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Dyslipidemia in asthma: Treatable trait, or just a common comorbidity?

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Abstract

Asthma is a diverse disease that can be categorized into various phenotypes and endotypes, including obesity-related asthma and allergic asthma. "Treatable traits (TTs)" represent a new approach to managing asthma. Asthma accompanied by dyslipidemia would be a distinct asthma phenotype that is becoming increasingly common. Therefore, dyslipidemia can potentially serve as a target for the management of asthma. Nevertheless, it remains highly under-researched compared to other observable traits. Gaining knowledge about the clinical and inflammatory characteristics, underlying mechanisms, and potential therapeutic medications for asthma with dyslipidemia is crucial for its effective management. This review aimed to provide a comprehensive overview of asthma with dyslipidemia, consolidating existing knowledge and ongoing research.

Keywords: Asthma; Dyslipidemia; Treatable trait; Immunity; Mechanism

Introduction

Asthma is a global public health problem that affects approximately 300 million people worldwide and causes approximately 1000 deaths per day.[1,2] In China, the prevalence of asthma in adults aged ≥20 years is 4.2%, corresponding to 45.7 million Chinese people.[3] Clearly, this disease poses a huge health burden on society and individuals with the disease. Asthma has been defined as a heterogeneous disease that can be divided into different phenotypes and endotypes,[1] which can be used to refine asthma management. In recent years, "treatable traits (TTs)" have been proposed as a new paradigm for the 21st century management of chronic airway diseases such as asthma. The "TTs" approach aims to provide individualized assessment and precise treatment for patients with asthma based on their specific phenotype or endotype, and it is considered the preferred approach towards managing airway diseases using precision medicine. TTs are defined as disease characteristics that are identifiable and measurable, clinically relevant, and treatable. Generally, TTs comprise three different domains: pulmonary, extrapulmonary, and behavioral/lifestyle/risk factors.[4] Because many extrapulmonary traits are present as comorbidities that may affect asthma severity and control,[5,6] identifying these comorbidities as extrapulmonary TTs and targeting them is important in asthma management. Obesity is a common comorbidity of asthma and has been identified as an extrapulmonary TT.[7,8] Obesity is a primary cause of metabolic dysfunction that can lead to metabolic syndromes including dyslipidemia, hyperglycemia, and hypertension.[9] Although there is increasing evidence demonstrating the impact of obesity and metabolic syndrome on the development, severity, clinical features, and management of asthma,[7,10] few studies have explored the effects of dyslipidemia on asthma alone. Limited evidence shows that correlations exist between blood lipid profiles and asthma, independent of body mass index (BMI).[11–13] Recently, we found that dyslipidemia can affect asthma independent of obesity and other components of metabolic syndrome, highlighting the importance of considering dyslipidemia as an extrapulmonary TT in asthma management.[14]

Dyslipidemia is a condition of abnormal serum lipid levels, including abnormal levels in one or more routine clinical lipid tests for triglyceride (TG), total cholesterol

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(TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).[15] Due to racial and dietary differences, the cut-off values for identifying dyslipidemia differ across countries. In American adults, dyslipidemia is defined as TG >2.25 mmol/L, TC ≥6.20 mmol/L, LDL-C >4.13 mmol/L or HDL-C <1.03 mmol/L.[16] In Chinese adults, dyslipidemia is defined as TG ≥ 1.7 mmol/L, TC ≥ 5.20 mmol/L, LDL-C ≥3.4 mmol/L or HDL-C <1.0 mmol/L.[17] Because lipid levels change with growth and maturation, normal values for children differ from those for adults. Dyslipidemia in children is determined based on an established range of lipids and lipoproteins in the pediatric population.[18] In recent years, the increasing prevalence of dyslipidemia has become a significant global public health concern. According to a World Health Organization (WHO) report,[19] the age-adjusted prevalence of dyslipidemia is 47.7% in America, 53.7% in Europe, and 30.3% in the Asia Pacific region. In China, the 2018 national survey revealed the prevalence of dyslipidemia was 35.6% in adults aged ≥18 years,[15] which was higher than the results from the 2015 national survey.[20] Thus, the disease burden caused by dyslipidemia cannot be ignored.

Considering the high global prevalence of dyslipidemia, coupled with the fact that dyslipidemia can play a significant role in asthma, it is imperative to understand the mechanistic link. Therefore, in this review, we summarize the epidemiology of asthma with dyslipidemia and describe the clinical and inflammatory features and underlying mechanisms of asthma with dyslipidemia. Finally, we summarize potential therapeutic drugs targeting asthma with dyslipidemia.

Epidemiological Links Between Asthma and Dyslipidemia

Epidemiological studies have found that the prevalence of dyslipidemia among asthma patients ranges from 12.4 to 45.7%.[14,21–24] To be specific, in elderly patients with asthma (aged ≥65 years), the prevalence of dyslipidemia is 35.97%.[23] In those with severe asthma, the prevalence of dyslipidemia is 16%.[24] In addition, the prevalence of dyslipidemia shows a female predominance, with dyslipidemia occurring in 20.78% of female asthma patients, compared to 19.52% of male asthma patients.[23]

Several studies have reported that dyslipidemia is involved in the development of asthma.[11–13,25–31] For example, a cross-sectional study led by Ko *et al*[26] and a case-control study by Ramaraju *et al*[13] have found that higher serum lipid levels are associated with a higher risk of asthma. A retrospective cohort study by Lim *et al*[27] and a prospective cohort study conducted by Vinding *et al*[11] also confirmed that higher serum lipid levels were significantly associated with the presence of asthma. Notably, a 5-year follow-up cohort study of 3982 children in Cyprus by Yiallouros *et al*[25] found that children with a low serum HDL-C level at age 11–12 years had an increased risk for development of asthma during adolescence (ages 15–17 years). The estimated odds ratios (ORs) were 1.89 (95% confidence interval [CI]: 1.19–3.00) and 1.89 (95% CI: 1.02–3.53) for ever asthma and active asthma respectively. This association remained significant after further adjustments for BMI and maximal oxygen consumption. Further, hypercholesterolemia has been identified as a potential risk factor for asthma, independent of obesity.[32] The association between asthma and elevated LDL-C levels is amplified in overweight and obese individuals.[33] A pronounced sex difference in the relationships between asthma, lipid profiles, and obesity has been identified,[33] which may be attributed to varying dietary patterns among males and females or the influence of steroid hormones. Recently, Liu *et al*[34] used the Mendelian randomization approach to explore the relationship between dyslipidemia and asthma and found a causal relationship between higher levels of LDL-C, TC, and lower levels of HDL-C and an increased risk of asthma. Although a few studies have found no association between the risk of asthma and dyslipidemia, these findings are limited by study design, sample size, and population characteristics.[35,36] Collectively, dyslipidemia is a risk factor for asthma.

The impact of asthma on lipid levels remains to be determined. Reports regarding serum lipid levels among individuals with asthma are inconsistent, with some studies demonstrating either higher,[37–39] lower,[12,25,40,41] or unchanged,[42–45] levels of HDL-C compared to control groups. Regarding TC, TG, and LDL-C, studies have observed elevations,[13,32,33,39,46] reductions,[37,45,47] or no significant changes,[42–44,48] in asthma patients compared to the control groups. Due to differences in research designs and small sample sizes, larger studies are needed to better understand these contradictory findings. In addition, medications for asthma may affect lipid levels. Long-term use of medium to high-dose inhaled corticosteroid (ICS) has the potential to induce systemic effects and may increase the requirement for cholesterol-lowering medications.[49] And long-term use of oral corticosteroids (OCs) in asthma patients can lead to a range of adverse effects, including dyslipidemia.[50] Collectively, this evidence suggests that it is prudent to monitor blood lipid levels in patients with asthma who require long-term medication, especially ICS and even OCs. Currently, several biologics are available for asthma patients with severe disease. However, the effects of biologics on blood lipid levels in asthmatic patients have not yet been reported. Given that interleukin (IL)-6 biologics have adverse effects on blood lipids in rheumatoid arthritis,[51,52] lipid level monitoring in asthmatic patients using biologics is also worth considering.

Asthma with Dyslipidemia: A Specific Phenotype

Asthma is a heterogeneous disease that can be categorized into different phenotypes. Several asthma phenotypes have been identified, including eosinophilic asthma, allergic asthma, neutrophilic asthma, and obesity-related asthma.[53] Phenotyping asthma is instrumental in elucidating the heterogeneous manifestations of the disease, thereby guiding tailored treatment strategies. We identified distinct characteristics in asthmatics with dyslipidemia compared to those with normal lipid levels, including demographics, lung function, and asthma control, indicating that "dyslipidemia-associated asthma" would be a specific phenotype.[14] Recently, Park *et al*[54] suggested the presence of an asthma phenotype with

metabolic dysfunction, which includes central obesity, insulin resistance, dyslipidemia, and vitamin D deficiency.

Clinical Characteristics of Asthma with Dyslipidemia

Asthma patients with dyslipidemia are older, have elevated BMI, and are more often female.[14] Several studies have demonstrated that dyslipidemia is associated with worse airway obstruction in adults with asthma. Serum cholesterol is negatively correlated with lung function (forced expiratory volume in one second [FEV_1]% predicted).[55] Low HDL-C levels are associated with reduced forced vital capacity (FVC) and FEV_1, and these findings are consistent in men and women.[56] Our previous prospective cohort study confirmed these findings, reporting that the dyslipidemia group had worse FEV_1% predicted, maximal mid-expiratory flow (MMEF)% predicted, and FEV_1/FVC ratio than the normal lipid group, and the difference remained significant even after adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose.[14] Based on its density and size, LDL-C can be categorized into seven distinct subclasses (LDL-1 to LDL-7). LDL-1 shows a positive correlation with predicted FVC% and FEV_1%, whereas LDL-3 displays an inverse association with FVC% and FEV_1% in adults with asthma.[57] Moreover, serum levels of HDL-C and apolipoprotein A-I (apoA-I) are positively associated with FEV_1, whereas serum levels of TG, LDL-C, apolipoprotein B (apoB), and the apoB/apoA-I ratio are negatively correlated with FEV_1 in atopic asthmatic subjects.[58] Taken together, these findings suggest that dyslipidemia can impair lung function in adult patients with asthma.

Consistent with the view that comorbidities may affect asthma severity and control, several studies have shown that asthmatic individuals with dyslipidemia have more severe asthma and worse asthma control. Increased plasma cholesterol has been reported to be independently associated with severe asthma (OR = 1.98; 95% CI: 1.05–3.73).[55] Our previous study[14] also reported that dyslipidemia is associated with a higher risk of severe asthma (adjusted OR = 2.055, 95% CI: 1.102–3.832). And when dividing patients into groups with normal and abnormal blood lipid levels, the dyslipidemia group had a higher proportion of uncontrolled asthma (32.1% *vs.* 21.3%; $P = 0.007$) compared with the normal lipid group, and dyslipidemia was a risk factor for uncontrolled asthma (adjusted OR = 1.808, 95% CI: 1.167–2.801) after adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose.[14] Furthermore, hyperlipidemia was significantly associated with asthma exacerbations (AEs).[59] Recently, our prospective cohort study[14] based on the Australasian Severe Asthma Network (ASAN) presented compelling evidence demonstrating that dyslipidemia is associated with increased AEs, independent of other components of metabolic syndrome.

Inflammatory Characteristics of Asthma with Dyslipidemia

Asthma is a highly complex chronic inflammatory airway disease that can be classified into different endotypes and phenotypes.[60] The current paradigm broadly categorizes airway inflammation into two distinct groups: Type 2 (T2) and non-T2 asthma. T2 asthma is typically characterized by eosinophilic airway inflammation and elevated levels of T2 cytokines, including IL-4, IL-5, and IL-13. Biomarkers of T2 asthma include elevated blood or sputum eosinophils and fraction of exhaled nitric oxide (FeNO). Some studies have explored the relationship between dyslipidemia and inflammatory biomarkers in asthma. In atopic asthmatics, blood eosinophils are negatively correlated with serum HDL-C levels and total HDL particles and positively correlated with serum TG levels.[61] Serum periostin levels negatively correlate with total HDL particles. Serum TC, LDL-C, and apoB levels are positively associated with FeNO.[62] In addition, atopy has been used to define T2 asthma.[1] High levels of HDL-C were found to be associated with decreased risk of aeroallergen sensitization (adjusted OR = 0.27; 95% CI: 0.01–0.70; $P = 0.01$), while high TG levels were associated with aeroallergen sensitization (adjusted OR = 2.01; 95% CI: 1.14–3.56; $P = 0.02$).[11] These findings suggest that dyslipidemia may be linked to T2 inflammation in asthma. However, in our previous study,[14] compared to the normal lipid group, the dyslipidemia group had lower immunoglobulin E (IgE) levels and was less atopic, with an increased risk of nonallergic asthma, indicating the presence of non-T2 inflammation. Taken together, these findings suggest that dyslipidemia may have an effect on asthma through both T2 and non-T2 pathways.

Underlying Mechanisms for Asthma with Dyslipidemia

The mechanistic basis for the relationship between asthma and dyslipidemia has not been established, but some potential factors including common etiologies (genetics, diet and nutrients), cytokines and inflammation, oxidative stress, microbiome, or metabolic dysfunction as following may be involved [Figure 1].

Shared genetic vulnerability

Multiple studies have verified the significant roles of genetic factors in the development of asthma and altered lipid levels [Figure 1].[63–65] Orosomucoid 1-like 3 (*ORMDL3*) is a gene universally confirmed to be associated with asthma susceptibility and has recently been identified as a crucial modulator of lipid metabolism.[66,67] Lipid metabolism is closely associated with dyslipidemia and atherosclerosis. Ma *et al*[68] reported that *ORMDL3* contributes to the risk of atherosclerosis in the Chinese Han population and mediates oxidized low-density lipoprotein-induced autophagy in endothelial cells, indicating that *ORMDL3* may be a shared genetic risk factor for asthma, atherosclerosis, and dyslipidemia. In addition, *IL10* gene polymorphisms at position-1082 are associated with serum HDL-C and TG concentrations,[69] as well as pediatric asthma in Chinese individuals.[70] Furthermore, in a cohort of children in Cyprus, Yiallouros *et al*[71] found that two single nucleotide polymorphisms (*TNFA* rs3093664 and *PRKCA* rs9892651) located in different genetic loci were correlated with both wheezing and HDL-C levels. Specifically, the relationship between

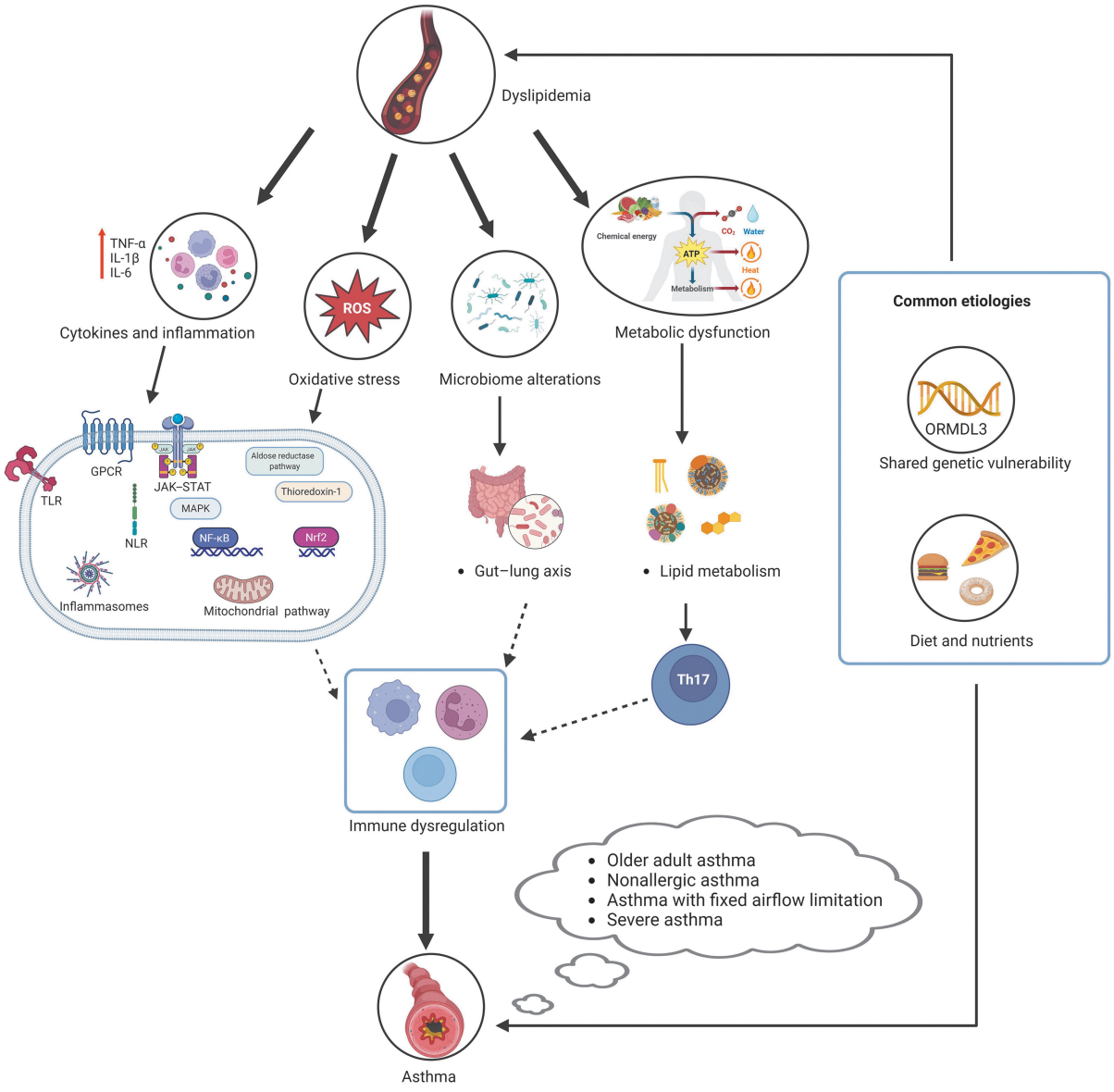

Figure 1: Underlying mechanisms in asthma with dyslipidemia. Shared genetic vulnerability and diet and nutrients, can affect both dyslipidemia and asthma. Dyslipidemia may affect asthma via cytokines and inflammation, oxidative stress, microbiome alterations, and metabolic dysfunction. Created with BioRender.com. GPCR: G-protein-coupled receptor; IL: Interleukin; JAK–STAT: Janus kinase-signal transducer and activator of transcription; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-kappa B; NLRs: NOD-like receptors; Nrf2: Nuclear factor erythroid 2-related factor 2; ORMDL3: ORMDL sphingolipid biosynthesis regulator 3; ROS: Reactive oxygen species; Th: T helper; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor-α.

TNFA rs3093664 and wheezing is partially mediated through its influence on HDL-C levels, while the association between *PRKCA* rs9892651 and wheezing seems to occur independently of HDL-C levels. These studies suggest that asthma with dyslipidemia may partly originate from overlapping genetic susceptibilities. However, to confirm these genetic associations, future research is needed to directly explore the genetic differences between asthma combined with dyslipidemia and asthma alone.

Diet and nutrients

An increasing amount of evidence indicates that diet and nutrients play a significant role in the development and management of asthma [Figure 1].[72,73] An animal study has found that hypercholesterolemia induced by a high-cholesterol/high-fat diet may lead to Toll-like receptors (TLRs)/nuclear factor -kappa B (NF-κB) pathway-related low-grade pulmonary inflammation in C57BL/6J mice, which could alter the lungs' immune response to various environmental exposures.[74] In human, our previous study reported a dose-response pattern between fast food consumption, especially of hamburgers, and asthma: the adjusted odds ratio of current asthma associated with hamburger consumption was 1.59 (95% CI: 1.13–2.25).[75] And our other two studies have found that a high-fat meal can augment neutrophilic airway inflammation and suppress bronchodilator recovery in asthma,[76] and the underlying mechanism for this phenomenon may involve differences in gene expression changes due to a

high-fat meal between asthmatics and healthy controls.[77] Further, our study suggested that increased consumption of a high-fat diet can elevate circulating saturated fatty acids, which alter innate immune responses by activating inflammatory signaling pathways such as NF-κB, reactive oxygen species (ROS), and mitogen-activated protein kinase (MAPK), thereby promoting NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-dependent airway inflammation in asthma.[78] A healthy diet has protective effects against asthma and wheezing in children.[79] Adopting a healthy diet that is abundant in antioxidants and fiber can mitigate the adverse effects of oxidative stress and systemic inflammation in obesity-related asthma.[80]

Diet and nutrients can also influence lipid levels.[81] Unhealthy dietary patterns, including excessive intake of saturated fatty acids, trans fatty acids, soft drinks, and refined carbohydrates are strongly associated with the development of dyslipidemia.[82] Managing dyslipidemia, especially lowering LDL-C and TC levels, can be effectively achieved by altering the macronutrient composition of the diet.[81] Healthy dietary patterns such as the Mediterranean diet, which is characterized by a high intake of plant foods such as fruits and vegetables and an increased intake of monounsaturated and omega-3 fats, may be a rational option for protecting against asthma and dyslipidemia.[83,84] Intermittent fasting is characterized by brief intervals of intense energy restriction (involving a 75–100% reduction in caloric intake on fasting days), interspersed with days of 'regular' or 'normal' eating. This dietary approach encompasses various fasting types such as alternate-day fasting, the 5:2 diet, and time-restricted eating. Alternate day calorie restriction may be effective in improving asthma symptoms and asthma control and these improved clinical findings were associated with decreased levels of serum cholesterol and TG,[85] indicating that intermittent fasting may have a potential effect on asthma with dyslipidemia. Collectively, diet and nutrients may play an important role in asthma with dyslipidemia.

Cytokines and inflammation

Dyslipidemia induces a state of low-grade systemic inflammation, characterized by the upregulation of various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, etc.[86–88] These cytokines also play significant roles in the initiation and progression of asthma. Studies have reported increased TNF-α concentrations in the airways of individuals with severe asthma.[89,90] TNF-α contributes to disease pathology through multiple mechanisms: it promotes the recruitment of inflammatory cells, stimulates the production of inflammatory mediators, and induces oxidative stress, airway hyperresponsiveness, and tissue remodeling.[91] Fatty acids trigger a signaling cascade through TLR4 that leads to the assembly of the NLRP3 inflammasome and activation of caspase-1, which ultimately cleaves and releases mature IL-1β from its inactive precursor. IL-1β can drive inflammation by promoting T-helper (Th) 17 cell differentiation.[92] As a key biomarker of systemic inflammation and metabolic dysfunction, IL-6 is found to be associated with severe asthma. And elevated IL-6 levels clinically correlate with worse lung function and more frequent exacerbations in asthma.[93]

In addition, the pathophysiological mechanisms of asthma are closely related to inflammation triggered by immune responses. This involves multiple inflammatory signaling pathways, including TLRs and NOD-like receptors (NLRs), Janus kinase-signal transducer and activator of transcription (JAK-STAT), NF-κB, inflammasomes, MAPK, and G-protein-coupled receptor (GPCR) pathways.[94] Each of these pathways contributes to the progression and severity of asthma. The inflammation triggered by dyslipidemia also involves inflammatory pathways such as MAPK, JAK-STAT, and NF-κB.[95,96] Therefore, we hypothesize that dyslipidemia may participate in the pathophysiological mechanisms of asthma by releasing inflammatory mediators and regulating the inflammatory signaling pathways. However, the signaling mechanisms by which dyslipidemia modulates inflammation to affect asthma remain to be established. Future research is required to confirm this mechanism.

Oxidative stress

Oxidative stress is a key contributor to the development of asthma, resulting from an imbalance between ROS generation and antioxidant capacity, which induces cellular injury and promotes inflammatory processes. Oxidative stress is involved in the pathophysiological mechanisms of asthma through multiple signaling pathways, including the nuclear factor erythroid 2-related factor 2 (Nrf2), NF-κB, thioredoxin-1, mitochondrial, MAPK, and aldose reductase pathways.[94] Dyslipidemia can lead to oxidative stress and increase the production of ROS.[97] Animal studies revealed that asthmatic-hyperlipidemic rats exhibited a significant increase in serum concentrations of nitrite and malondialdehyde, alongside a significant decrease in total thiol content and the activities of superoxide dismutase and catalase.[98,99] These changes collectively indicate an exacerbation of oxidative damage. In addition, oxidized LDL can activate the MAPK signaling pathway, leading to MAPK phosphorylation, which generates abundant ROS, promotes monocyte accumulation in the arterial wall, reduces collagen and extracellular matrix secretion by vascular smooth muscle cells, and ultimately induces cytotoxicity.[100] Furthermore, oxidized LDL has been found to be elevated in pulmonary diseases such as chronic obstructive pulmonary disease, and are associated with lung function, inflammation, and oxidative stress.[101] Therefore, dyslipidemia may contribute to the development and progression of asthma by inducing oxidative stress via the aforementioned signaling pathways. However, further research is needed to confirm which specific pathways are involved and how they regulate the pathological processes of asthma.

Microbiome alterations

The microbiome performs several crucial functions in the development, regulation, and maintenance of healthy immune responses, while dysbiosis and the resulting imbalance in microbiota-related immunological processes

contribute significantly to the development of a number of diseases, including asthma and dyslipidemia.[102,103] Crosstalk between the microbiome and asthma has been established [Figure 1].[104] Perturbation of airway, skin, and gut microbiomes coincides with asthma-associated immune dysfunction.[105] The microbiome is associated with the origin, phenotype, persistence, and severity of asthma.[106] And the gut microbiome can influence asthma by modulating immune responses through the gut–lung axis.[107] In addition, the gut microbiome can modulate lipid metabolism and is associated with lipid levels in humans. Negative correlations were observed between gut microbiome diversity and TG and LDL levels, whereas HDL-C was positively linked with microbial richness.[108–110] The composition and function of the gut microbiome are dynamic and can be influenced by dietary factors, including the quantity and type of lipids. Therefore, dietary lipids might affect asthma by interacting with the gut microbiome. Whether dyslipidemia affects asthma via the airway microbiome requires further investigation.

Metabolic dysfunction

Metabolic dysfunction is a broad concept and dyslipidemia is a manifestation of metabolic dysfunction [Figure 1]. Dyslipidemia is closely related to and may be a consequence of lipid metabolism disorders.[111] Lipid metabolism is an intricate physiological process encompassing the uptake, transportation, biosynthesis, and degradation of lipids that are integral to numerous bodily functions.[112] Accumulating evidence from laboratory and clinical studies has highlighted the pivotal role of lipid metabolism in the pathogenesis of asthma.[113] Genes associated with lipid metabolism, including *ASAH1*, *ACER3*, and *SGPP1*, play pivotal roles in the development of asthma and regulate the immune microenvironment.[114] Th17 cells, which play a crucial role in the pathogenesis of steroid-resistant asthma, are connected to lipid metabolism by modulating retinoid-related orphan receptor gamma t (RORγt) activation.[115] The activation of the Yes-associated protein/hypoxia inducible factor-1α/microRNA-182/early growth response 2 signaling pathway may foster Th17 cell differentiation, intensify asthma progression, and deteriorate lipid metabolism dysregulation, pointing to a possible therapeutic strategy for asthma management.[116] And abnormal lipid metabolism has been shown to correlate with disease severity and IgE levels in patients with asthma.[117]

In addition, a potential link between lipid metabolism and lung dysfunction has been established in individuals with mild to moderate asthma.[118] In two Trans-Omics for Precision Medicine Initiative cohorts, five metabo-endotypes of asthma with differences in lung function were discovered and validated, and the identification of cholesterol esters, TGs, and fatty acids as significant factors in determining metabo-endotypes indicates that imbalances in pulmonary surfactant homeostasis could potentially contribute to the severity of asthma.[119] Cholesterol is a crucial component of the pulmonary surfactant.[120] Recent advancements in understanding the interplay between circulating cholesterol and the lungs have revealed that the lungs possess a distinct requirement for sterol uptake and metabolism, and cholesterol homeostasis is necessary for pulmonary physiology.[121,122] Therefore, an imbalance in cholesterol metabolism may significantly affect lung immunity and function.

Immunology of asthma with dyslipidemia

Asthma is an inflammatory airway disease involving various inflammatory cytokines, immune cells, and activation of several inflammatory cascades. Dyslipidemia can affect asthma by activating immune pathways and amplifying airway inflammation [Figure 2]. The airway epithelium is an important barrier against external stimuli such as air pollutants and respiratory pathogens. Disruption of the airway epithelial barrier is a key driver of asthma initiation, persistence, and exacerbation.[123] Airway epithelial injury can initiate an inflammatory cascade in asthma by releasing epithelium-derived cytokines, namely IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).[124] Dyslipidemia can enhance systemic inflammation by upregulating IL-1β and IL-6, which can also influence the airway epithelium.[86,125] Circulating IL-1β can cause airway epithelial cell dysfunction.[126] Thus, dyslipidemia may affect asthma immunology by initiating abnormal airway epithelial responses.

Dyslipidemia can affect asthma by influencing various immune cells. $CD4^+$ T helper (Th) cells play a key role in the orchestration of airway inflammation. When exposed to allergens, T cells are activated, leading to the clonal proliferation of allergen-specific Th cells. These Th cells assume diverse phenotypes, several of which may contribute to asthma pathogenesis. For example, Th2 cells secrete IL-4, IL-5, and IL-13; Th1 cells produce interferon (IFN)-γ; and Th17 cells secrete IL-17A. Dyslipidemia can induce a switch from a Th1 to a Th2 response.[127] In addition, dyslipidemia can amplify Th2 and Th17 responses by increasing the production of Th2 and Th17 cytokines, including IL-4 and IL-17A.[128]

Neutrophils are strongly linked to corticosteroid insensitivity and severe asthma; thus, dyslipidemia may affect asthma treatment response and severity via neutrophils. IL-6 and IL-8 are inflammatory cytokines associated with both neutrophilic asthma (NA) and dyslipidemia.[86] Dyslipidemia may amplify neutrophilic inflammation in asthma by increasing IL-6 and IL-8 levels. In addition, neutrophil extracellular traps (NETs) play an important role in NA.[129] Hypercholesterolemia can impair the clearance of NETs and promote inflammation, ultimately exacerbating asthma.[130]

Macrophages play a pivotal role in the pathogenesis of asthma. When exposed to local micro-environments, recruited macrophages undergo polarization and transform into either classically activated (M1) or alternatively activated (M2) phenotypes.[131] Macrophage polarization has been linked to the pathogenesis of asthma. Lipopolysaccharide (LPS), IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are potent activators that promote the polarization of macrophages towards the M1 phenotype.[132] Conversely, M2 macrophages are induced by cytokines, such as IL-4, IL-13, and IL-10. M1 polarization leads to increased expression of Th1 and

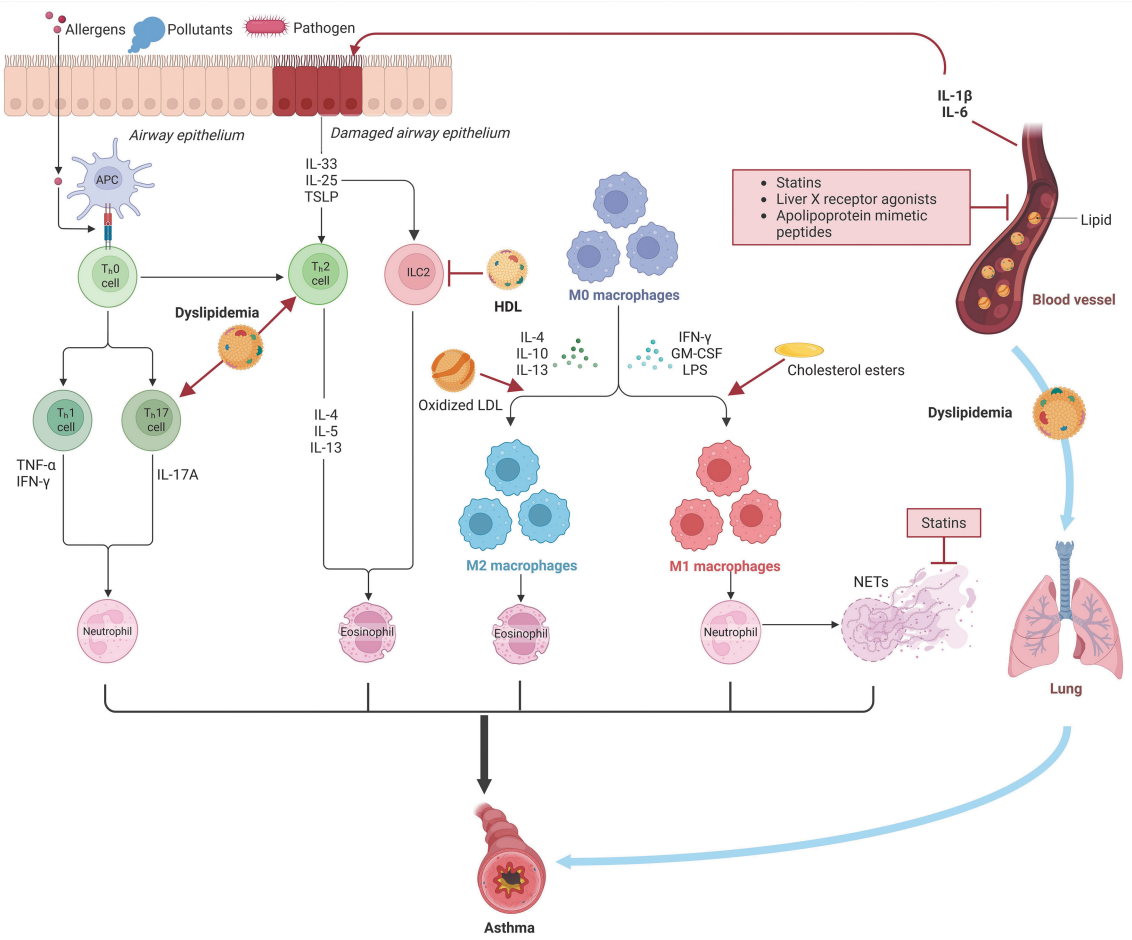

Figure 2: Immunology in asthma with dyslipidemia. The immunology of asthma involves an intricate cascade of immune cells, cytokines, and chemokines. Dyslipidemia can induce pro-inflammatory cytokines such as IL-1β and IL-6, which could damage airway epithelium and initiate cascade reactions of asthma. Further, dyslipidemia can affect the cascade reaction of asthma via Th2, Th17, ILCs, and macrophage cells. Created with BioRender.com. APC: Antigen-presenting cell; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HDL: High-density lipoprotein; IFN-γ: Interferon-gamma; IL: Interleukin; ILC2: Group 2 innate lymphoid cell; LDL: Low-density lipoprotein; Th: T helper; LPS: Lipopolysaccharide; TNF-α: Tumor necrosis factor-α; NETs: Neutrophil extracellular traps; TSLP: Thymic stromal lymphopoietin.

Th17 cells, whereas M2 polarization predominantly elicits a Th2 cell response.[131] Oxidized LDL is also involved in macrophage polarization towards M2 phenotype,[133] thereby contributing to T2 inflammation. While the accumulation of cholesterol esters triggers a shift in the polarity of murine macrophages, directing them toward classically activated inflammatory phenotypes (M 1),[134] contributing to non-T2 inflammation. Thus, dyslipidemia can affect asthma by regulating macrophage polarization, triggering T2 or non-T2 inflammation. In addition, group 2 innate lymphoid cells (ILC2) also play a significant role in asthma.[135] HDL-C decreases the levels of ILC2 and Th2 cytokines, demonstrating a protective role in asthma inflammation.[136]

Potential Therapeutic Drugs Targeting Asthma with Dyslipidemia

Statins

Statins are lipid-lowering agents widely prescribed for the management of hyperlipidemia and cardiovascular diseases. Statins exhibit lipid-lowering activity by inhibiting 3-hydroxymethyl-3-glutaryl coenzyme A reductase, a pivotal enzyme involved in cholesterol production. Recently, statins have been found to exhibit pleiotropic effects, including anti-inflammatory, anti-fibroproliferative, and immunomodulatory effects, independent of their cholesterol-lowering abilities.[137,138] The pleiotropic effects of statins suggest that they may be effective against asthma.

Cellular and animal experiments using statins to treat asthma have been well studied. Several cellular experiments have shown that statins have inhibitory effects on cytokine and chemokine production,[139–141] as well as bronchial wall remodeling.[142–144] These effects have also been confirmed in mouse asthma models. As shown in Table 1,[98,99,145–170] most studies have used ovalbumin (OVA)-induced murine models of allergic asthma to explore the effects of statins. Statin treatment has been shown to decrease airway inflammation, reduce Th2 cytokines such as IL-4, IL-5, and IL-13, and improve airway remodeling and airway hyperresponsiveness (AHR). A few studies have used obese- or hyperlipidemic mouse models of asthma. In a mouse model of obesity and asthma induced by a high-fat diet and OVA, simvastatin treatment effectively reduced glucose, lipid, leptin, and neutrophil percentages, while also improving airway inflammation

Table 1: Effects of statins on asthma in animal models.

Study	Disease model	Pharmacological agent	Outcome
McKay *et al*[145]	OVA-induced murine model of allergic asthma	Simvastatin	↓ The total inflammatory cell infiltrate and eosinophilia in the BALF
			↓ BALF IL-4, IL-5
			↓ IL-4, IL-5, IL-6, and IFN-γ in thoracic lymph node cultures from simvastatin-treated mice
Xu *et al*[146]	OVA-induced murine model of asthma	Simvastatin	↓ Airway remodeling and hyperresponsiveness
			↓ BALF eosinophils, lymphocytes, macrophagocytes and neutrophils
			↓ BALF CCL-11, IL-4, and IL-5
			↑ BALF IFN-γ
			↓ Eosinophil infiltration, mucus production and collagen deposition in the lung tissues
Ahmad *et al*[147]	OVA-induced murine model of asthma	Simvastatin	↓ BALF total cell count, macrophage, and eosinophil
			↓ Mucus hypersecretion, airway remodeling, and AHR
Zeki *et al*[148]	OVA-induced murine model of asthma	Simvastatin	↓ Total lung lavage leukocytes, eosinophils, and macrophages
			↓ BALF IL-4, IL-13, and TNF-α
			↑ Lung compliance
			↓ Airway hyperreactivity
Kim *et al*[149]	OVA-induced mouse allergic asthma model	Simvastatin	↓ OVA-specific IgE level, BALF total inflammatory cells, macrophages, neutrophils, and eosinophils
			↓CD40, CD40L, and VCAM-1 expression, mRNA and protein levels of IL-4, IL-13 and TNF-α, goblet cells, activities of MMPs, small G proteins, MAP kinases, and NF-κB
Liu *et al*[150]	OVA-specific asthma model in mice	Simvastatin	↓ Airway responsiveness, BALF IL-4, IL-5, IL-13
			↓ $CD4^+$ cells; $CD4^+/CD8^+$ T-cell ratio
			↓ VCAM-1 and ICAM-1 proteins
Gu *et al*[151]	OVA-induced asthma mouse model	Simvastatin	↑ Autophagy-related protein Atg5, LC3B, and Beclin1 expression and autophagosome formation in lung tissue
			↑ IFN-γ
			↓ IL-4, IL-5 and IL-13; extracellular matrix deposition
Mohammadian *et al*[152]	OVA-induced asthma model in mouse	Simvastatin	↓ WBC counts, neutrophils, and eosinophils
Jha *et al*[153]	House dust mite challenged murine model of allergic asthma	Simvastatin	↓ TNF-α, CXCL1, IL-6, IL-4, IL-1β, and IFN-γ
			↓ Goblet cell hyperplasia, neutrophil, and eosinophil influx
Zeki *et al*[154]	OVA-induced mouse model of allergic asthma	Simvastatin	↓ Goblet cell hyperplasia, arginase-1 protein expression, and total arginase enzyme activity
Han *et al*[155]	High-fat diet and OVA sensitization and challenge to establish a mouse model of obesity and asthma	Simvastatin	↓ Glucose, lipid, leptin, neutrophil percentage, airway inflammation, and remodeling
Chen *et al*[156]	A mouse model of severe asthma with neutrophil-predominant inflammation (OVA+LPS mice)	Simvastatin	↓ BALF total cell, neutrophil counts, IL-4, IL-1β, IFN-γ, and IL-17A, perivascular and peribronchial leukocyte infiltration, mucus production; proportions of Th2 and Th17, AHR
			↓ NET formation in BALF and lung tissue
			↑ Treg cells
Sharif-Askari *et al*[157]	OVA-induced mouse model of asthma	Simvastatin	↓ Infiltration of both effector memory T and central memory T memory subtypes, IL-4, IL-13
			↓ ICAM-1 and VCAM-1 levels in the lung homogenate
Saadat *et al*[98,99,158]	Asthmatic, hyperlipidemic, and asthmatic-hyperlipidemic rat models (asthmatic animals were sensitized with OVA)	Rosuvastatin	↓ WBC counts, neutrophilia, eosinophilia, and monocytes, IL-6, IL-10
			↓ Tracheal responsiveness to methacholine, muscle hypertrophy, and emphysema
			↓ Oxidative stress by decreasing nitrite and malondialdehyde concentrations
			↑ Th1/Th2 balance
			↑ Total thiol content, superoxide dismutase, and catalase activities
Zhu *et al*[159]	OVA-induced murine model of chronic asthma	Rosuvastatin	↓ BALF total inflammatory cells, lymphocytes, macrophages, neutrophils, and eosinophils
			↓ BALF IL-4, IL-5, IL-13, and TNF-α
			↓ Histological mucus index and gamma-aminobutyric acid type A receptor β2 expression

(*continued*)

Table 1

(continued)

Study	Disease model	Pharmacological agent	Outcome
Liu *et al*[160]	OVA-exposed mice model of asthma	Atorvastatin	↓ Tissue transglutaminase and triggering receptor expressed on myeloid cells-1 in lung tissue, lymphocytes and eosinophils, AHR, lung collagen deposition, airway wall area, airway smooth muscle thickness, and pathological changes in the lung
			↓ TNF-α, IL-8, IL-13, and IL-17 in serum
Blanquiceth *et al*[161]	OVA-induced model of allergic asthma	Atorvastatin	↑ Tregs in mediastinal lymph nodes and IL-10 in lungs
			No significant changes were observed in the number of inflammatory cells in the BALF, OVA-specific immunoglobulin E in the serum, and Th2 cytokines in the lungs
Fırıncı *et al*[162]	OVA-induced murine model of chronic asthma	Atorvastatin	↓ Thicknesses of basement membrane and subepithelial smooth muscle layer, height of epithelium, number of mast and goblet cells
			↓ IL-4 and IL-5 levels of the lung tissue
Lee *et al*[163]	Obesity-related asthma mouse model:	Pravastatin	↓ BALF IL-4, IL-5, and IL-17
	C57BL/6 mice were fed a high-fat diet to induce obesity with or without OVA sensitization and challenge		↓ Serum leptin and adiponectin ratio
			↓ Airway inflammation of lung tissues and AHR
Wu *et al*[164]	An asthma mouse model:	Pravastatin	↓ Airway resistance, bronchial tube thickness, and goblet cell hyperplasia in lung tissues
	Mice were sensitized and challenged with OVA to establish the asthma model		↓ BALF eosinophil counts and total inflammatory cell counts, IL-4, IL-17
			↑ BALF $CD4^+$ $CD25^+$ $Foxp3^+$ Treg, IFN-γ
Yeh *et al*[165]	Male C57BL/6 mice were fed either a control diet or a diet supplemented with 2% cholesterol after sensitization and inhalation exposure to OVA	Pravastatin	↓ Eosinophil infiltration
			↓ BALF IL-5, PGE2, and MCP-1
			↑ IL-12
Zeki *et al*[166]	OVA-induced murine allergic asthma	Pravastatin	↓ Airway goblet cell hyperplasia/metaplasia; airway hypersensitivity
			↓ BALF TNF-α and keratinocyte-derived chemokine
Imamura *et al*[167]	OVA-induced mouse model of asthma	Pravastatin	↓ BALF eosinophilia
			↓ Serum total IgE, OVA-specific IgE, and OVA-specific IgG1 levels
			↓ IL-17, Th17 response
Huang *et al*[168]	OVA-induced mice model of asthma	Pravastatin/Atorvastatin	↓ AHR
			↓ Th1- and Th2-mediated antibody responses, reducing serum specific IgE, IgG, IgG1, and IgG2a levels
			↓ BALF IL-4, IL-5, and IFN-γ
			↑ BALF IL-10
Chiba *et al*[169]	Rats with experimental asthma:	Lovastatin	↓ Total cholesterol levels
	Rats were sensitized and repeatedly challenged with 2,4-dinitrophenylated *Ascaris suum* antigen		↓ Bronchial smooth muscle hyperresponsiveness
			↓ BALF cell counts
Chiba *et al*[170]	OVA-induced mouse model of asthma	Lovastatin	↓ Airway eosinophilia

AHR: Airway hyperresponsiveness; Atg5: Autophagy protein 5; BALF: Bronchoalveolar lavage fluid; CCL: Chemokine (C-C motif) ligand; CD40L: CD40 ligand; CXCL: C-X-C motif chemokine ligand; Foxp3: Forkhead box protein P3; ICAM: Intercellular adhesion molecule; IFN-γ: Interferon-gamma; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IL: Interleukin; LC3B: Microtubule-associated protein 1 light chain 3 beta; LPS: Lipopolysaccharide; MAP: Mitogen activated protein; MCP: Monocyte chemoattractant protein; MMP: Matrix metalloproteinase; mRNA: Messenger RNA; NET: Neutrophil extracellular trap; NF-κB: Nuclear factor-kappa B; OVA: Ovalbumin; PGE2: Prostaglandin E2; Th: T helper; TNF: Tumor necrosis factor; VCAM: Vascular cell adhesion molecule; WBC: White blood cell. ↑: Increase; ↓: Decrease.

and remodeling, suggesting a therapeutic effect of simvastatin on obesity-associated asthma.[155] Pravastatin treatment in obese asthmatic mice alleviates allergic airway inflammation and AHR through the inhibition of Th2- and Th17-associated signaling pathways.[163] In asthmatic-hyperlipidemic animals, rosuvastatin treatment modulates the Th1/Th2 balance and reduces AHR, lung inflammation, and oxidative stress.[98,99,158] Pravastatin has also been shown to inhibit allergic pulmonary inflammation in OVA-induced asthmatic mice fed with 2% cholesterol.[165] Furthermore, simvastatin, while inhibiting Th2 inflammation, suppresses Th17-mediated neutrophilic inflammation and airway hyperreactivity by reducing peptidyl arginine deiminase 4 (PAD4) expression

Table 2: Effects of statins on asthma in clinical research.

Study	Design	No. and participants	Duration	Serum lipid levels before and after statin treatment	Serum lipid levels before and after non-statin or placebo treatment	Effect of statin therapy
Park *et al*[177]	Retrospective study with 1:1 propensity score matching: statin and non-statin groups	1090 asthma patients	Electronic medical record data spanning 28 years	LDL levels before and after statin treatment: 104 ± 6 *vs*. 86 ± 7 mg/dL	LDL levels before and after non-statin treatment: 104 ± 5 *vs*. 104 ± 5 mg/dL	Statin use is associated with a lower risk of asthma exacerbation; there was no significant difference in the risk of asthma-related hospitalization between statin and non-statin groups.
Mehrabi *et al*[173]	Placebo-controlled randomized clinical trial: atorvastatin 40 mg/d or similar placebo	80 patients with asthma	8 weeks	Serum lipid levels before *vs*. after atorvastatin treatment: TC: 162.00 ± 52.20 *vs*. 134.15 ± 29.90 mg/dL; LDL-C: 110.15 ± 41.00 *vs*. 94.35 ± 35.70 mg/dL; HDL-C: 40.58 ± 11.09 *vs*. 44.00 ± 7.88 mg/dL; TG: 138.6 ± 17.8 *vs*. 104.0 ± 25.5 mg/dL	Serum lipid levels before *vs*. after placebo treatment: TC: 150.80 ± 42.40 *vs*. 156.90 ± 44.00 mg/dL; LDL-C: 101.98 ± 29.30 *vs*. 101.05 ± 29.66 mg/dL; HDL-C: 44.65 ± 9.32 *vs*. 41.40 ± 8.20 mg/dL; TG: 126.4 ± 9.80 *vs*. 125.8 ± 9.0 mg/dL	Spirometric changes, blood eosinophil count, or serum periostin levels: –
Kim *et al*[178]	Case-control study: statin users and non-statin users. Statins included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.	88,780 asthma patients and 88,780 control participants	1 year	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin use was associated with a reduced risk of asthma-related ED visits, hospitalizations, and systemic steroid use.
Wang *et al*[179]	Retrospective cohort study: statin users and non-statin users	117,595 adult patients with asthma	36 months	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin use is associated with the decreased risk of asthma-related ED visits and/or hospitalizations.
Thomson *et al*[180]	Randomized controlled trial comparing atorvastatin (40 mg/d) versus placebo for 4 weeks, followed by inhaled beclometasone (BDP: 400 mg/d) for a further 4 weeks	39 smokers with mild to moderate asthma	8 weeks	Serum lipid levels were not detected	Serum lipid levels were not detected	Sputum concentrations of CCL7, IL-12p70, sCD40L, FGF-2, CCL4, TGF-α and MMP-8: ↓
Tse *et al*[181]	Retrospective cohort study using Medco Health Solutions administrative database: statin users and non-statin users. Statin therapy included simvastatin, lovastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, cerivastatin, and pitavastatin.	6652 asthmatics with recent exacerbation	1 year follow-up	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin use is associated with fewer ED visits; no significant associations were found between statin use and asthma-related hospitalizations.
Zeki *et al*[182]	Retrospective, cross-sectional study: statin users and non-users. Statin therapy included simvastatin, lovastatin, atorvastatin, and pravastatin.	165 severe asthma patients	Median statin use was for 1 year	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin use was associated with improved asthma control. There were no significant differences in lung function, corticosteroid or rescue bronchodilator use or peripheral eosinophilia between statin users and non-users.

(*continued*)

Table 2

(continued)

Study	Design	No. and participants	Duration	Serum lipid levels before and after statin treatment	Serum lipid levels before and after non-statin or placebo treatment	Effect of statin therapy
Tse *et al*[176]	Propensity score-matched cohort study: statin users and non-statin users	16,696 asthma patients	36 months	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin exposure was associated with decreased odds of asthma-related ED visits and oral corticosteroid dispensings. There were no significant differences in asthma-related hospitalizations between statin users and non-users.
Lokhandwala *et al*[183]	Propensity-matched retrospective cohort study using Mississippi Medicaid data from 2002 to 2004: statin exposed and unexposed	1473 asthma patients	1 year	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin exposure was associated with decreased odds of asthma-related hospitalization and ER visits.
Moini *et al*[172]	Double-blind randomized clinical trial: atorvastatin 40 mg/d or placebo	62 patients with persistent mild to moderate asthma	8 weeks	Serum lipid levels before *vs.* after atorvastatin treatment: TC: 205.71 ± 68.90 *vs.* 162.85 ± 51.23 mg/dL; LDL-C: 118.32 ± 39.81 *vs.* 83.39 ± 31.31 mg/dL; HDL-C: 48.71 ± 10.05 *vs.* 50.85 ± 10.89 mg/dL; TG: 121.96 ± 43.17 *vs.* 104.25 ± 35.53 mg/dL	Serum lipid levels before *vs.* after placebo treatment: TC: 204.41 ± 48.24 *vs.* 202.65 ± 48.22 mg/dL; LDL-C: 118.76 ± 41.76 *vs.* 117.65 ± 41.23 mg/dL; HDL-C: 49.72 ± 7.71 *vs.* 49.27 ± 7.71 mg/dL; TG: 120.21 ± 42.42 *vs.* 120.41 ± 41.48 mg/dL	ACT score, spirometry, or blood eosinophil count: –
Braganza *et al*[184]	Randomized double-blind parallel group trial: atorvastatin 40 mg/d *vs.* placebo (4 weeks); then ICS added to both groups (4 weeks)	71 smokers with mild-to-moderate asthma	8 weeks	Serum lipid levels before *vs.* after atorvastatin treatment: TC: 5.15 ± 0.89 *vs.* 3.62 ± 0.76 mmol/L; LDL-C: 3.19 ± 0.82 *vs.* 1.89 ± 0.62 mmol/L; HDL-C: 1.24 ± 0.35 *vs.* 1.29 ± 0.35 mmol/L; TG: 1.59 ± 0.87 *vs.* 1.02 ± 0.35 mmol/L	Serum lipid levels before *vs.* after placebo treatment: TC: 5.67 ± 1.12 *vs.* 5.34 ± 0.90 mmol/L; LDL-C: 3.49 ± 0.99 *vs.* 3.46 ± 0.87 mmol/L; HDL-C: 1.26 ± 0.31 *vs.* 1.23 ± 0.27 mmol/L; TG: 2.18 ± 1.41 *vs.* 1.74 ± 1.29 mmol/L	Asthma quality of life score: ↑; morning PEF: –
Huang *et al*[185]	Nationwide population-based study: statin users and non-statin users. Statins included atorvastatin, lovastatin, simvastatin, fluvastatin, pravastatin, and rosuvastatin.	11,808 asthma patients	4.66±2.32 years	Serum lipid levels were not detected	Serum lipid levels were not detected	Statin use was associated with reduced hospitalization for asthma attack.
Maneechotesuwan *et al*[186]	Double-blind study: simvastatin 10 mg/d or matched placebo	50 patients with mild asthma receiving a low dose of ICS	10 weeks (2-week run-in period and 8-week treatment)	Serum lipid levels before *vs.* after simvastatin treatment: Cholesterol: 197.0 (177.8, 249.0) *vs.* 155.5 (136.3, 185.3) mg/dL; LDL-C: 136.5 (117.8, 182.5) *vs.* 95.0 (77.5, 108.0) mg/dL	Serum lipid levels before *vs.* after placebo treatment: cholesterol: 208.0 (179.3, 220.3) *vs.* 201.0 (177.0, 229.5) mg/dL; LDL-C: 132.5 (126.3, 151.3) *vs.* 133.5 (119.3, 154.5) mg/dL	Sputum eosinophil percentages: ↓
Cowan *et al*[175]	Randomized, placebo-controlled, crossover trial: simvastatin 40 mg/d	43 asthma patients on ICS	≥3 months	Serum lipid levels were not detected	Serum lipid levels were not detected	ACQ ↓, FEV_1 ↑, sputum eosinophils ↓

(*continued*)

Table 2
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Study	Design	No. and participants	Duration	Serum lipid levels before and after statin treatment	Serum lipid levels before and after non-statin or placebo treatment	Effect of statin therapy
	or placebo, with simultaneous ICS reduction until loss of control, then ICS increase until control					
Hothersall *et al*[174]	Double-blind randomized controlled crossover trial: oral atorvastatin 40 mg daily or matched placebo	54 adults with atopic asthma on ICS	22 weeks (2×8 weeks treatment plus 6-week washout)	Serum lipid levels after atorvastatin therapy: Cholesterol: 3.3 (2.9, 3.9) mmol/L; TG: 0.9 (0.6, 1.3) mmol/L; HDL-C: 1.2 (1.1, 1.5) mmol/L	Serum lipid levels after placebo therapy: Cholesterol: 5.1 (4.5, 5.7) mmol/L; TG: 1.1 (0.8, 1.6) mmol/L; HDL-C: 1.4 (1.1, 1.7) mmol/L	Mean morning PEF, spirometry, or ACQ score: – Sputum macrophages and leukotriene B4: ↓
Menzies *et al*[171]	Randomized, double-blind crossover trial: simvastatin *vs.* placebo after withdrawing anti-inflammatory medications	16 patients with mild to moderate asthma on ICS	1 month	Serum lipid levels before *vs.* after simvastatin treatment: TC: 4.7 ± 0.2 *vs.* 3.6 ± 0.2 mmol/L; LDL-C: 2.4 ± 0.2 *vs.* 1.0 ± 0.1 mmol/L; HDL-C: 1.6 ± 0.1 *vs.* 1.5 ± 0.1 mmol/L	Serum lipid levels before *vs.* after placebo treatment: TC: 4.7 ± 0.2 *vs.* 4.6 ± 0.2 mmol/L; LDL-C: 2.4 ± 0.2 *vs.* 2.3 ± 0.2 mmol/L; HDL-C: 1.6 ± 0.1 *vs.* 1.4 ± 0.1 mmol/L	Peripheral eosinophil, lung volumes, or airway resistance: –

ACQ: Asthma control questionnaire; ACT: Asthma control test; BDP: Beclomethasone dipropionate; CCL: Chemokine (C-C motif) ligand; ED: Emergency department; ER: Emergency room; FEV_1: Forced expiratory volume in one second; FGF: Fibroblast growth factor; HDL-C: High-density lipoprotein cholesterol; ICS: Inhaled corticosteroid; IL: Interleukin; LDL-C: Low-density lipoprotein cholesterol; MMP: Matrix metalloproteinase; PEF: Peak expiratory flow; sCD40L: Soluble CD40 ligand; TC: Total cholesterol; TG: Triglyceride; TGF: Transforming growth factor. –: No change; ↑: Increase; ↓: Decrease.

and inhibiting NETosis in a mouse model of severe asthma with neutrophil-predominant inflammation induced by OVA and LPS.[156]

Despite promising results from preclinical studies, clinical studies using statins to protect against asthma have produced underwhelming or contradictory results [Table 2].[171–186] Several studies with case-control or retrospective cohort designs, have reported that statins have protective effects on asthma clinical outcomes, such as asthma-related emergency department visits,[176,178] or hospitalizations.[179,185] In contrast, a number of randomized clinical trials found that statins did not affect inflammation or clinical asthma outcomes.[171–175] The reasons for these heterogeneous results can be explained by several potential contributing factors such as short-term treatment duration, small sample size, type of statin used, and variations in asthma endotypes.[121] Previous clinical trials on human asthma have all used approved oral statin administration, which may hinder lung bioavailability because of extensive liver metabolism, potentially reducing the bioactive dose in the lungs.[187] Rodent studies have suggested that inhaled statins might be a superior choice,[146,166] but this route of administration has not yet been approved for human use. Therefore, the measurement of drug concentration in the lungs in future studies is prudent. In addition, almost all current clinical studies have been conducted among patients with mild, moderate, or severe asthma without specific phenotypic classification, which may lead to an inability to properly assess the effects of an intervention on different asthma phenotypes. Furthermore, none of these clinical studies have characterized blood lipid levels or identified patients with asthma and dyslipidemia. Meanwhile, it is unclear whether statins influence asthma through lipid-lowering, anti-inflammatory effects, or both. Thus, the effects of statins on specific phenotypes of asthmatic patients with dyslipidemia require further research.

Other promising therapeutic drugs

Additional cholesterol-targeting agents, including liver X receptor (LXR) agonists and apolipoprotein mimetic peptides, have been investigated in asthma models. Activation of LXR can inhibit the expression of proinflammatory mediators in human airway smooth muscle cells,[188] and attenuate IgE production and airway remodeling in a mouse model of chronic asthma,[189] indicating that the modulation of LXR activity may be a new therapeutic approach for asthma. However, other studies reported contradictory results. LXR agonists increase airway inflammation, AHR, and airway remodeling in animal models.[190–192] Hence, further investigation of the effects of these drugs on asthma is required.

Apolipoproteins, such as apoA-I and apolipoprotein E (apoE), are crucial constituents of lipoprotein particles that facilitate the efficient transportation of cholesterol, TGs, and phospholipids between plasma and cells. The pivotal roles of apolipoproteins in lung disease pathogenesis and therapy are gaining increasing recognition due to their ability to alleviate inflammation, oxidative stress, and tissue remodeling while improving adaptive immunity

and host defense.[193] In animal models of asthma, apoA-I mimetic peptides such as 5A and D-4F can attenuate the development of airway inflammation and AHR.[194,195] The action of 5A in reducing airway inflammation was mediated by the reduction of Th2 and Th17 cytokines as well as C–C chemokines. Intranasal administration of 5A also inhibited neutrophilic airway inflammation in OVA-challenged ApoA-I-deficient mice.[196] Taken together, the 5A and D-4F apoA-I mimetic peptides may be a novel therapeutic approach for asthma. ApoE mimetic peptides inhibited airway inflammation, AHR, goblet cell hyperplasia, IgE production, and the expression of Th2 and Th17 cytokines in a house dust mite-induced model of murine asthma via an LDL receptor-dependent mechanism,[197] suggesting a potential treatment option for asthma. In addition, whether other novel lipid-lowering drugs, such as proprotein convertase subtilisin/kexin type 9 and inclisran, can be applied for the treatment of asthma patients with dyslipidemia requires further research.

Conclusion

A thorough understanding of asthma and dyslipidemia is clinically significant. Asthma with dyslipidemia would be a specific phenotype of asthma, with an increasing prevalence worldwide. Asthma with dyslipidemia is characterized by older age, elevated BMI, female predominance, worse lung function, airway obstruction, severe asthma, and worse asthma control. Dyslipidemia can influence asthma inflammation via both the T2 and non-T2 pathways. Finding surrogate or complementary signature biomarkers that can accurately identify asthma with dyslipidemia phenotypes is a pivotal direction for future research and may contribute to the effective management of asthma. Several underlying mechanisms have been identified to explain asthma with dyslipidemia; however, the underlying pathological pathways remain unclear. Importantly, dyslipidemia is a significant TT for asthma [Figure 3]. Identifying new potential therapeutic targets for asthma with dyslipidemia may improve the prognosis of patients with asthma, including those with severe and steroid-insensitive asthma. Finally, we provide some suggestions for future research. The development and utilization of animal models of asthma with dyslipidemia will help better understand the phenotype of dyslipidemia-associated asthma. Future clinical trials should not generalize asthma phenotypes and should isolate this phenotype for specific research. With advances in biotechnology, the application of multi-omics technologies, including single-cell transcriptomics, microbiomics, and metabolomics, can comprehensively explore this phenotype.

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Conflicts of interest

None.

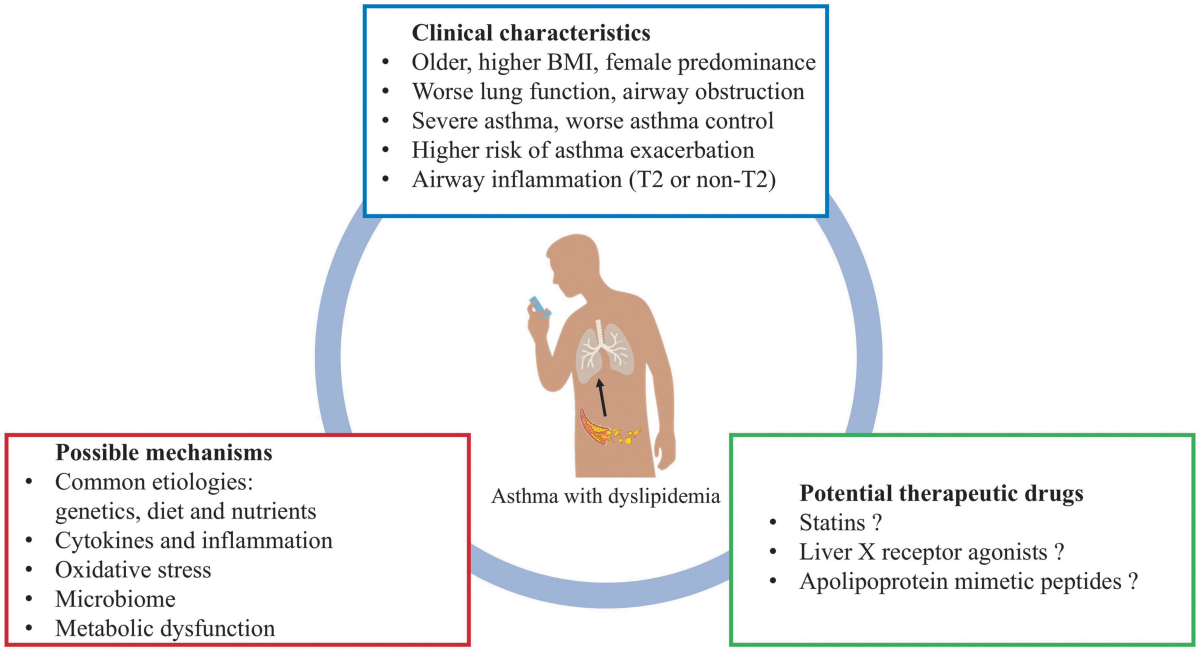

Figure 3: Clinical characteristics, possible mechanisms and potential therapeutic drugs for asthma with dyslipidemia. Dyslipidemia can act as a treatable trait in asthma management with precision medicine. Targeted lipid-lowering drugs including statins, liver X receptor agonists, and apolipoprotein mimetic peptides may improve asthma outcomes, such as asthma control, asthma exacerbation, lung function, and clinical remission.

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