase A pathway.[75] Furthermore, GLP-1 has been shown to improve both dysregulated arginine metabolism and advanced glycation end-product–mediated inflammation, which are frequent pathophysiologic processes in obesity and asthma.[76] Treatment with GLP-1R agonists leads to improved airway function regardless of blood glucose levels in T2DM patients with no underlying obstructive pulmonary disorders.[77] Interestingly a retrospective review of electronic medical records from an academic medical center found that participants with T2DM and asthma taking GLP-1R agonists had considerably reduced rates of asthma exacerbation than those treated with other antidiabetic drugs.[78]

Anxiety/depression There is a substantial overlap between anxiety, depression, and asthma.[9] Anxiety problems impact around 49% of individuals with severe asthma, as compared with 29% of patients with other chronic respiratory illnesses.[9] Patients with asthma and depression have a higher frequency of psychological issues[9] and a higher death rate.[79] The latter finding can be explained by the fact that concomitant depression causes poor adherence to asthma treatments and, as a result, an increased risk of disease worsening and emotional discomfort in patients.[9] IgE-mediated pathways cannot explain the link between asthma and depression.[9] However, dysregulation of the serotonin system might play a role, although data on the relationship between serotonin and asthma are conflicting.[6] Serotonin, acting on $5\text{-}HT_{2A}$ receptors, induces ASM contraction.[80] It also stimulates alveolar macrophages to secrete T2 inflammatory cytokines. There is mounting evidence that one or more independent variables, either environmental or genetic,

may influence the risk of both asthma and anxiety disorders.[81] Systemic inflammation may also play a role.[82] Frequent and high doses of systemic corticosteroids used for severe asthmatic patients may lead to neurotoxicity and cognitive deficits,[83] while oral corticosteroid usage is unlikely to be the cause of the higher risk of depression in asthma patients.[84] Since anxiety and depression can modify the perception of specific asthma symptoms,[85] psychological therapy and breathing exercises can help the patients improve their QoL and minimize the risk of overmedication, and help identify individuals with true asthma-related exacerbations.[4]

Discussion The presence of comorbid conditions complicates asthma management in all age groups and can significantly affect asthma control, the persistence of symptoms, and even the natural history of the disease. Identification and treatment of asthma comorbidities are considered essential, especially in the approach to difficult-to-control asthma. However, it has not yet been determined if management of asthma reduces the prevalence of comorbidities, whether their treatment improves asthma control, or whether the existence of comorbidity alters asthma therapy.

Further prospective studies should look at these complex issues. However, this review used an empirical approach, without trustworthy evidence concerning the link(s) between asthma and its comorbidities. Indeed, the mechanisms connecting asthma with the associated comorbidities are yet to be determined. Understanding these connections is critical for the development of an effective treatment to overcome them. However, this will not be a simple process, owing to the heterogeneity of asthma. Now, we can distinguish a wide range of asthma endophenotypes.[86] Furthermore, there is a significant overlap between these endophenotypes, making it challenging to identify a single phenotype. Due to the high variability of asthma, the existing data do not yet allow us to confirm whether a given endophenotype of asthma may be associated with a specific comorbidity and subsequently establish the probable link(s) between asthma and this comorbidity.

Recently, the interactions between atopy-related disorders (rhinitis and asthma) have been discussed.[87] Although each disorder can exist independently, the genetic proclivity to develop atopy determines their real comorbid nature. As previously stated, asthma and allergic rhinitis share similar causes and pathogenesis, as characterized by inflammatory cell infiltrates.[12] Furthermore, barrier failure, in combination with exposure to a changing environment, may contribute to the fast progression of these 2 atopic disorders. However, since upper airway disorders, including nonallergic rhinitis, are a risk factor for asthma, simultaneous involvement of the upper and lower airways may likely occur independently of IgE and perhaps also of T2 inflammation. In fact, in patients with markedly increased total serum IgE levels (>1000 kU/l), the 2 most commonly associated comorbid conditions were airway infections and rhinosinusitis.[88]

The link between upper and lower airway disease extends to COPD, implying that comorbid airway disorders are connected regardless of the etiology. In fact, nasal congestion may affect the lower airways due to impaired filtration and humidification of inspired air. In addition, challenges with cold, dry air increase lower airway resistance, and many respondents to these tests have no evidence of allergic disease. This suggests that alterations in the upper airway can cause autonomous dysregulation of the lower airways. Due to anatomical, neurological, and systemic inflammatory linkage, respiratory comorbidities may all be connected.[87]

Systemic inflammation may constitute a possible link between extrapulmonary comorbidities and asthma because it is a common phenomenon in many of these disorders, and at least in specific asthma endophenotypes.[89] Several mediators (eg, IL-6 and asymmetric dimethylarginine, which is an inhibitor of all nitric oxide synthase isoforms) have been linked to asthma and a variety of comorbidities ranging from obesity to cardiovascular and psychiatric disorders, implying that, in addition to disease-specific mediators, mediators that drive systemic inflammation may play a significant role in the cluster of diseases that are comorbidities of asthma.[89] Nonetheless, it is still unknown whether low-grade systemic inflammation has local effects on the lung parenchyma and causes or exacerbates airway inflammation. If inflammation affects the systemic circulation, anti-inflammatory therapy may minimize the incidence of comorbidities.

The function of nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation in the development of asthma and related comorbidities is becoming clearer as clinical data accumulate.[90,91] A substantial body of evidence supports the significance of reactive oxygen species and mitochondrial dysfunction in inflammasome activation, both of which are frequent in obesity, diabetes, and asthma.[92] NLRP3 then generates the caspase-1 enzyme, which converts pro–IL-1β to its proinflammatory version, IL-1β. The activation of the NLRP3 inflammasome in the lungs results in increased neutrophil infiltration and activation leading to neutrophil extracellular trap formation, worsening of asthma symptoms, reduced lung function, and increased steroid resistance.[90] These features are significant in developing innovative T2-low asthma therapies, particularly for steroid-refractory severe asthma linked with comorbidities such as obesity and diabetes, and neutrophilic inflammation. There is evidence that macrolide antibiotics, including azithromycin, may influence NLRP3 responses;[93] however, further research is warranted.

Conclusion The identification of comorbidities must become an essential component of asthma care. Furthermore, a comprehensive assessment of their impact is required to ensure that they are appropriately treated and / or controlled to reduce their influence on asthma. This scenario becomes much more problematic when the extrapulmonary comorbidities are considered, since they might significantly complicate the overall care of individuals with severe asthma. Furthermore, the pathogenetic pathways linking severe asthma and extrapulmonary comorbidities are still unknown, which explains why they may often be misdiagnosed as diseases related to asthma treatment.

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REFERENCES

1 Fuhlbrigge A, Lockey RF. Asthma and comorbid conditions. J Allergy Clin Immunol Pract. 2021; 9: 3909-3910.

2 Louis R, Satia I, Ojanguren I, et al. European Respiratory Society guidelines for the diagnosis of asthma in adults. Eur Respir J. 2022 Feb 15. [Epub ahead of print].

3 McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of chronic airway diseases. Chron Respir Dis. 2019; 16: 1479973119867954.

4 Rogliani P, Sforza M, Calzetta L. The impact of comorbidities on severe asthma. Curr Opin Pulm Med. 2020; 26: 47-55.

5 Gibson PG, McDonald VM, Granchelli A, Olin JT. Asthma and comorbid conditions-pulmonary comorbidity. J Allergy Clin Immunol Pract. 2021; 9: 3868-3875.

6 Cardet JC, Bulkhi AA, Lockey RF. Nonrespiratory comorbidities in asthma. J Allergy Clin Immunol Pract. 2021; 9: 3887-3897.

7 Gaffin JM, Castro M, Bacharier LB, Fuhlbrigge AL. The role of comorbidities in difficult-to-control asthma in adults and children. J Allergy Clin Immunol Pract. 2022; 10: 397-408.

8 Tomisa G, Horváth A, Sánta B, et al. Epidemiology of comorbidities and their association with asthma control. Allergy Asthma Clin Immunol. 2021; 17: 95.

9 Cazzola M, Segreti A, Calzetta L, Rogliani P. Comorbidities of asthma: current knowledge and future research needs. Curr Opin Pulm Med. 2013; 19: 36-41.

10 Wang R, Mihaicuta S, Tiotiu A, et al. Asthma and obstructive sleep apnoea in adults and children - an up-to-date review. Sleep Med Rev. 2022; 61: 101564.

11 Paiva Ferreira LKD, Paiva Ferreira LAM, Monteiro TM, et al. Combined allergic rhinitis and asthma syndrome (CARAS). Int Immunopharmacol. 2019; 74: 105718.

12 Stachler RJ. Comorbidities of asthma and the unified airway. Int Forum Allergy Rhinol. 2015; 5 (Suppl 1): S17-S22.

13 Siroux V, Ballardini N, Soler M, et al. The asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults. Allergy. 2018; 73: 1447-1458.

14 Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015; 46: 1308-1321.

15 Tschopp JM, Sistek D, Schindler C, et al. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. Allergy. 1998; 53: 608-613.

16 Massoth L, Anderson C, McKinney KA. Asthma and chronic rhinosinusitis: diagnosis and medical management. Med Sci (Basel). 2019; 7: 53.

17 Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004; 113: 86-93.

18 Benjamin MR, Stevens WW, Li N, et al. Clinical characteristics of patients with chronic rhinosinusitis without nasal polyps in an academic setting. J Allergy Clin Immunol Pract. 2019; 7: 1010-1016.

19 Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract. 2016; 4: 565-572.

20 Lee TJ, Fu CH, Wang CH, et al. Impact of chronic rhinosinusitis on severe asthma patients. PLoS One. 2017; 12: e0171047.

21 Canonica GW, Malvezzi L, Blasi F, et al. Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: evidences from the Severe Asthma Network Italy (SANI) registry. Respir Med. 2020; 166: 105947.

22 Chung SD, Chen PY, Lin HC, Hung SH. Comorbidity profile of chronic rhinosinusitis: a population-based study. Laryngoscope. 2014; 124: 1536-1541.

23 Ren L, Zhang N, Zhang L, Bachert C. Biologics for the treatment of chronic rhinosinusitis with nasal polyps - state of the art. World Allergy Organ J. 2019; 12: 100050.

24 Christensen PM, Heimdal JH, Christopher KL, et al. ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions. Eur Respir Rev. 2015; 24: 445-450.

25 Traister RS, Fajt ML, Whitman-Purves E, et al. A retrospective analysis comparing subjects with isolated and coexistent vocal cord dysfunction and asthma. Allergy Asthma Proc. 2013; 34: 349-355.

26 Narayan G, Narayana GK, Prabhakar K. All that wheezes are not asthma. J Emerg Trauma Shock. 2013; 6: 61-62.

27 Jansrud Hammer I, Halvorsen T, Vollsaeter M, et al. Conundrums in the breathless athlete; exercise-induced laryngeal obstruction or asthma? Scand J Med Sci Sports. 2022 Feb 3. [Epub ahead of print].

28 Connett GJ, Thomas M. Dysfunctional breathing in children and adults with asthma. Front Pediatr. 2018; 6: 406.

29 Denton E, Bondarenko J, Tay T, et al. Factors associated with dysfunctional breathing in patients with difficult to treat asthma. J Allergy Clin Immunol Pract. 2019; 7: 1471-1476.

30 Rogliani P, Ora J, Puxeddu E, Cazzola M. Airflow obstruction: is it asthma or is it COPD? Int J Chron Obstruct Pulmon Dis. 2016; 11: 3007-3013.

31 Cazzola M, Rogliani P. Do we really need asthma-chronic obstructive pulmonary disease overlap syndrome? J Allergy Clin Immunol. 2016; 138: 977-983.

32 Morissette M, Godbout K, Côté A, Boulet LP. Asthma COPD overlap: insights into cellular and molecular mechanisms. Mol Aspects Med. 2022; 85: 101021.

33 Hosseini M, Almasi-Hashiani A, Sepidarkish M, Maroufizadeh S. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. Respir Res. 2019; 20: 229.

34 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Accessed April 19, 2022.

35 García-Clemente M, Enríquez-Rodríguez AI, Iscar-Urrutia M, et al. Severe asthma and bronchiectasis. J Asthma. 2020; 57: 505-509.

36 Zhang SQ, Xiong XF, Wu ZH, et al. Clinical features of asthma with comorbid bronchiectasis: a systematic review and meta-analysis. Medicine (Baltimore). 2021; 100: e23858.

37 Chang HS, Lee TH, Jun JA, et al. Neutrophilic inflammation in asthma: mechanisms and therapeutic considerations. Expert Rev Respir Med. 2017; 11: 29-40.

38 Polverino E, Rosales-Mayor E, Dale GE, et al. The role of neutrophil elastase inhibitors in lung diseases. Chest. 2017; 152: 249-262.

39 Imam JS, Duarte AG. Non-CF bronchiectasis: orphan disease no longer. Respir Med. 2020; 166: 105940.

40 Truong T. The overlap of bronchiectasis and immunodeficiency with asthma. Immunol Allergy Clin North Am. 2013; 33: 61-78.

41 Matsumoto H. Bronchiectasis in severe asthma and asthmatic components in bronchiectasis. Respir Investig. 2022; 60: 187-196.

42 Crimi C, Campisi R, Nolasco S, et al. Type 2-high severe asthma with and without bronchiectasis: a prospective observational multicentre study. J Asthma Allergy. 2021; 14: 1441-1452.

43 Carpagnano GE, Scioscia G, Lacedonia D, et al. Severe uncontrolled asthma with bronchiectasis: a pilot study of an emerging phenotype that responds to mepolizumab. J Asthma Allergy. 2019; 12: 83-90.

44 Perotin JM, Wheway G, Tariq K, et al. Vulnerability to acid reflux of the airway epithelium in severe asthma. Eur Respir J. 2022 Jan 7. [Epub ahead of print].

45 Brew BK, Almqvist C, Lundholm C, et al. Comorbidity of atopic diseases and gastro-oesophageal reflux evidence of a shared cause. Clin Exp Allergy. 2022 Feb 7. [Epub ahead of print].

46 Global Initiative for Asthma. Global strategy for asthma management and prevention (updated 2021). http://www.ginasthma.org/. Accessed April 20, 2022.

47 Chan WW, Chiou E, Obstein KL, et al. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. Arch Intern Med. 2011; 171: 620-629.

48 Cazzola M, Rogliani P, Calzetta L, Matera MG. Bronchodilators in subjects with asthma-related comorbidities. Respir Med. 2019; 151: 43-48.

49 Kopsaftis Z, Yap HS, Tin KS, et al. Pharmacological and surgical interventions for the treatment of gastro-oesophageal reflux in adults and children with asthma. Cochrane Database Syst Rev. 2021; 5: CD001496.

50 Hekking PP, Amelink M, Wener RR, et al. Comorbidities in difficult-to--control asthma. J Allergy Clin Immunol Pract. 2018; 6: 108-113.

51 Liu H, Fu Y, Wang K. Asthma and risk of coronary heart disease: a meta-analysis of cohort studies. Ann Allergy Asthma Immunol. 2017; 118: 689-695.

52 Wee JH, Park MW, Min C, et al. Association between asthma and cardiovascular disease. Eur J Clin Invest. 2021; 51: e13396.

53 Ingebrigtsen TS, Marott JL, Vestbo J, et al. Coronary heart disease and heart failure in asthma, COPD and asthma-COPD overlap. BMJ Open Respir Res. 2020; 7: e000470.

54 Sultana RV, McKenzie DP, Fahey MT, et al. Beta-blocker use is an independent risk factor for thunderstorm asthma. Emerg Med Australas. 2019; 31: 955-960.

55 Gurgone D, McShane L, McSharry C, et al. Cytokines at the interplay between asthma and atherosclerosis? Front Pharmacol. 2020; 11: 166.

56 Liu CL, Zhang JY, Shi GP. Interaction between allergic asthma and atherosclerosis. Transl Res. 2016; 174: 5-22.

57 Triggiani M, Patella V, Staiano RI, et al. Allergy and the cardiovascular system. Clin Exp Immunol. 2008; 153 (Suppl 1): 7-11.

58 Zhang B, de Vries F, Setakis E, van Staa TP. The pattern of risk of myocardial infarction in patients taking asthma medication: a study with the General Practice Research Database. J Hypertens. 2009; 27: 1485-1492.

59 Naing C, Ni H. Statins for asthma. Cochrane Database Syst Rev. 2020; 7: CD013268.

60 Sunata K, Kabata H, Kuno T, et al. The effect of statins for asthma. A systematic review and meta-analysis. J Asthma. 2022; 59: 801-810.

61 Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017; 377: 1119-1131.

62 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007; 175: 661-666.

63 Keselman A, Heller N. Estrogen signaling modulates allergic inflammation and contributes to sex differences in asthma. Front Immunol. 2015; 6: 568.

64 Sharma N, Akkoyunlu M, Rabin RL. Macrophages-common culprit in obesity and asthma. Allergy. 2018; 73: 1196-1205.

65 van Huisstede A, Rudolphus A, Castro Cabezas M, et al. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. Thorax. 2015; 70: 659-667.

66 Brumpton BM, Camargo CA Jr, Romundstad PR, et al. Metabolic syndrome and incidence of asthma in adults: the HUNT study. Eur Respir J. 2013; 42: 1495-1502.

67 Yeh HC, Punjabi NM, Wang NY, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care. 2008; 31: 741-746.

68 Yang G, Han YY, Forno E, et al. Glycated hemoglobin A_{1c}, lung function, and hospitalizations among adults with asthma. J Allergy Clin Immunol Pract. 2020; 8: 3409-3415.

69 Cazzola M, Calzetta L, Rogliani P, et al. High glucose enhances responsiveness of human airways smooth muscle via the Rho/ROCK pathway. Am J Respir Cell Mol Biol. 2012; 47: 509-516.

70 Cazzola M, Rogliani P, Calzetta L, et al. Targeting mechanisms linking COPD to type 2 diabetes mellitus. Trends Pharmacol Sci. 2017; 38: 940-951.

71 Torres RM, Souza MDS, Coelho ACC, et al. Association between asthma and type 2 diabetes mellitus: mechanisms and impact on asthma control. A literature review. Can Respir J. 2021; 2021: 8830439.

72 Thuesen BH, Husemoen LL, Hersoug LG, et al. Insulin resistance as a predictor of incident asthma-like symptoms in adults. Clin Exp Allergy. 2009; 39: 700-707.

73 Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. Am J Respir Cell Mol Biol. 2014; 51: 251-261.

74 Rodbard HW, Bays HE, Gavin JR 3rd, et al. Rate and risk predictors for development of self-reported type-2 diabetes mellitus over a 5-year period: the SHIELD study. Int J Clin Pract. 2012; 66: 684-691.

75 Rogliani P, Calzetta L, Capuani B, et al. Glucagon-like peptide 1 receptor: a novel pharmacological target for treating human bronchial hyperresponsiveness. Am J Respir Cell Mol Biol. 2016; 55: 804-814.

76 Ojima A, Ishibashi Y, Matsui T, et al. Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of streptozotocin-induced diabetic rats by blocking advanced glycation end product-induced protein arginine methyltranferase-1 expression. Am J Pathol. 2013; 182: 132-141.

77 Rogliani P, Matera MG, Calzetta L, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. Respir Med. 2019; 154: 86-92.

78 Foer D, Beeler PE, Cui J, et al. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. Am J Respir Crit Care Med. 2021; 203: 831-840.

79 Lin P, Li X, Liang Z, Wang T. Association between depression and mortality in persons with asthma: a population-based cohort study. Allergy Asthma Clin Immunol. 2022; 18: 29.

80 Cazzola M, Matera MG, D'Amato G, Rossi F. Effects of serotonin on airways: recent developments. Allergy. 1995; 50: 1-10.

81 Roy-Byrne PP, Davidson KW, Kessler RC, et al. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry. 2008; 30: 208-225.

82 Pace TW, Mletzko TC, Alagbe O, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006; 163: 1630-1633.

83 Wolkowitz OM, Lupien SJ, Bigler ED. The "steroid dementia syndrome": a possible model of human glucocorticoid neurotoxicity. Neurocase. 2007; 13: 189-200.

84 Walters P, Schofield P, Howard L, et al. The relationship between asthma and depression in primary care patients: a historical cohort and nested case control study. PLoS One. 2011; 6: e20750.

85 Stanescu S, Kirby SE, Thomas M, et al. A systematic review of psychological, physical health factors, and quality of life in adult asthma. NPJ Prim Care Respir Med. 2019; 29: 37.

86 Cazzola M, Ora J, Cavalli F, et al. Treatable mechanisms in asthma. Mol Diagn Ther. 2021; 25: 111-121.

87 Diaz-Cabrera NM, Sánchez-Borges MA, Ledford DK. Atopy: a collection of comorbid conditions. J Allergy Clin Immunol Pract. 2021; 9: 3862-3866.

88 Wu G, Hu H, Zhang T, et al. Profiles of sensitization and comorbidity in asthma patients with markedly increased serum total IgE (>1000kU/L). Allergy Asthma Proc. 2022; 43: 124-132.

89 Kankaanranta H, Kauppi P, Tuomisto LE, Ilmarinen P. Emerging comorbidities in adult asthma: risks, clinical associations, and mechanisms. Mediators Inflamm. 2016; 2016: 3690628.

90 Williams EJ, Negewo NA, Baines KJ. Role of the NLRP3 inflammasome in asthma: relationship with neutrophilic inflammation, obesity, and therapeutic options. J Allergy Clin Immunol. 2021; 147: 2060-2062.

91 Haneklaus M, O'Neill LA. NLRP3 at the interface of metabolism and inflammation. Immunol Rev. 2015; 265: 53-62.

92 Kim SR, Kim DI, Kim SH, et al. NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation. Cell Death Dis. 2014; 5: e1498.

93 Shukla SD, Taylor SL, Gibson PG, et al. Add-on azithromycin reduces sputum cytokines in non-eosinophilic asthma: an AMAZES substudy. Thorax. 2021; 76: 733-736.