Asthma Phenotype with Metabolic Dysfunction

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INTRODUCTION

The cardinal pathologic features of asthma are chronic eosinophilic bronchitis with T helper 2 (Th2) inflammation, bronchial smooth muscle hyperplasia, easy shedding of the epithelium, the presence of mucus plug in the bronchi, and thickening of the subepithelial basement membrane. Several asthma phenotypes, such as allergic asthma, non-allergic asthma, occupational asthma, and aspirin-sensitive asthma, have been suggested. However, the pathologic features of these phenotypes are remarkably similar, and an essential element among them is type 2 inflammation by Th2 and group 2 innate lymphoid (ILC2) cells. Antibodies have been authorized by the US Food and Drug Administration (FDA) or European Medicines Agency or are supported by successful phase 3 results: anti-IgE, anti-interleukin (IL)-5, anti-IL-5 receptor, anti-IL-4Rα, and anti-thymic stromal lymphopoietin, all of which block type 2 inflammation.

Some researchers have suggested the presence of a neutrophilic asthma phenotype. Neutrophilic bronchial inflammation can be induced by respiratory viral, fungal, or bacterial infections. Recent studies have shown that the lower airway is not a sterile organ, with the presence of numerous microbiomes. In addition to microbes and infections in the airway, exposure to toxic inhalants, including air pollutions, particulate matters, smoking, and occupational irritants, can also induce neutrophilic inflammation. These exposures are ubiquitous, and the majority of asthma patients may not be plausible to avoid them. In addition, patients with asthma frequently have a respiratory comorbidity, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, nontuberculous mycobacterium infection, or diffuse panbronchiolitis, which are characterized by the presence of neutrophils in the airway. As many as 20% of patients with asthma have a comorbidity of bronchiectasis, and 20% of all patients with obstructive airway diseases exhibit the overlapping phenotype of asthma and COPD. Furthermore, the fluctuating nature of type 2 inflammation or possible spontaneous remission status of asthma phenotypes.
may lure the concept of a specific neutrophilic asthma phenotype. Although monoclonal antibodies, such as anti-tumor necrosis factor (TNF)-α or anti-IL-17, have shown partial responses, they have not met the primary endpoints of phase 3 clinical trials, suggesting the minor role of neutrophils in asthma. Moreover, they resulted in unacceptable adverse reactions in these clinical trials.

However, patients with asthma and metabolic dysfunction have additional pathogenic and pathologic features from those with Th2 inflammation. Metabolic dysfunction, typically presented as metabolic syndrome, has several important clinical features, including central obesity, insulin resistance/glucose intolerance, dyslipidemia, and vitamin D (VitD) deficiency. It is well known that asthma is difficult to treat in patients with obesity, due in part to inadequate response to inhaled corticosteroids. Recently, epidemiological studies using big data have suggested that the treatment of insulin resistance and VitD supplementation have beneficial effects on asthma management. Meanwhile, a cohort study of patients with exacerbation-prone asthma suggests that metabolic dysfunction is the key factor of asthma exacerbation. These features emphasize the role of metabolic dysfunction for the pathogenesis of asthma and the presence of an asthma phenotype with metabolic dysfunction. As the prevalence of obesity and metabolic dysfunction continue to soar globally, the gravity of these conditions on asthma is also reinforced. In this review, I summarize the recent studies on metabolic dysfunction and asthma, as well as the suggested mechanisms of asthma aggravation (Fig. 1).

**ASTHMA WITH OBESITY**

Obesity has been recognized as one of the risk factors for asthma development and exacerbation. Patients with asthma and obesity are vulnerable to asthma exacerbation by nitric oxide exposure. However, the underlying mechanisms that explain how obesity affects asthma remain obscure. One plausible hypothesis is that obesity has mechanistic effects on the lungs that result in difficulty of breathing. Obesity can increase lung elastance, thereby reducing forced expiratory volume and increasing expiratory reserve volume, peripheral airway resistance, and airway hyperresponsiveness. Additionally, obesity is the well-known risk factor for gastroesophageal reflux disease (GERD), which can make asthma control difficult. Another explanation is obesity-induced neutrophilic or pauci-inflammatory lung lesions. Adipose tissue is the largest immune organ and produces various proinflammatory mediators, such as C-reactive protein (CRP), TNF-α, transforming growth factor (TGF)-β, leptin, and IL-6. Adipose tissue-derived macrophages have been regarded as the primary source of these proinflammatory cytokines. In the absence of inflammation, 10%–35% of circulating IL-6 may come from adipose tissue, and it induces CRP production. van Huisstede, et al. showed that bariatric surgery decreased CRP from 36 mg/L to 7.1 mg/L in patients with asthma and obesity at 1 year after bariatric surgery. The causal relationship of obesity and asthma has been supported by weight reduction studies in patients with asthma and obesity. Both surgical and medical intervention studies have showed an improvement in asthma medication or symptom scores. Additionally, a cohort study of patients with exacerbation-prone asthma showed that serum IL-6 is the biomarker of asthma exacerbation, supporting the intrac-table nature of patients with asthma and obesity or metabolic dysfunction. Furthermore, an in vivo murine model of high-fat diet (HFD)-induced obesity showed the consistent feature of proinflammatory lesion in the lung. The bronchoalveolar lavage fluid of obese mice exhibits a characteristically greater number of alveolar macrophages. These macrophages can produce TNF-α, TGF-β1, and other proinflammatory media-
tors,22 which may also aggravate the type 2 inflammation.28 Moreover, obesity is associated with insulin resistance and decreased VitD levels, both of which contribute to asthma aggravation.29-31 Previously, we demonstrated that HFD-induced obesity is significantly associated with airway hyperresponsiveness and peribronchial lung fibrosis through increased insulin resistance and VitD deficiency, which contribute to enhanced TGF-β1 secretion from the bronchial epithelium.23,32

One complicating factor is the ethnic and gender differences in the diagnostic criteria of obesity. There is no globally accepted definition of obesity, and significant ethnic differences exist. The World Health Organization defines "overweight" as a body mass index (BMI) of 25.0–29.9 and "obesity" as a BMI of 30 kg/m² or greater.34 However, the Japanese Society of Obesity specifies obesity as a BMI of 25 kg/m² or greater, without suggesting the overweight criteria.35 This difference is due to population differences: approximately 10%–20% of Caucasian populations have a BMI of more than 30 kg/m², while only 2%–3% of the Japanese population have a BMI of more than 30 kg/m².35,36 Waist circumference criteria for abdominal obesity are markedly different by ethnicity and gender (Table 1).35,37 Interestingly, the waist circumference criteria for central obesity is higher in Caucasian, South Asian, and Chinese men but higher in Japanese women. Although no report has been published on the ethnic differences in the effect of obesity on asthma, these ethnic differences in obesity criteria must be considered when studying the effect of obesity on asthma.

In summary, these studies suggest that obesity can aggravate asthma through the physiologic and mechanic effects of increased elasticity of the chest wall and the lungs, as well as lung fibrosis and GERD aggravation. Additionally, obesity induces VitD deficiency, as well as secretion of proinflammatory mediators from adipose tissue. All of these factors may make it difficult to control asthma in patients with obesity. Clinical trials for weight reduction modalities on patients with asthma and obesity have consistently supported the causal relationship between obesity and asthma control.

**VITAMIN D DEFICIENCY AND ASTHMA**

VitD has been recognized as a key player in calcium and bone metabolism, but it is a pleiotropic hormone. The active form of VitD—1, 25-dihydroxyvitamin D—binds to the VitD receptor (VDR) and forms a heterodimer with the retinoid X receptor. This receptor then binds to the VitD response element in DNA to upregulate or downregulate more than 200 genes. VDRs are found in all tissues including antigen-presenting cells, such as alveolar macrophages and dendritic cells, bronchial epithelial cells, and lung fibroblasts.38,39 Many epidemiological and clinical studies have linked VitD deficiency to various respiratory diseases, such as asthma,12,40,41 chronic obstructive pulmonary disease,42 cystic fibrosis, and respiratory infections.43 Prenatal VitD deficiency may contribute to diminished tracheal and bronchial cartilage formation and then decreased airway diameter, leading to increased airway resistance.44 Additionally, VitD is important in immune regulation. Antigen-presenting cells, such as macrophages and dendritic cells, produce 1, 25-dihydroxyvitamin D from 25-hydroxyvitamin D, and have an important role in normal development of these antigen-presenting cells and antigen processing.39 VitD also enhances regulatory T-cell immunity, and through this mechanism, it may suppress Th1 and Th2 cell-induced inflammation.45 An in vivo neonatal mouse model showed that VitD deficiency aggravates eosinophilic inflammation with increased CD3+ CD4+ T1ST2+ helper cells and reduced CD4+ IL-10+ regulatory T cells in the lungs; these changes were reversed by VitD supplementation.46 Furthermore, VDRs can enhance the production of antimicrobial peptides, such as cathelicidin and β-defensin,47,48 and can prevent respiratory viral infection, which is the most important trigger factor for asthma exacerbation and a risk factor for the development of asthma. These results have led to many randomized clinical trials for VitD supplementation in VitD-deficient asthma patients; however, these trials have shown controversial results.49-51

Interestingly, obesity is a well-known risk factor for VitD deficiency. Several mechanisms have been suggested for the decreased level of VitD in obesity. At first, it was proposed that VitD is sequestered in adipose tissue52 and VitD produced in the skin by UV may be diluted with increasing fat mass.53 Additionally, obesity may decrease the expression of CYP2R1, hepatic 25-hydroxyase, which may contribute to 25-hydroxyvitamin D deficiency.54 Ramirez, et al.55 showed that VDRs are found in the respiratory epithelium and lung fibroblasts. TGF-β1 is well known as the key player in the development of lung fibrosis and airway remodeling in asthma.52 Importantly, VitD reduces TGF-β1-stimulated lung fibroblast proliferation and decreases collagen, fibronectin, and α-smooth muscle actin fibroblast production, and TGF-β1-mediated epithelial-mesenchymal transformation.56-58 Our previous study demonstrated that VitD supplementation can prevent the expression of obesity-related lung fibrosis and airway hyperresponsiveness through the suppression of RAS and TGF-β1 expression in a murine model of HFD-induced VitD deficiency.59 The mechanism of how VitD attenuates TGF-β1 signaling remains obscure. However, since VDRs can negatively regulate the profibrotic effects of TGF-β1 signaling by inhibiting phosphorylated Smad-2/3, VitD supplementation may prevent fibrosis of the lungs, skin, or other

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**Table 1. Ethnic Differences in Abdominal Obesity Criteria by Waist Circumference**

| Ethnic group          | Waist circumference (cm) | Men       | Women     |
|-----------------------|--------------------------|-----------|-----------|
| European Caucasian   | >94                      | >80       |           |
| Japanese              | >85                      | >90       |           |
| South Asian and Chinese | >90                    | >80       |           |

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INSULIN RESISTANCE AND ASTHMA

Obesity and insulin resistance are closely intermingled. Obesity is a well-known risk factor for metabolic dysfunction and type 2 diabetes. Increased free fatty acid (FFA) levels in obesity induces hepatic gluconeogenesis, followed by insulin hypersecretion from pancreas. Additionally, FFA reduces insulin sensitivity in the muscle by inhibiting insulin-mediated glucose uptake. Obesity-induced proinflammatory status results in aggravation of insulin resistance and lipolysis of triglycerides in adipose tissue, which leads to higher FFA levels and makes vicious cycle. Furthermore, obesity-induced VitD deficiency triggers insulin resistance by impairing insulin sensitivity and insulin secretion from pancreatic β-cells.

Recent epidemiological studies have shown the relationship between asthma control and anti-diabetes medications, suggesting the importance of insulin resistance in asthma pathogenesis. A big data analysis using US National Health and Nutrition Examination Survey data showed that insulin resistance further strengthens the association between obesity and asthma. Another big data analysis of nondiabetic patients with asthma showed the link between glycated hemoglobin A1c (HbA1c) levels and asthma-related hospitalization, as well as an inverse relationship between HbA1c and FEV1. Hyperinsulinemia may enhance bronchoconstriction by vagal nerve stimulation and the loss of inhibitory M3 muscarinic receptor function without any changes in smooth muscle contractility to acetylcholine. In another study evaluating the effects of insulin on bronchial smooth muscle, insulin was found to enhance extracellular matrix laminin expression and contribute to the maintenance of hypercontractility in the airway smooth muscle. Additionally, our previous study showed that insulin resistance induced by obesity can enhance TGF-β expression, lung fibrosis, and airway hyperresponsiveness in a murine model. These findings suggest that insulin resistance may attenuate the response to conventional asthma management and aggravate the severity of asthma.

Previous studies have shown the beneficial role of metformin for asthma management. In a retrospective cohort study of 1332 patients with asthma and diabetes in Taiwan, metformin use decreased asthma-related hospitalization [odds ratio (OR), -0.21] and asthma exacerbation (OR, -0.39). These results were replicated with different large databases of electronic health records. Patients with asthma and diabetes who used metformin had less emergency room visits compared to those who did not use metformin. Interestingly, this effect was independent of glycemic control and the degree of obesity. It is well known that metformin could improve insulin resistance. An in vivo study using an HFD obesity mouse model showed that metformin can suppress allergen-induced eosinophilic inflammation as well as the production of proinflammatory TNF-α, eotaxin, and nitric oxide.

A retrospective cohort study of patients with type 2 diabetes and asthma showed that glucagon-like peptide 1 receptor (GLP-1R) agonist treatment decreases the exacerbation and symptoms of asthma compared to other antidiabetic treatment modalities. This finding was preserved even after adjusting for several compounding factors, including BMI and HbA1c. These protective effects are independent of baseline and changes of BMI and serum HbA1c levels by GLP-1R agonist treatment. GLP-1 is secreted postprandially from the intestines and the central nervous system and lowers serum glucose levels through the secretion of insulin and the suppression of glucagon from pancreas. Additionally, GLP-1R agonists can induce weight loss by increasing satiety by acting to GLP-1 receptor in brain. This feature led the US FDA to approve liraglutide and semaglutide for the management of obesity.

In addition to these beneficial effects on obesity and insulin tolerance, an GLP-1R agonist can suppress allergic inflammation. GLP-1R has also been found in the respiratory epithelium. A murine model of allergic asthma showed that an GLP-1R agonist can suppress allergen-induced IL-33 and thymic stromal lymphopoietin secretions from the respiratory epithelium, as...
well as the activity of ILC2 cells. Interestingly, GLP-1R agonists can also suppress obesity–related pro-inflammation. We evaluated the effects of SGLT-2 inhibitor (empagliflozin) and GLP-1R agonist (dulaglutide) in a murine HFD-induced obesity model. Both drugs attenuated the release of obesity-related proinflammatory mediators, as well as airway hyperresponsiveness and lung fibrosis; they also had additive effects on obesity-related pathologies. These studies suggest that these agents are the promising therapeutic modality for patients with asthma and obesity.

These preclinical and retrospective big data studies have shown that some antidiabetic medications, such as metformin, and GLP-1R agonists may be helpful for the management of asthma, suggesting the causal relationship of increased insulin resistance and aggravation of asthma. However, some studies have found that these beneficial effects of GLP-1R agonist on asthma are not associated with the important confounding factors of glycemic control or obesity. Although these results may throw the possible anti-inflammatory roles of GLP-1R agonists and metformin, these data were based on a retrospective cohort and could be vulnerable to insufficiently uncontrolled confounding factors. Therefore, strict and well-designed prospective clinical studies are required before recommending these antidiabetic drugs in clinical practice.

CONCLUSION

Th2 inflammation is the most important determinant for asthma pathogenesis. However, metabolic dysfunction may aggravate asthma. Obesity, VitD deficiency, and insulin resistance are frequently intermingled, and all of them contribute to the pathogenesis of asthma phenotype with metabolic dysfunction. Various mechanisms of this phenotype on asthma aggravation have been suggested, and clinicians should consider the diverse aspects of metabolic dysfunction when treating patients with asthma.

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