Dyslipidemia Is Associated With Worse Asthma Clinical Outcomes: A Prospective Cohort Study

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INTRODUCTION

Asthma is a heterogeneous disease with diverse clinical phenotypes. It affects 1% to 18% of the population in different countries.1 Different phenotypes are triggered by complex geneenvironment interactions and respond differently to inhaled corticosteroids (ICSs) or oral corticosteroids and have different clinical characteristics, including asthma exacerbations (AEs).2,3 Severe AEs can be fatal and can create an enormous burden on the health care system.1 It is essential to identify risk factors for AEs and to have a management plan, which can reduce AEs and improve a patient's overall well-being and quality of life .

Dyslipidemia, defined as extreme deviations in lipids or lipoprotein levels, including high triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c), has been widely documented to be associated with cardiovascular disease,4 type 2 diabetes,5 and chronic kidney disease.6 Recent studies have found that dyslipidemia has also been associated with asthma and related disorders,7,8 even in nonobese patients.9 However, the underlying mechanisms of the link between asthma and dyslipidemia are unclear. The most commonly recognized mechanisms linking dyslipidemia conditions and asthma involve inflammation and airway hyperreactivity.9-11

A large number of previous studies focused on lipid profile and asthma prevalence.12-16 For example, a study found asthma prevalence to be greater in adolescents with a high TC level and high TG/HDL-c ratio in Korea.12 Furthermore, low HDL-c in Cypriot children was associated with an increased risk of asthma in adolescence.13 A meta-analysis including 20 studies found that patients in the asthma group had higher levels of LDL-c and TC compared with those in the control group.14 These findings suggested the potential association between dyslipidemia and asthma. Furthermore, some studies found that low HDL-c and high LDL-c were negatively related to FEV1% predicted.15,16 However, few studies have focused on the relationship of dyslipidemia with asthma control and asthma phenotypes. Importantly, there is a paucity of prospective cohort studies exploring the relationship between dyslipidemia and AEs. We hypothesized that dyslipidemia would be associated with worse asthma clinical outcomes. Our primary goal was to identify the relationships between dyslipidemia and future AEs. Our secondary objective was to explore the association between dyslipidemia and asthma phenotypes. This knowledge can assist in the development of strategies to prevent AEs and improve asthma management.

METHODS Design overview and participants

This study, with an observational cohort study design, explored the relationships of dyslipidemia with AEs on the basis of the ongoing prospective database of the Australasian Severe Asthma Network.3,17 This study was reviewed and approved by the Institutional Review Board at West China Hospital, Sichuan University, Chengdu, China (no. 2014-30). Informed consent was obtained from all participants.

Patients aged 18 years or older with stable asthma were consecutively enrolled in the asthma clinic of West China Hospital from June 2015 to August 2019. All patients with asthma had a physician diagnosis based on the American Thoracic Society (ATS)18 and Global Initiative for Asthma guidelines.1 This included the history of episodic respiratory symptoms and evidence of reversible airflow obstruction, including bronchodilator responsiveness (with an improvement in FEV1 of 12% and 200 mL from baseline after 400 mg of salbutamol) or airway hyperresponsiveness (causing a decrease in FEV1 of >20%) in response to a provocative dose of methacholine (<2.565 mg). Stable asthma was defined as no exacerbation or respiratory tract infection for at least 1 month before enrollment. Patients with rheumatoid arthritis, chronic liver disease, or other severe unstable chronic diseases were excluded. We also excluded those who were unable to perform the required measurements.

Data collection and assessments

At baseline, we used a structured questionnaire to collect clinical data, which included demographic characteristics, medications, asthma history, body mass index (BMI), atopy status, and asthma control.19 Asthma control was determined by the 6-item Asthma Control Questionnaire score (a score of 1.5 was classified as uncontrolled asthma and a score of <1.5 as controlled or partially controlled asthma).19 All the patients underwent fractional exhaled nitric oxide (FENO)20 (Aerocrine, Solna, Sweden) and spirometry tests21 according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations. Blood sampling, including full blood cell count with differential (Sysmex XN-9000, Sysmex, Kobe, Japan), IgE (Beckman Immage 800, Brea, CA, USA), and serum lipid (Cobas 8000, Roche, Switzerland) tests were performed. The sputum induction and analysis were performed as described in our previous study.22

Definition of dyslipidemia

Blood samples were collected after an overnight fast for at least 8 hours, and the time of blood sampling was fixed between 8 and 9 AM on the following day.23 According to the guidelines for managing dyslipidemia,24,25 normal levels of TGs (<1.7 mmol/L), TC (<5.2 mmol/L), LDL-c (<3.4 mmol/L), and HDL-c (1.0 mmol/L) were defined. In this study, the subjects were classified into 2 groups: (1) the dyslipidemia group (DLG) (with abnormal levels of 1 or more of the aforementioned 4 lipids) and (2) the normal-lipidemia group (NLG) (with normal levels of TGs, TC, LDL-c, and HDL-c).

Spirometry

All subjects underwent baseline lung function tests after withholding ICSs/long-acting b2-agonists, anticholinergics, or oral therapy with aminophylline, leukotriene receptor antagonist for at least 24 hours, and short-acting b2-agonists for 6 hours or longer.21 According to ATS/ERS recommendations,21 FEV1, forced vital capacity (FVC), FEV1/FVC ratio, and maximal mid-expiratory flow (MMEF) were measured using the MedGraphics CPES/D USB (MedGraphics, Minneapolis, MN, USA). Normative values of pulmonary function tests in Chinese adults were used to calculate the predicted FEV1, FVC, and MMEF to determine the percent predicted indices.26

Definitions of asthma phenotypes

Asthma clinical and inflammatory phenotypes including older adult asthma,27,28 obese asthma,29 allergic/nonallergic asthma,30 early-onset asthma,31 asthma with fixed airflow limitation,1,3 severe asthma,1 eosinophilic asthma,32,33 and type 2 (T2)/non-T2 asthma34 were evaluated in this study.

Specifically, older adult asthma was defined as asthma in subjects 65 years or older.27,28 Obese asthma was defined as asthma in subjects with a BMI of 30 kg/m2 or more.29 Allergic asthma30 was defined as asthma with a positive skin prick test result and symptoms in response to allergen exposure. Otherwise, it was defined as nonallergic asthma. Skin prick tests were performed on 11 common allergens: dog hair, cat hair, cockroach, pollen (ragweed, birch, maize, and London plane), mold (Alternaria tenuis and Aspergillus fumigatus), and house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae).28,30 Symptoms in response to allergen exposure were characterized by seasonal variation (not due to infection) and/or symptoms (ie, wheezing, shortness of breath, chest tightness, and cough) when exposed to freshly cut grass, house dust, molds, cats, dogs, or other furbearing animals.30 Early-onset asthma was defined as physician diagnosis before the age of 12 years.31 Asthma with fixed airflow limitation was defined as asthma with FEV1/FVC less than 70% after inhalation of salbutamol.1,3 Severe asthma was defined as asthma that required the Global Initiative for Asthma steps 4 and 5 treatment regimens, which needed moderate- to high-dose ICSs to prevent from becoming "uncontrolled," or asthma that remained "uncontrolled" despite this treatment for at least 6 months.1 or equal to 0.3 109 cells/L.32,33 T2 asthma34 was defined as Eosinophilic asthma was defined as asthma with sputum eosino- asthma having 2 or more of the following: eosinophil count greater phils greater than or equal to 3% or blood eosinophils greater than than or equal to 0.30 109 cells/L, IgE level greater than or equal to 100 IU/mL, or FENO level greater than or equal to 30 parts per billion; otherwise, it was defined as non-T2 asthma.

Assessment of AEs

All participants were prospectively followed for 1 year. Asthma outcomes included severe AEs and moderate to severe AEs. The detailed definitions were based on the criteria of the ATS/ERS Task Force.35 Severe AEs were those that presented as hospitalizations and emergency department (ED) visits needing systemic corticosteroids or that required outpatient corticosteroid use for more than 3 days.35 A moderate AE was defined as asthma that required an unscheduled visit with a prescription for extra controller therapy, doubling or even greater increases in ICS dose, but not requiring systemic glucocorticoids because of worsening asthma symptoms.35 All patients were followed up for 12 months through regular face-to-face visits (or telephone calls, if unavailable). Medication adherence information and the frequency and severity of AEs were collected using a short, structured questionnaire. Only 1 occurrence was recorded if hospitalizations, ED visits, or unscheduled visits from a primary care setting took place within 1 week of each other.

Statistical analysis

Determination of the sample size in this study and the power indicated in our post hoc analyses are reported in this article's Online Repository.

Continuous variables were presented as mean SD or median (quartile 1, quartile 3). The percentage was shown for categorical data such as sex and asthma phenotypes. Differences between groups were analyzed by using either the Student t test or the MannWhitney U test. When necessary, covariate adjustment for confounders by

covariance analysis was used. Categorical data were compared using the c2 test or the Fisher test.

Logistic regression models were used to evaluate the relationships between dyslipidemia and asthma phenotypes at baseline, followed by calculation of odds ratio (OR) with a 95% CI. Then, negative binomial regression models were used to investigate the association between dyslipidemia and AEs (frequency) during longitudinal follow-up, followed by calculation of rate ratio with a 95% CI. To exclude the influence of statins, we performed sensitivity analyses to explore the associations between dyslipidemia and asthma outcomes after excluding the patients who were receiving statins. Statistical analysis was performed using the IBM SPSS 21.0 software (SPSS, Chicago, IL). All tests were 2-tailed, and a P value less than .05 was considered statistically significant. To adjust for multiple tests, the false-discovery rateeadjusted P value (ie, the q value) was further provided (a value of .05 was accepted as significant).36

To further adjust for potential confounding factors in this study, we tried to use propensity score matching (PSM) to explore associations between dyslipidemia and AEs. Patients in DLG were matched 1:1 to patients in NLG using nearest-neighbor matching. Standardized mean differences less than 0.03 were considered balanced.

RESULTS

Demographic and clinical characteristics

A total of 496 patients with asthma were screened for this study, but serum lipid data were available for 477 patients (Figure 1). Subjects with asthma were divided into the NLG (n ¼ 259) and the DLG (n ¼ 218) according to their serum lipid status. There were 99 (20.8%), 158 (33.1%), 106 (22.2%), and 29 (6.1%) subjects with dyslipidemia due to abnormal TGs, TC, LDL-c, and HDL-c, respectively. The demographic and clinical characteristics of all subjects are presented in Table I. Compared with the NLG subjects, the DLG subjects were older (42.2 13.73 vs 50.14 12.61 years; P < .001; q ¼ 7.85 109), had a lower proportion of females (70.3% vs 58.3%; P ¼ .006; q ¼ .016), and had higher BMI (22.44 3.51 vs 23.65 3.38 kg/ m2; P < .001; q ¼ .001). Compared with the NLG , the DLG had a higher proportion of subjects with uncontrolled asthma (21.3% vs 32.1%; P ¼ .007; q ¼ .017), and dyslipidemia was a risk factor for uncontrolled asthma (ORadj, 1.808; 95% CI, 1.167-2.801) after adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose (see Table E1). The DLG had lower IgE levels, but higher absolute counts of blood lymphocytes and monocytes, and percentage of monocytes, compared with the NLG (all P < .05). There were no differences in smoking status, maintenance ICS dose, statin use, asthma duration, or airway inflammation (including FENO, sputum neutrophils, eosinophils, lymphocytes, and macrophages) (all P > .05) (Table I).

Airway obstruction assessed by spirometry

The DLG had worse FEV1% predicted (70.12% 21.52% vs 76.73% 19.04%), MMEF% predicted (41.97% 24.37% vs 50.25% 24.74%), and FEV1/FVC ratio (63.02% 12.82% vs 69.04% 13.04%) compared with the NLG (all P < .05 and all q < .05). After adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose, differences remained statistically significant (all P < .05 and all q < .05) (Table II).

Asthma phenotypes

Figure 2 shows the difference in asthma phenotypes between the DLG and the NLG (see Table E2). The DLG had a significantly greater proportion of older adult asthma (16.1% vs 7.7%; P ¼ .005; q ¼ .015), nonallergic asthma (38.3% vs 24.5%; P ¼ .001; q ¼ .004), asthma with fixed airflow limitation (54.1% vs 32.0%; P < .001; q ¼ 3.16 105), and severe asthma (17.0% vs 9.3%; P ¼ .011; q ¼ .023) than the NLG.

Logistic regression models were used to evaluate the relationship between dyslipidemia and asthma phenotypes. After adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose, dyslipidemia was associated with a higher risk of older adult asthma (ORadj, 2.257; 95% CI, 1.200-4.243), nonallergic asthma (ORadj, 1.781; 95% CI, 1.1662.720), asthma with fixed airflow limitation (ORadj, 2.259; 95% CI, 1.502-3.396), and severe asthma (ORadj, 2.055; 95% CI, 1.102-3.832) (Figure 3; see Table E3). However, there were no associations between dyslipidemia and other phenotypes (obese, early-onset, eosinophilic, and non-T2 asthma phenotypes) (Figure 3; see Table E3).

Dyslipidemia and AEs

Four hundred forty-seven patients completed the 12-month follow-up with AE data (Table III). The rate of loss to followup did not differ much between the DLG and the NLG (12 [5.5%] vs 18 [6.9%]; P ¼ .517), and baseline characteristics of the 447 patients who completed the 12-month follow-up in the cohort were very similar in comparison with the baseline characteristics of the 477 patients (see Table E4). Of the 447 patients, 41 (9.17%) patients experienced severe AEs in the 12-month follow-up. Compared with the NLG (n ¼ 241), more severe AEs occurred in the DLG (n ¼ 206) (6.6% vs 12.1%; P ¼ .045; q ¼ .048). Also, the frequencies of severe AEs were greater in the DLG than in the NLG (0.20 0.69 vs 0.12 0.67; P ¼ .022; q ¼ .034) (Table III). However, there was no difference of distribution of exacerbation-prone asthma between the NLG and the DLG (0.4% vs 1.5%; P ¼ .126) (see Table E5). Of the 447 patients, 121 (27.1%) patients experienced moderate to severe AEs in the 12-month follow-up. Compared with the NLG (n ¼ 241), more moderate to severe AEs occurred in the DLG (n ¼ 206) (24.9% vs 29.6%); however, the difference was not statistically significant (P ¼ .263). Also, the frequencies of moderate to severe AEs were greater in the DLG than in the NLG (0.66 1.45 vs 0.49 1.50); however, the difference was not statistically significant (P ¼ .183). Accordingly, as for individual AEs, more patients in the DLG (n ¼ 206) underwent hospitalizations compared with those in the NLG (n ¼ 241) (10.7% vs 5.4%; P ¼ .038; q ¼ .044), accompanied with greater frequencies (0.15 0.47 vs 0.07 0.31; P ¼ .039; q ¼ .044). Similar results were found in patients using outpatient corticosteroids. However, there were no significant differences in ED visits and unscheduled visits between the NLG and the DLG
(Table III).

The multivariable negative binomial regression models indicated that in the 12-month follow-up period, dyslipidemia was associated with increased frequencies of severe AEs (adjusted rate ratio [RRadj], 1.910; 95% CI, 1.075-3.395) and moderate to severe AEs (RRadj, 1.435; 95% CI, 1.019-2.019) after adjusting for age, sex, BMI, smoking, asthma duration, FEV1% predicted, ICS dose, medication adherence, hypertension, and fasting blood glucose (Figure 4; see Table E6).

Sensitivity analyses

In sensitivity analyses, after excluding the patients who were receiving statins, results of the association of dyslipidemia with airway obstruction (Table II), asthma

phenotypes (Figure 3; see Table E3), and AEs (Figure 4; see Table E6) did not differ significantly from the results of the main analysis.

PSM-based subgroup analysis

In the PSM-based subgroup analysis, 350 patients with stable asthma were included in the NLG and the DLG (n ¼ 175 for both groups). There were no differences in measured confounders, including age, sex, BMI, smoking, hypertension, fasting blood glucose, and age of asthma onset (see Table E7). Furthermore, the DLG had a higher percentage (12.6% vs 6.0%; P ¼ .036) and frequency (0.25 0.78 vs 0.10 0.35; P ¼ .033) of severe AEs compared with the NLG, mainly including a higher percentage (10.8% vs 4.8%; P ¼ .040) and frequency (0.15 0.49 vs 0.06 0.28; P ¼ .039) of hospitalizations (see Table E8 in this article's Online Repository). In logistic regression models, dyslipidemia was also an independent risk factor for severe AEs (RRadj, 2.648; 95% CI, 1.129-6.162; P ¼ .025) (see Table E9). Similar results were also found in negative binomial regression models (RRadj ¼ 2.845; 95% CI, 1.455-5.563; P ¼ .002) (see Table E10 in this article's Online Repository at).

Independent associations of the 4 lipids with airway obstruction, asthma phenotypes, and AEs

Independent associations of the 4 lipids with airway obstruction (see Table E11), asthma phenotypes (see Table E12), and AEs (see Table E13 in this article's Online Repository at www. jaci-inpractice.org) were explored. The high TC group had worse FEV1/FVC ratio and was associated with older adult

FIGURE 4. Associations between dyslipidemia and AEs in the 12-month follow-up period on the basis of negative binomial regression models in the main and sensitivity analyses. Sensitivity analyses were performed after excluding the patients who were receiving statins.

asthma, nonallergic asthma, and asthma with fixed airflow limitation. High TC was a risk factor for hospitalization. High TG was associated with obese asthma. High LDL-c was related to asthma with fixed airflow limitation and severe asthma. Detailed descriptions are given in this article's Online Repository at www. jaci-inpractice.org.

DISCUSSION

To our knowledge, this is the first prospective cohort study to explore the clinical significance of dyslipidemia with asthma control, asthma phenotypes, and future AEs. Our results show that dyslipidemia is related to worse asthma control, airway obstruction, nonallergic asthma, and severe asthma phenotypes, and it is also an independent risk factor for AEs, after adjusting for potential confounders. These findings highlight the importance of dyslipidemia in asthma management.

Blood lipids are widely assessed in clinical settings because dyslipidemia is an independent risk factor for cardiovascular disease.4 Our study found that the subjects with dyslipidemia were older, had higher BMI, and were more likely to be male, as found in previous studies.37-39 It is well understood that dyslipidemia is related to BMI,36 with previous studies reporting a relationship between obesity and asthma, suggesting dyslipidemia to be intermediary.10,40 However, some studies have indicated that dyslipidemia is independently linked to pulmonary function and sensitization,7,8 even in nonobese patients.9 In our study, we found that although the DLG had a slightly higher mean BMI, there was a lot of overlap in BMI between the DLG and the NLG, and

there was no difference in the proportion of obese subjects in the DLG and the NLG, suggesting that dyslipidemia is relatively independent of obesity41 in this asthma cohort.

In our study, dyslipidemia was also found to be associated with airway obstruction. Consistent with our results, Barochia et al15 found that in allergic asthma, large HDL nuclear magnetic resonance particles were positively correlated with FEV1, whereas TC and LDL-c were associated with more severe airflow obstruction. Furthermore, LDL-c was associated with airway obstruction, including 50% of forced expiratory flow and specific airway resistance.16 In this regard, our results add to earlier findings that dyslipidemia is a risk factor for severe airway obstruction independent of BMI.16,41

Our study found that compared with the NLG, the DLG was associated with uncontrolled asthma, had lower IgE levels, and was less atopic. The DLG also had an increased risk of nonallergic asthma after adjusting for age, sex, BMI, ICS dose, smoking, hypertension, and fasting blood glucose. This is consistent with the lower IgE and atopy rates that we observed in the DLG, which also indicated the presence of non-T2 inflammation. Several previous studies corroborate our findings.42-44 One study reported that intravenous administration of HDL enriched with a-1-antitrypsin (an elastase inhibitor) to cigarette smokeeexposed mice reduced the number of bronchoalveolar lavage fluid neutrophils and macrophages, as well as IL-6, TNFa, and monocyte chemoattractant protein-1.42 Moreover, by deleting the gene that encodes apolipoprotein A-I (a major structural protein of HDL-c), ovalbumin-challenged Apoa1(/) mice presented a neutrophilic-predominant, non-T2 asthma phenotype, with an increase in airway neutrophils, but T2 cytokines (IL-4, IL-5, and IL-13) were not increased.43,44 Moreover, in our study, there was no difference in ICS dose of severe asthma grouped by lipid status (see Table E14), and we found that dyslipidemia was a risk factor for severe asthma, which was also in line with previous studies.45,46 For example, Jiang et al45 found that TGs positively correlated with asthma severity. Furthermore, Misso et al46 identified that increased TC was independently associated with severe asthma.

AE risk can be reduced; however, it may not be eliminated in some individuals, despite optimal guideline-directed treatment.47 Many risk factors mediate the occurrence of AEs. Previously published studies showed that diabetes and other components of metabolic syndrome were associated with AEs.48-50 Dyslipidemia is an important component of the metabolic syndrome.51 Our study with a prospective cohort design expanded the findings that dyslipidemia is an independent risk factor for AEs, after adjusting for other components of the metabolic syndrome. Some other studies are consistent with our findings. For example, a cross-sectional study found that compared with persons with mild to moderate asthma or the control group, increased plasma cholesterol was independently associated with severe asthma.46 Furthermore, a cluster analysis identified that a cluster with high eosinophil count, uric acid, TC, transaminase, alanine transferase, and high-sensitive C-reactive protein levels had a higher risk of AEs.52 In our study, the DLG had a higher proportion of severe asthma and worse asthma control at baseline, both of which were positively associated with future AEs.1 The possible differences in inflammation mentioned earlier between the DLG and the NLG may partly explain the difference in AEs. Interestingly, statins, which have beneficial effects on cardiovascular diseases by targeting dyslipidemia, also have antiinflammatory effects.53 A case-control study of 16,700 adults with asthma found

that statin use was related to decreased risk of asthma-related ED visits and less oral corticosteroid use.54 These observations require further investigation to determine the mechanism by which dyslipidemia may contribute to AE risk. Randomized controlled trials are needed to determine whether statins may be beneficial in asthma management.

A recent investigation found that 33.8% of community residents in China had dyslipidemia.55 However, the rates of awareness and treatment of dyslipidemia in China were significantly low.56 The same results were found in our study. Our findings (dyslipidemia was associated with severe asthma and increased AEs) highlighted the importance of dyslipidemia in asthma management, which was independent of other components of the metabolic syndrome. In addition, in recent years, some have argued for a “treatable trait” approach, which would suggest dyslipidemia as an “extrapulmonary trait.”28,57,58 Further studies are needed to explore the role of dyslipidemia as an extrapulmonary trait in asthma and to evaluate whether asthma outcomes would be improved by modifying this trait. But this study has several limitations that need to be addressed. First, blood lipids have been tested only once during the 1-year cohort study. Furthermore, we cannot rule out the effects of ICSs on blood lipids, although there was no difference in ICS dose between the 2 groups. Most of the patients (>80%) in our study had adult-onset asthma. Further studies should be conducted to characterize the association between dyslipidemia and asthma outcomes in early-onset asthma phenotype. At the planning stage of any clinical study, the determination of the sample size is a very important process to show the validity, accuracy, and reliability of the study. However, to our knowledge, no published studies have indicated the associations between dyslipidemia and future AEs in a prospective cohort study design until now. Our post hoc analyses showed that the power of this study was sufficient to support our findings. However, further studies are needed to validate our findings in larger populations in different settings and races. This study was exploratory, so we used a standard a level of 0.05 ($P < .05$), which may produce falsepositive results. However, the false-discovery rateeadjusted P value (ie, the q value) indicated that the associations between dyslipidemia and asthma outcomes in this study were statistically significant. Future studies are needed to validate the generalizability of our findings from the exploratory analyses. In addition, we did not investigate the underlying mechanisms of dyslipidemia and asthma and this is an important area for future research.

CONCLUSIONS

This study highlights the clinical relevance of dyslipidemia in asthma management, which is associated with worse asthma control, airway obstruction, severe asthma phenotype, and being a risk factor for future AEs. These findings highlight the importance of considering dyslipidemia as an extrapulmonary trait in asthma management. Further studies are needed to evaluate blood lipids as a potential therapeutic target for asthma.

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