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Asthma Phenotype with Metabolic Dysfunction

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Asthma is chronic eosinophilic bronchitis with the dominancy of T helper 2 (Th2) inflammation. However, patients with asthma and metabolic dysfunction have pathogenic and pathological differences from those with Th2 inflammation. Metabolic dysfunction, typically presented as metabolic syndrome, has several important clinical components including central obesity, insulin resistance or glucose intolerance, dyslipidemia, and vitamin D deficiency. Data from large epidemiological studies support the significance of these components in the control of asthma and their contribution to airway remodeling, suggesting the presence of an asthma phenotype with metabolic dysfunction. These components are quite interactive with each other, so it is difficult to reveal the individual role of each. It is well known that asthma is difficult to treat in patients with obesity, due in part to inadequate response to inhaled corticosteroids. Additionally, vitamin D deficiency and insulin resistance have been regarded as aggravating factors of asthma control and airway remodeling. Recent clinical and in vivo studies have revealed the specific mechanisms of these components, which may aggravate asthma control and airway remodeling. In this review article, I summarize the recent studies and unmet needs for patients with asthma and metabolic dysfunction.

Key Words: Asthma, metabolic dysfunction, obesity, vitamin D deficiency, insulin resistance

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.[1] The significance of type 2 inflammation has been emphasized by newly developed monoclonal antibody treatments for severe uncontrollable asthma phenotypes. Several 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,[2] 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,[3,4] nontuberculous mycobacterium infection,[5] or diffuse panbronchiolitis,[6] 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.[7] Furthermore, the fluctuating nature of type 2 inflammation or possible spontaneous remission status of asthma

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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,[8-10] 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.[11,12] Meanwhile, a cohort study of patients with exacerbation-prone asthma suggests that metabolic dysfunction is the key factor of asthma exacerbation.[13] 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).

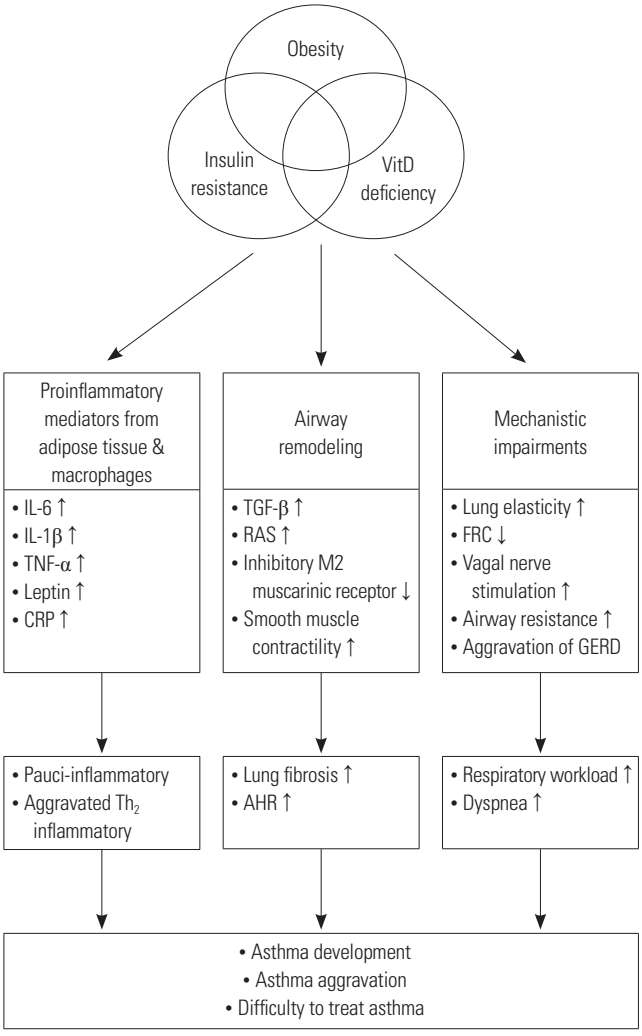

Fig. 1. Suggested mechanisms of metabolic dysfunction in patients with asthma. AHR, airway hyperresponsiveness; CRP, C-reactive protein; FRC, functional residual capacity; GERD, gastroesophageal reflux disease; RAS, renin-angiotensin system; TNF, tumor necrosis factor; VitD, vitamin D; IL, interleukin.

ASTHMA WITH OBESITY

Obesity has been recognized as one of the risk factors for asthma development and exacerbation.[14] Patients with asthma and obesity are vulnerable to asthma exacerbation by nitric oxide exposure.[15] 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.[16,17] Additionally, obesity is the well-known risk factor for gastroesophageal reflux disease (GERD),[18] which can make asthma control difficult.[19] Another explanation is obesity-induced neutrophilic[20] or pauci-inflammatory lung lesions.[21] 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.[22] Adipose tissue-derived macrophages have been regarded as the primary source of these proinflammatory cytokines.[23,24] In the absence of inflammation, 10%–35% of circulating IL-6 may come from adipose tissue,[25] and it induces CRP production.[26] van Huisstede, et al.[22] 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.[27] 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,[13] supporting the intractable 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-

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tors,[23] 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.[32,33]

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/m^2 or greater.[34] However, the Japanese Society of Obesity specifies obesity as a BMI of 25 kg/m^2 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/m^2, while only 2%–3% of the Japanese population have a BMI of more than 30 kg/m^2.[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 mechanistic 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 retinoic X receptor.

Table 1. Ethnic Differences in Abdominal Obesity Criteria by Waist Circumference[37]

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

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+ T 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 tissue[52] 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-hydroxylase, which may contribute to 25-hydroxyvitamin D deficiency.[54] Ramirez, et al.[38] 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.[55] 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.[38] 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.[33] 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

major organs.[38,56,57] Interestingly, several nonalcoholic fatty liver disease rodent experimental studies already have reported the attenuation of steatosis and liver fibrosis by VitD supplementation.[58-61] The renin-angiotensin system (RAS) may be important for lung fibrosis in obesity. The activation of RAS by VitD deficiency is a well-known phenomenon[62,63] and may contribute to fibrosis in the lungs.[64] Shi, et al.[65] showed that VitD deficiency over-activates the RAS and increases TGF-β1 expression, leading to lung fibrosis. Interestingly, COVID-19 uses angiotensin-converting enzyme 2 receptor for invading the host cell. Some investigators have suggested that VitD supplementation for the deficiency subjects may be helpful to prevent COVID-19 infection through suppression of the RAS and production of antimicrobial peptides.[66]

Considering the high prevalence of VitD deficiency in the real world,[67] clinicians should consider VitD deficiency for the management of asthma. The recommended level of serum VitD concentration for asthma patients is unclear. If the serum level of 25-hydroxyvitamin D is below 15 μg/L, parathyroid levels increase while bone density decreases. Therefore, more than 20 μg/L (50 nmol/L) of 25-hydroxyvitamin D has been recommended for maintaining bone density. However, the optimal concentration of VitD for immune regulation and the maintenance of immunological homeostasis is contested. Many guidelines have recommended maintaining 25-hydroxyvitamin D levels at more than 30 μg/L (75 nmol/L), considering the pleiotropic function of VitD.[68] Further studies are needed to determine the ideal serum concentration of VitD in patients with asthma. As the effect of VitD supplementation on asthma may require long-term administration, long-term and large-scale randomized clinical trials are required.

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.[69] Furthermore, obesity-induced VitD deficiency triggers insulin resistance by impairing insulin sensitivity[70] and insulin secretion from pancreatic β-cells.[71,72]

Recent epidemiological studies have shown the relationship between asthma control and anti-diabetes medications, suggesting the importance of insulin resistance in asthma pathogenesis.[11,73] 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.[31] 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.[11] Hyperinsulinemia may enhance bronchoconstriction by vagal nerve stimulation and the loss of inhibitory M_2 muscarinic receptor function without any changes in smooth muscle contractility to acethylcholine.[74] 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.[75] Additionally, our previous study showed that insulin resistance induced by obesity can enhance TGF-β1 expression, lung fibrosis, and airway hyperresponsiveness in a murine model.[32] 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).[76] These results were replicated with different large databases of electronic health records.[77] 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.[78]

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.[73] 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.[79,80]

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.[81] 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

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well as the activity of ILC2 cells.[82] 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.[83] 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.[73,82,83]

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.[73] 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 compounding 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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REFERENCES

1. Barnes PJ. Asthma. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine, 20e. 20th ed. New York: McGraw-Hill Education; 2018. p.1957-69.
2. Global Initiative for Asthma. Global strategy for asthma management, 2020 [accessed on 2021 August 22]. Available at: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.
3. Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, et al. Qualitative analysis of high-resolution CT scans in severe asthma. Chest 2009;136:1521-8.
4. Lee SC, Son KJ, Park HJ, Jung JY, Park SC, Jeong SH, et al. Long-term prognosis of asthma-bronchiectasis overlapped patients: a nationwide population-based cohort study. Allergy Asthma Immunol Res 2021;13:908-21.
5. Uno S, Asakura T, Morimoto K, Yoshimura K, Uwamino Y, Nishimura T, et al. Comorbidities associated with nontuberculous mycobacterial disease in Japanese adults: a claims-data analysis. BMC Pulm Med 2020;20:262.
6. Park KH, Park HJ, Lee JH, Park JW. Single center experience of five diffuse panbronchiolitis patients clinically presenting as severe asthma. J Korean Med Sci 2015;30:823-8.
7. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. Thorax 2015;70:683-91.
8. Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlén SE, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. Am J Respir Crit Care Med 2009;179:549-58.
9. Taillé C, Poulet C, Marchand-Adam S, Borie R, Dombret MC, Crestani B, et al. Monoclonal anti-TNF-α antibodies for severe steroid-dependent asthma: a case series. Open Respir Med J 2013;7:21-5.
10. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am J Respir Crit Care Med 2013;188:1294-302.
11. Yang G, Han YY, Forno E, Yan Q, Rosser F, Chen W, et al. Glycated hemoglobin A1c, lung function, and hospitalizations among adults with asthma. J Allergy Clin Immunol Pract 2020;8:3409-15.e1.
12. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol 2011;127:1294-6.
13. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, et al. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. Am J Respir Crit Care Med 2020;202:973-82.
14. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175:661-6.
15. Permaul P, Gaffin JM, Petty CR, Baxi SN, Lai PS, Sheehan WJ, et al. Obesity may enhance the adverse effects of NO2 exposure in urban schools on asthma symptoms in children. J Allergy Clin Immunol 2020;146:813-20.e2.
16. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, et al. The nonallergic asthma of obesity. A matter of distal lung compliance. Am J Respir Crit Care Med 2014;189:1494-502.
17. Al-Alwan A, Bates JH, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, et al. The nonallergic asthma of obesity. A matter of distal lung compliance. Am J Respir Crit Care Med 2014;189:1494-502.
18. Spivak H, Hewitt MF, Onn A, Half EE. Weight loss and improvement of obesity-related illness in 500 U.S. patients following laparoscopic adjustable gastric banding procedure. Am J Surg 2005;189:27-32.
19. Macgregor AM, Greenberg RA. Effect of surgically induced weight loss on asthma in the morbidly obese. Obes Surg 1993;3:15-21.
20. Schuliga M, Javeed A, Harris T, Xia Y, Qin C, Wang Z, et al. Trans-

forming growth factor-β-induced differentiation of airway smooth muscle cells is inhibited by fibroblast growth factor-2. Am J Respir Cell Mol Biol 2013;48:346-53.
21. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. Am J Respir Crit Care Med 2012;186:598-605.
22. van Huisstede A, Rudolphus A, Castro Cabezas M, Biter LU, van de Geijn GJ, Taube C, et al. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. Thorax 2015;70:659-67.
23. Kim JY, Sohn JH, Lee JH, Park JW. Obesity increases airway hyperresponsiveness via the TNF-α pathway and treating obesity induces recovery. PLoS One 2015;10:e0116540.
24. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.
25. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 1997;82:4196-200.
26. Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects. Circulation 1999;99:2221-2.
27. Eneli IU, Skybo T, Camargo CA Jr. Weight loss and asthma: a systematic review. Thorax 2007;63:671-6.
28. Dietze J, Böcking C, Heverhagen JT, Voelker MN, Renz H. Obesity lowers the threshold of allergic sensitization and augments airway eosinophilia in a mouse model of asthma. Allergy 2012;67:1519-29.
29. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013;10:e1001383.
30. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690-3.
31. Cardet JC, Ash S, Kusa T, Camargo CA Jr, Israel E. Insulin resistance modifies the association between obesity and current asthma in adults. Eur Respir J 2016;48:403-10.
32. Park YH, Oh EY, Han H, Yang M, Park HJ, Park KH, et al. Insulin resistance mediates high-fat diet-induced pulmonary fibrosis and airway hyperresponsiveness through the TGF-β1 pathway. Exp Mol Med 2019;51:1-12.
33. Han H, Chung SI, Park HJ, Oh EY, Kim SR, Park KH, et al. Obesity-induced vitamin D deficiency contributes to lung fibrosis and airway hyperresponsiveness. Am J Respir Cell Mol Biol 2021;64:357-67.
34. World Health Organization. Obesity. Preventing and managing the global epidemic: report of a WHO Consultation on Obesity. Geneva: World Health Organization; 1997.
35. Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. Circ J 2002;66:987-92.
36. Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990-1994. Int J Obes Relat Metab Disord 1998;22:684-7.
37. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
38. Ramirez AM, Wongtrakool C, Welch T, Steinmeyer A, Zügel U, Roman J. Vitamin D inhibition of pro-fibrotic effects of transforming growth factor beta1 in lung fibroblasts and epithelial cells. J Steroid Biochem Mol Biol 2010;118:142-50.
39. Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, Eliopoulos AG, et al. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol 2003;170:5382-90.
40. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol 2010;125:995-1000.
41. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med 2010;181:699-704.
42. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2012;156:105-14.
43. Bergman P, Norlin AC, Hansen S, Rekha RS, Agerberth B, Björkhem-Bergman L, et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. BMJ Open 2012;2:e001663.
44. Saadoon A, Ambalavanan N, Zinn K, Ashraf AP, MacEwen M, Nicola T, et al. Effect of prenatal versus postnatal vitamin D deficiency on pulmonary structure and function in mice. Am J Respir Cell Mol Biol 2017;56:383-92.
45. Barrat FJ, Cua DJ, Boonstra A, Richards DF, Crain C, Savelkoul HF, et al. In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. J Exp Med 2002;195:603-16.
46. Vasiliou JE, Lui S, Walker SA, Chohan V, Xystrakis E, Bush A, et al. Vitamin D deficiency induces Th2 skewing and eosinophilia in neonatal allergic airways disease. Allergy 2014;69:1380-9.
47. Heulens N, Korf H, Mathyssen C, Everaerts S, De Smidt E, Dooms C, et al. 1,25-dihydroxyvitamin D modulates antibacterial and inflammatory response in human cigarette smoke-exposed macrophages. PLoS One 2016;11:e0160482.
48. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007;179:2060-3.
49. Forno E, Bacharier LB, Phipatanakul W, Guilbert TW, Cabana MD, Ross K, et al. Effect of vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels: the VDKA randomized clinical trial. JAMA 2020;324:752-60.
50. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med 2017;5:881-90.
51. Pfeffer PE, Hawrylowicz CM. Vitamin D in asthma: mechanisms of action and considerations for clinical trials. Chest 2018;153:1229-39.
52. Pramyothin P, Biancuzzo RM, Lu Z, Hess DT, Apovian CM, Holick MF. Vitamin D in adipose tissue and serum 25-hydroxyvitamin D after roux-en-Y gastric bypass. Obesity (Silver Spring) 2011;19:2228-34.
53. Drincic A, Fuller E, Heaney RP, Armas LA. 25-Hydroxyvitamin D response to graded vitamin D_3 supplementation among obese adults. J Clin Endocrinol Metab 2013;98:4845-51.
54. Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, et al. Obesity decreases hepatic 25-hydroxylase activity causing low serum 25-hydroxyvitamin D. J Bone Miner Res 2019;34:1068-73.

https://doi.org/10.3349/ymj.2022.63.1.1

55. Ojiaku CA, Yoo EJ, Panettieri RA Jr. Transforming growth factor β1 function in airway remodeling and hyperresponsiveness. The missing link? Am J Respir Cell Mol Biol 2017;56:432-42.
56. Zerr P, Vollath S, Palumbo-Zerr K, Tomcik M, Huang J, Distler A, et al. Vitamin D receptor regulates TGF-β signalling in systemic sclerosis. Ann Rheum Dis 2015;74:e20.
57. Tzilas V, Bouros E, Barbayianni I, Karampitsakos T, Kourtidou S, Ntassiou M, et al. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. Pulm Pharmacol Ther 2019;55:17-24.
58. Beilfuss A, Sowa JP, Sydor S, Beste M, Bechmann LP, Schlattjan M, et al. Vitamin D counteracts fibrogenic TGF-β signalling in human hepatic stellate cells both receptor-dependently and independently. Gut 2015;64:791-9.
59. Zhang H, Shen Z, Lin Y, Zhang J, Zhang Y, Liu P, et al. Vitamin D receptor targets hepatocyte nuclear factor 4α and mediates protective effects of vitamin D in nonalcoholic fatty liver disease. J Biol Chem 2020;295:3891-905.
60. Abramovitch S, Dahan-Bachar L, Sharvit E, Weisman Y, Ben Tov A, Brazowski E, et al. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. Gut 2011;60:1728-37.
61. Dong B, Zhou Y, Wang W, Scott J, Kim K, Sun Z, et al. Vitamin D receptor activation in liver macrophages ameliorates hepatic inflammation, steatosis, and insulin resistance in mice. Hepatology 2020;71:1559-74.
62. Park JE, Pichiah PBT, Cha YS. Vitamin D and metabolic diseases: growing roles of vitamin D. J Obes Metab Syndr 2018;27:223-32.
63. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol 2004;89-90:387-92.
64. Uhal BD, Li X, Piasecki CC, Molina-Molina M. Angiotensin signalling in pulmonary fibrosis. Int J Biochem Cell Biol 2012;44:465-8.
65. Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. Sci Rep 2017;7:3312.
66. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res 2021;292:198235.
67. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85:860-8.
68. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol 2018;175:125-35.
69. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415-28.
70. Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly men. Diabetologia 1997;40:344-7.
71. Leung PS. The potential protective action of vitamin D in hepatic insulin resistance and pancreatic islet dysfunction in type 2 diabetes mellitus. Nutrients 2016;8:147.
72. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science 1980;209:823-5.
73. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. Am J Respir Crit Care Med 2021;203:831-40.
74. Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. Am J Respir Cell Mol Biol 2014;51:251-61.
75. Dekkers BG, Schaafsma D, Tran T, Zaagsma J, Meurs H. Insulin-induced laminin expression promotes a hypercontractile airway smooth muscle phenotype. Am J Respir Cell Mol Biol 2009;41:494-504.
76. Li CY, Erickson SR, Wu CH. Metformin use and asthma outcomes among patients with concurrent asthma and diabetes. Respirology 2016;21:1210-8.
77. Wu TD, Fawzy A, Akenroye A, Keet C, Hansel NN, McCormack MC. Metformin use and risk of asthma exacerbation among asthma patients with glycemic dysfunction. J Allergy Clin Immunol Pract 2021;9:4014-20.e4.
78. Calixto MC, Lintomen L, André DM, Leiria LO, Ferreira D, Lellis-Santos C, et al. Metformin attenuates the exacerbation of the allergic eosinophilic inflammation in high fat-diet-induced obesity in mice. PLoS One 2013;8:e76786.
79. Grill HJ. A role for GLP-1 in treating hyperphagia and obesity. Endocrinology 2020;161:bqaa093.
80. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab 2021 Oct 6. [Epub]. Available at: https://doi.org/10.1016/j.molmet.2021.101351.
81. Rogliani P, Calzetta L, Capuani B, Facciolo F, Cazzola M, Lauro D, et al. Glucagon-like peptide 1 receptor: a novel pharmacological target for treating human bronchial hyperresponsiveness. Am J Respir Cell Mol Biol 2016;55:804-14.
82. Toki S, Newcomb DC, Printz RL, Cahill KN, Boyd KL, Niswender KD, et al. Glucagon-like peptide-1 receptor agonist inhibits aeroallergen-induced activation of ILC2 and neutrophilic airway inflammation in obese mice. Allergy 2021;76:3433-45.
83. Park HJ, Han H, Oh EY, Kim SR, Park KH, Lee JH, et al. Empagliflozin and dulaglutide are effective against obesity-induced airway hyperresponsiveness and fibrosis in a murine model. Sci Rep 2019;9:15601.