REVIEW

https://doi.org/10.4046/trd.2017.80.2.113
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2017;80:113-135

trd Tuberculosis & Respiratory Diseases

Asthma and the Risk of Rheumatoid Arthritis: An Insight into the Heterogeneity and Phenotypes of Asthma

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Asthma is traditionally regarded as a chronic airway disease, and recent literature proves its heterogeneity, based on distinctive clusters or phenotypes of asthma. In defining such asthma clusters, the nature of comorbidity among patients with asthma is poorly understood, by assuming no causal relationship between asthma and other comorbid conditions, including both communicable and noncommunicable diseases. However, emerging evidence suggests that the status of asthma significantly affects the increased susceptibility of the patient to both communicable and noncommunicable diseases. Specifically, the impact of asthma on susceptibility to noncommunicable diseases such as chronic systemic inflammatory diseases (e.g., rheumatoid arthritis), may provide an important insight into asthma as a disease with systemic inflammatory features, a conceptual understanding between asthma and asthma-related comorbidity, and the potential implications on the therapeutic and preventive interventions for patients with asthma. This review discusses the currently under-recognized clinical and immunological phenotypes of asthma; specifically, a higher risk of developing a systemic inflammatory disease such as rheumatoid arthritis and their implications, on the conceptual understanding and management of asthma. Our discussion is divided into three parts: literature summary on the relationship between asthma and the risk of rheumatoid arthritis; potential mechanisms underlying the association; and implications on asthma management and research.

Keywords: Asthma; Arthritis, Rheumatoid; Risk; Comorbidity; Epidemiology; Genetic Heterogeneity; Phenotype

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Received: Oct. 20, 2016
Revised: Dec. 3, 2016
Accepted: Dec. 8, 2016

Introduction

Asthma is a common and debilitating chronic condition, affecting more than 235 million people worldwide (4.3% to 8.6% of adults and 2.8% to 37% of children)[1-3]. In Korea, the prevalence of asthma among adults is estimated at 5,707 cases per 100,000 individuals[4]. In the United States, it is estimated that asthma affects nearly 10% of the population and is the most common chronic illness in children[5,6]. Over the last four decades, the prevalence of asthma has markedly increased and trends suggest a continued increase worldwide[7]. Numerous studies have investigated the mechanistic underpinnings of asthma and suggested asthma as a chronic respiratory disease characterized by type-2 inflammation, primarily T helper Type 2 (T_H2) lymphocyte overactivity in the airways, resulting in airway hyperresponsiveness[8]. While the role of T_H2-

predominant immune environment in the pathogenesis of asthma at an airway level (e.g., innate immune dysfunction of bronchial epithelial cells) is well established[9,10], little is known about how the immune dysfunction underlying asthma is related to increased susceptibility to communicable and non-communicable diseases in such patients.

The emerging literature has shown the increased risk of common and serious infections among patients with asthma. For example, Talbot et al.[11] demonstrated the increased risk of invasive pneumococcal disease among patients with asthma, compared to controls (adjusted odds ratio [aOR], 2.4; 95% confidence interval [CI], 1.9–3.1). This finding has been corroborated by several independent studies[12-20], including a population-based case-control study by Juhn et al.[21], which showed an increased risk of developing serious pneumococcal disease among patients with asthma across all ages (aOR, 2.40; 95% CI, 0.88–6.56; p=0.09) and among adults (aOR, 6.70; 95% CI, 1.64–27.30; p=0.01), after controlling for high-risk conditions for invasive pneumococcal disease and smoking exposure. We extended the investigations to the relationship between asthma and nonpneumococcal infections and showed increased risks of *Streptococcus pyogenes* infection (aOR, 1.40; 95% CI, 1.12–1.74; p=0.003)[22] and of *Bordetella pertussis* among individuals with asthma compared with those without asthma (aOR, 1.73; 95% CI, 1.12–2.67; p=0.013)[23]. Recently, we demonstrated that this is true for nonrespiratory infections such as reactivation of latent infection of herpes zoster[24-26] and community-acquired *Escherichia coli* blood stream infections[27]. These findings have been confirmed by several independent studies[28-30]. Furthermore, patients with asthma may have a suboptimal cell-mediated immune response to measles, mumps, and rubella vaccine viruses[31], which indeed increases the risk of vaccine-preventable diseases such as varicella[32] and pertussis[23]. All of these results suggest that the immune dysregulation of asthma has systemic effects that go beyond airway dysfunction (Table 1).

Along these lines, we and others have shown the close associations between asthma and proinflammatory diseases. A recent population-based retrospective matched cohort study demonstrated that patients with asthma had an increased risk of clinical conditions with immune dysregulation such as diabetes mellitus (DM) (hazard ratio [HR], 2.11; 95% CI, 1.43–3.13; p<0.001) and coronary heart disease (CHD) (HR, 1.47; 95% CI, 1.05–2.06; p=0.02)[33]. Another independent study reported that active asthma contributed to the risk of myocardial infarction (aOR, 2.33; 95% CI, 1.12–4.82)[34]. Other independent studies corroborate the associations between asthma and risk of both DM[35,36] and CHD[37,38]. The associations of asthma with other chronic inflammatory diseases including acute coronary syndrome[39], irritable bowel disease[40], chronic kidney disease[41], and cancer[42] have also been reported.

In this review, we chose to summarize the current literature on the association between asthma and the risk of rheumatoid arthritis (RA) due to the following reasons. First, RA is a systemic autoimmune, chronic inflammatory disorder that leads to painful joint destruction, classically associated with an excessive proinflammatory response by T helper type 1 (T_H1) lymphocytes[43-45]. While the conventional theory states that there is an inverse relationship between T_H1 and T_H2 diseases, recent studies suggest positive or no relationship. Thus, determining the association of asthma with the risk of RA may provide an insight into the heterogeneity of asthma, specifically RA (as an asthma-related comorbidity [ARC]) as an asthma phenotype affecting a subgroup of patients with asthma. Second, a recent paper showed that while a subgroup of patients with asthma showed an expected T_H2-high immune profile (e.g., subject cluster 2 within gene cluster 9), another subgroup demonstrated a gene expression of T_H1-predominant inflammatory pathway such as tumor necrosis factor α (TNF-α)[46]. These data suggest that a subgroup of asthma may exhibit a systemic inflammatory feature caused by T_H1-predominant inflammation. Thus, a better understanding of the relationship between asthma and RA with Th1-predominant inflammatory pathway such as TNF-α may allow us to acquire the conceptual feasibility for the coexistence of T_H2 and T_H1 conditions. Finally, as T_H1-mediated disorders, such as RA, are conventionally thought to be inversely related to T_H2-mediated disorders, such as asthma, the current conceptual framework or understanding of the relationship between asthma as a T_H2 condition and systemic inflammatory diseases (e.g., RA) as T_H1 conditions is limited to the counter-regulatory T_H1/T_H2 theory, which is unsuitable to account for a positive relationship between asthma and proinflammatory diseases. Thus, other potential biological plausibility need to be fully considered in order to understand the relationship between asthma and systemic inflammatory diseases such as RA, which provides an understanding of the positive association between these two conditions.

This review will discuss the following: (1) the current literature pertaining to the relationship between asthma and the risk of RA, (2) potential immunogenetic mechanisms underlying such association, and (3) implications on asthma management and research.

Asthma and Risk of RA

In this discussion, our review addresses the relationship between asthma and the risk of RA regardless of its type and heterogeneity as the current literature is limited in addressing the association of asthma with different types of RA. Also, we limited our review to the literature written in English and the exposure status included both asthma or lung functions and other atopic conditions. We described the literature according to the causal direction: positive, inverse (negative), and no association as the current literature pertaining to the relation-

Table 1. A list of pathogens and the relative risk of infection in subjects with and without asthma

Study	Adjusted odds ratio, relative risk, or %	95% Confidence interval	p-value	Population
Pneumococcus				
Talbot et al.[11], 2005	2.4	1.9–3.1	-	Children and adults aged 2–49 years
Juhn et al.[21], 2008	Adults only, 6.7 Children and adults, 2.4	Adults only, 1.6–27.3 Children and adults, 0.9–6.6	Adults only, 0.01 Children and adults, 0.09	Adults >18 years only Children and adults
Flory et al.[17], 2009	2.1	1.5–2.9	<0.0001	Adults
Pilishvili et al.[14], 2010	1.5	1.1–2.1	-	Children aged 3 to 59 months
Klemets et al.[15], 2010	High risk asthma*, 12.3 (matched odds ratio) Low risk asthma†, 2.8 (matched odds ratio)	High risk asthma, 5.4–28.0 Low risk asthma, 2.1–3.6	High risk asthma, <0.001 Low risk asthma, <0.001	Adults aged 18–49 years
Hsu et al.[16], 2011	Asthmatics vs. nonasthmatics, 65% vs. 31%	-	<0.05	Children <18 years
Bjur et al.[19], 2012	Relative risk, 19.33	11.41–32.75	<0.001	Children aged 12–18 years
Pelton et al.[18], 2014	Age <5 years, 1.6 Age 5–17 years, 2.1	1.0–2.4 1.4–3.2	- -	Age <5 years Age 5–17 years
Hasassri et al.[20], 2017	Active asthma vs. no asthma, 1.75	0.99–3.11	0.049	Children <18 years
Streptococcus pyogenes				
Frey et al.[22], 2009	1.40	1.12–1.74	0.003	Children < 18 years
Bordetella pertussis				
Capili et al.[23], 2012	1.73	1.12–2.67	0.013	Children and adults
Herpes zoster				
Kim et al.[25], 2013	2.09	1.24–3.52	0.006	Children
Forbes et al.[28], 2014	1.21	1.17–1.25	-	Adults
Esteban-Vasallo et al.[29], 2014	Men, 1.34; women, 1.32	Men, 1.27–1.42; women, 1.28–1.37	-	Adults
Wi et al.[26], 2015	2.56	1.08–6.56	0.032	Children
Kwon et al.[24], 2016	1.70	1.20–2.42	0.003	Adults aged >50 years
Escherichia coli				
Jackson et al.[30], 2005	Asthmatics vs. nonasthmatics, 5.5% vs. 1%	-	-	Adults >65 years
Bang et al.[27], 2013	3.51	0.94–13.11	0.062	Children and adults
Varicella				
Umaretiya et al.[32], 2016	1.63	1.04–2.55	0.032	Children

*High risk asthma, hospitalization for asthma in the past 12 months; four patients hospitalized for chronic obstructive pulmonary disease and their controls were excluded. †Low risk asthma: entitlement to a prescription drug benefit for asthma but no hospitalization for asthma in the past 12 months.

ship between asthma and the risk of RA is controversial. We summarized the current literature and details of each study are outlined in Tables 2–4.

1. Positive association between asthma and the risk of RA

There are eight studies available in the literature which showed a positive association between asthma and the risk of

https://doi.org/10.4046/trd.2017.80.2.113

RA (Table 2): three cohort studies[47-49], three case-control studies[50-52], and two cross-sectional studies[53,54].

The largest cohort study was conducted by Lai et al.[47] using a nationwide health claims database in Taiwan in which asthma and RA were defined by International Classification of Diseases (ICD) codes. Their results showed that asthma (adjusted hazard ratio [aHR], 1.67; 95% CI, 1.32-2.62) and allergic rhinitis (aHR, 1.62; 95% CI, 1.33–1.98) were significantly associated with an increased risk of RA. This association remained significant even after excluding those subjects who had concurrent diagnoses of asthma and allergic rhinitis. Of note, allergic rhinitis was independently associated with an increased risk of RA as well[47], which infers that chronic respiratory disorders, namely, asthma and allergic rhinitis, exhibit biological coherence with regard to the subsequent development of RA. Another population-based cohort study conducted in Finland by Kero et al.[48] corroborated the study findings by Lai et al.[47]; the effect size was in the range of relative risk of 2.66 (1.23–5.78) and overall results suggested that patients with asthma have an increased risk of RA, compared to those without asthma. Apart from the cohort study design, the main strength of these cohort studies is a large sample size representing the general population of each country, namely Taiwan[47], Finland[48], and Sweden[49]. At the same time, the major limitations of these cohort studies are the use of ICD-9 codes for asthma, resulting in a potential misclassification bias[47-49]; inclusion of subjects less than 7 years of age[48], which is much younger than the average age at which RA usually develops; and the fact that they did not fully adjust for possible confounders or risk factors for RA, such as socioeconomic status, smoking status, and/or body mass index (i.e., potential susceptibility bias)[47-49].

Because the incidence of RA is low, it is challenging to conduct a cohort study with adequate statistical power with suitable ascertainment of exposure (i.e., asthma status) and outcome (i.e., RA). Thus, case-control study design has been commonly implemented by previous studies. There are few population-based case-control studies[51]. De Roos et al.[51] conducted a nested case-control study among women included in the Agricultural Health Study in Iowa and North Carolina and defined asthma by questionnaire and RA by self-report plus confirmation by their physician. The overall effect size was odds ratio of 3.7 (95% CI, 1.3–10.5) for the association between asthma and the risk of RA[51]. The results were replicated by others[50,52]. Another case-control study investigated the prevalence of airway obstruction and bronchial reactivity to inhaled methacholine in 100 RA patients and 50 controls and found that a significantly higher number of patients with RA had a history of wheeze when compared with the controls (18% vs. 4%, $p<0.05$), that lung function measures, such as forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow at 25% and 75% of the pulmonary volume ($FEF_{25\text{-}75\%}$), forced expiratory flow at 25% ($FEF_{25\%}$), forced expiratory flow at 50% ($FEF_{50\%}$), and forced expiratory flow at 75% ($FEF_{75\%}$), were all significantly lower in the RA group, and that a significantly higher number of patients with RA showed bronchial reactivity to inhaled methacholine (55% vs. 16%, $p<0.05$), thus demonstrating objective evidence that RA patients may have decreased lung function[52]. The major limitations of these case-control studies were inclusion of women only[51], a questionnaire-based diagnosis of asthma[50,51] and/or RA[51], and a relatively small number of incident cases[51].

Of the two cross-sectional studies, the largest cross-sectional study was conducted by Dougados et al.[54] based on 3,920 patients with RA recruited in 17 countries where they defined RA by the 1987 American College of Rheumatology (ACR) classification criteria for RA[55]; there was no mention on how they diagnosed asthma. Of 3,920 patients with RA analyzed, the second most frequently associated disease (past or current) was asthma (6.6%) following depression (15%). Of note, their study is the first population-based, cross-sectional observational study to assess comorbidities among a large size of subjects with RA in 17 countries on five continents. One additional cross-sectional study has shown similar results of a higher prevalence of allergic respiratory diseases in patients with RA (16.6%) compared with that in the general population[53]. The major limitations of these cross-sectional studies are that they did not include control subjects[53,54], did not state how they defined asthma[54], and used an interview-based asthma diagnosis[53].

These eight epidemiological studies consistently support the positive association of asthma or lung functions and other atopic conditions such as allergic rhinitis with the risk of RA. Despite the differences in study settings, populations, designs, and ascertainment approaches for exposure and outcomes, the effect size was relatively consistent. The most striking aspect of these studies was that despite the broad range of different definitions of exposure status (e.g., asthma status or other atopic conditions by ICD codes or self-report, FEV_1 and FEV_1/FVC, and methacholine challenge test), they have shown "consistent findings" with regard to the positive association between asthma and the risk of RA and biological coherence. Also, considering the fact that treatments for severe asthma often include systemic corticosteroids and high-dose inhaled corticosteroids, corticosteroid administration did not obscure or mitigate the association between asthma and the risk of RA. Thus, although a population-based cohort study is needed using a well-defined population and suitable ascertainment of asthma and RA status, the existing evidence from these previous studies is quite compelling and strongly supports the association between asthma or other atopic conditions and the risk of RA.

2. Inverse (negative) association between asthma and the risk of RA

There are four studies available in the literature which

Table 2. Studies showing a positive association between asthma and the risk of rheumatoid arthritis

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Lai et al.[47], 2015	A nationwide population-based retrospective cohort study	Patients with allergic disease (n=170,570) Patients without allergic disease (n=170,238)	Asthma, allergic rhinitis, and atopic dermatitis (ICD-9 code)	RA (ICD-9 code)	Asthma (aHR, 1.67; 95% CI, 1.32–2.10) and allergic rhinitis (aHR, 1.62; 95% CI, 1.33–1.98) were significantly associated with incident RA. After controlling for potential confounders, patients with allergic diseases had a significantly higher risk of developing RA, with an aHR 1.24 (95% CI, 1.02–1.51).	There are significant associations between common allergic diseases and incident RA. Patients with more than one allergic disorder had an increased risk of incident RA.	Taiwan National Health Insurance Research Database To improve the diagnostic accuracy, only patients with at least three consistent diagnoses of the same allergic condition within the observational period were considered as a valid diagnosis. Diagnoses of RA that occurred before the allergic diseases were excluded. In a subgroup analysis, among patients with more than one allergic disease, the middle-aged and elderly female patients had a higher risk for developing RA.
Kero et al.[48], 2001	Population-based cohort study	59,865 Children identified by 1986 Finnish Medical Birth Register	Asthma (Finnish International Classification of Diseases)	RA, celiac disease, and type 1 diabetes (Finnish International Classification of Diseases)	Cumulative incidence of asthma in children with RA was significantly higher than in those without RA (10.0% vs. 3.4%, p=0.016). Cumulative incidence of asthma in children with celiac disease was significantly higher than in those without celiac disease (24.6% vs. 3.4%, p<0.001). Asthma tended to be more common in children with type 1 diabetes than in those without type 1 diabetes, but did not reach statistical significance (5.0% vs. 3.4%, p=0.221).	Th1 and Th2 diseases can coexist, indicating a common environmental etiology behind the disease processes.	No specific cause-effect relationship Data was pulled from 1987 Finnish Birth Register supplemented by several national health registers. Based on incidences of diseases within the first 7 years of life, it may limit power of study because asthma is usually diagnosed in adulthood.

Table 2. Continued

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Hemminki et al.[49], 2010	Nationwide retrospective cohort study	148,295 Asthmatic patients (78,996 men and 69,299 women); of whom, 3,006 were hospitalized for various autoimmune diseases	Asthma (ICD codes)	22 Autoimmune and related conditions including RA	The standardized incidence ratio (SIR) for RA was increased even when follow-up was started 5 years after the last asthma hospitalization (SIR, 1.83; 95% CI, 1.63–2.04)	Hospitalized asthma patients developed a number of subsequent autoimmune and related diseases.	No controls It only showed the percentages of various autoimmune diseases in asthma patients.
De Roos et al.[51], 2008	Nested case-control study	Women with RA (n=135) Controls (n=675)	Asthma (questionnaire inquiring about physician diagnosis given to women enrolled in the Agricultural Health Study)	RA (self-report followed by physician-confirmed diagnosis or 1987 American College of Rheumatology classification criteria)	Asthma or reactive lung disease was associated with risk of incident RA (OR, 3.7; 95% CI, 1.3–10.5).	Patients with asthma are at increased risk of developing RA.	No specific cause-effect relationship Small incidence cases No incident dates of asthma Only women were included.
Hassan et al.[52], 1994	Case-control study	Patients with RA (n=100) Controls (n=50)	Atopy (skin prick test), bronchial reactivity (inhaled methacholine test), airflow obstruction (pulmonary function tests)	RA (1987 American College of Rheumatology classification)	No difference in atopy between groups RA patients had a significantly higher history of wheeze compared with controls (18% vs. 4%, p<0.005). FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, $FEF_{25\%}$, $FEF_{50\%}$, and $FEF_{75\%}$ were all significantly lower in the RA group (p<0.05). A significantly higher number of patients with RA, compared with controls, showed bronchial reactivity to inhaled methacholine (55% vs. 16%, p<0.001).	In RA patients, both airflow obstruction and bronchial reactivity are significantly increased as compared with controls.	Skin prick tests, lung function tests and methacholine test were performed.

Table 2. Continued

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Karatay et al.[50], 2013	Case-control study	Patients with RA (n=247) Patients with AS (n=204) Patients with OA (n=259) Controls (n=225)	Asthma, hay fever, atopic dermatitis (questionnaire based on European Community Respiratory Health Survey and International Study of Asthma and Allergies in Childhood)	RA (1987 American College of Rheumatology criteria), OA, AS	Prevalence of asthma in the RA cohort was slightly higher vs. controls (13.36% vs. 12.44%), but did not reach statistical significance. Patients with RA had increased risks for hay fever, atopic dermatitis, and either atopy compared to the patients with OA (OR, 2.14; 95 % CI, 1.18–3.89; OR, 1.77; 95 % CI, 1.00–3.18; and OR, 3.45; 95 % CI, 1.10–10.87, respectively).	Prevalence of asthma in the RA cohort was slightly higher vs. controls (13.36% vs. 12.44%), but did not reach statistical significance.	No specific cause-effect relationship Results were not statistically significant. Asthma: questionnaire-based
Dougados et al.[54], 2014	Cross-sectional, observational, multi-center international study	3,920 Patients with RA recruited in 17 participating countries	Asthma (no mention of how the diagnosis of asthma was made)	RA (1987 American College of Rheumatology criteria)	Among RA patients, there is a high prevalence of comorbidities, most notably depression (15%) and asthma (6.6%).	Asthma was the second most frequently associated disease in patients with RA.	No mention of how the diagnosis of asthma was made No controls
Provenzano et al.[53], 2002	Outpatient-based cross-sectional study	126 Consecutively observed outpatients with RA	Allergic respiratory diseases including allergic rhinitis and asthma (interview and the administration of skin prick tests)	RA (1987 American College of Rheumatology criteria)	A higher prevalence of allergic respiratory diseases was found in patients with RA (16.6%) comparable to what was expected in the general population.	Patients with RA may be more susceptible to allergic respiratory diseases, challenging the hygiene hypothesis of a mutual antagonism of RA and atopy.	No controls Skin prick tests The presence of atopic disease did not seem to influence the severity of RA.

ICD-9: International Classification of Diseases 9; RA: rheumatoid arthritis; aHR: adjusted hazard ratio; CI: confidence interval; OR: odds ratio; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF: forced expiratory flow; AS: ankylosing spondylitis; OA: osteoarthritis.

Table 3. Studies showing an inverse (negative) association between asthma and the risk of rheumatoid arthritis

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Tirosh et al.[56], 2006	Population-based prospective cohort study	Asthmatics (n=37,641) Non-asthmatics (n=448,734)	Asthma (physician-diagnosed or pulmonary function test)	RA (medical record review, unknown RA criteria)	RA was lower in asthmatic vs. non-asthmatics (rate ratio, 2.21; 95% CI, 1.34–3.64; p=0.001).	Patients with asthma have a lower prevalence of RA compared with those without asthma.	Population included Israeli military recruits. Population-based study Ill-defined asthma status Unclear temporality The age of the study sample was too young (18–21) to develop RA. RA criteria were not clearly defined. Temporality between asthma status and RA was not fully established. The risk ratio was not adjusted for potential confounders and covariates.
Hilliquin et al.[57], 2000	Case-control study	Patients with RA (n=173) Controls (n=173)	Atopy (questionnaire inquiring about two or more flare ups of asthma, hay fever, or atopic eczema)	RA (1987 American College of Rheumatology criteria)	Cumulative incidence of atopy was significantly lower in RA patients vs. matched control (7.5% vs. 18.8%; p<0.01; OR, 0.39; 95% CI, 0.19–0.81)	These data support the concept that atopy protects against the future development of RA and that the two diseases could counterbalance each other.	Atopy was not clearly defined (included hay fever, asthma, eczema), so it cannot be concluded that there is a direct correlation between asthma and RA. Questionnaire was used for atopic symptoms and RA. No consistency Controls had higher socioeconomic status. Unclear lead-up or follow-up duration or health care access Cumulative incidence of atopy is very low (19%). Unreliable point prevalence of atopic conditions (point prevalence of atopy: RA subjects, 3.5%; controls, 16.2%, p<0.0001) Potential unsuitability of cases and controls A relatively small number of subjects were included.

Table 3. Continued

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Hajdarbegovic et al.[58], 2014	Case-control study	Patients with RA (n=133) Controls (n=124)	Atopy including symptoms of dermatitis, itching and flexural rash, hay fever, and asthma (Respiratory Health Survey)	RA (American Rheumatism Association criteria)	Asthma was lower in the RA group, but did not reach statistical significance (8% vs. 14%, p=0.086). Serologic evidence of atopy based on serum IgE level was less often found in RA than in controls (12% of RA group had serum IgE >100 kU/L vs. 21% of controls). A smaller percentage of RA group were sensitized to common aeroallergens than controls (22% vs. 33%, p=0.043). Having any atopic feature lowered the odds of having RA by roughly 60% (OR, 0.43; 95% CI, 0.25–0.75).	RA patients had a lower prevalence of clinical and serological atopic features, but did not reach statistical significance.	Questionnaire was used for asthma and RA. A relatively small number of subjects were included. No specific cause-effect relationship Unclear sampling frame Unclear case definition Potential unsuitability of cases and controls Inadequate adjustments
Rudwaleit et al.[59], 2002	Cross-sectional study	Patients with RA (n=487) Patients with AS (n=248) Controls (n=536)	Atopy including asthma, hay fever, and atopic dermatitis (questionnaire incorporating questions from the European Community Respiratory Health Survey and the International Study of Asthma and Allergies in childhood protocol)	RA (physician-diagnosed using the 1987 American Rheumatism Association criteria and RF positivity) AS (physician-diagnosed using 1984 modified New York Criteria)	Asthma was reported by 21/487 (4.3%) in RA vs. 35/536 (6.5%) in controls. Hay fever was reported by 42/487 (8.6%) in RA vs. 82/536 (15.3%) in controls (p=0.001). AD was reported by 14/487 (2.9%) in RA vs. 26/536 (4.9%) in controls (not significant). Prevalence of any atopy was reported by 64/487 (13.1%) in RA vs. 111/536 (20.7%) in controls (p=0.001).	Asthma was lower in RA group than controls (21/487, 4.3% vs. 35/487, 6.5%) but not significant. The overall atopy prevalence was associated with the risk of RA.	No specific cause-effect relationship As a result, a state of atopy appears to confer some protection from RA, but only very little—if any—susceptibility to AS. Course of RA may be less severe in subjects diagnosed with an atopic condition prior to the diagnosis of RA. Controls more selected from hospital staff: detection bias Lowest response rate for controls Outcome (atopy) limited to past 12 months (current asthma, not ever)

RA: rheumatoid arthritis; CI: confidence interval; OR: odds ratio; RF: rheumatoid factor; AS: ankylosing spondylitis; AD; atopic dermatitis.

Table 4. Studies showing no association between asthma and the risk of rheumatoid arthritis

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
Kaptanoglu et al.[60], 2004	Prospective hospital-based case-control study	Patients with RA (n=62) Patients with OA (n=61)	Asthma, hay fever, and eczema (questionnaire)	RA (1987 American College Rheumatology revised criteria)	No significant difference in asthma, hay fever, and eczema in RA patients vs. OA patients (3.2% vs. 6.5%, 14.5% vs. 22%, 1.6% vs. 6.5%, respectively) Wheezing was the only significantly different sign, and was higher in the RA group.	No significant difference in asthma between RA and OA patients (3.2% vs. 6.5%; p>0.05)	Not statistically significant Convenience samples for cases and controls No differences in IgE level between groups Skin prick test Small sample size Inadequate statistical power Osteoarthritis patients were used as controls.
Yun et al.[33], 2012	Population-based, retrospective matched cohort study	Asthmatics (n=2,392) Non-asthmatics (n=4,784)	Asthma (predetermined asthma criteria)	RA (Rochester Epidemiology Project diagnostic index codes [ICD and Berkson codes])	Incidence rates of RA in nonasthmatics and asthmatics were 175.9 and 227.9, respectively. There was a no significantly increased risk for RA among patients with asthma (adjusted hazard ratio, 1.30; CI, 0.78–2.19; p=0.31).	No significant risk for RA among patients with asthma	Approximately 45% of the study participants were <18 years old at the end of the follow-up. This might have reduced the statistical power in detecting an association between asthma and RA because the average age of RA diagnosis is usually in late adulthood. Retrospective study design
Olsson et al.[61], 2003	Retrospective hospital-based case-control	Patients with RA (n=263) Controls (n=541)	Asthma, AR, and eczema (questionnaire)	RA (1987 American College Rheumatology revised criteria)	No association was seen between RA and asthma (OR, 1.4; 0.6–3.1) and eczema. RA was inversely associated with certain manifestations of rhinitis (itchy-watery eyes within last year; OR, 0.4; 0.2–0.9).	No significant relationship between asthma and RA	No specific cause-effect relationship Inadequate statistical power Imprecise definitions of exposure variables Unclear sample frame AR, asthma, and eczema: postal questionnaire based

Table 4. Continued

Author	Study design	Study population	Exposure	Outcome	Result	Conclusion	Comment
O'Driscoll et al.[63], 1985	Cross-sectional study	Two sets of studies: 266 Atopic patients Patients with RA (n=40) vs. controls (n=40)	Atopy: skin prick tests or RAST Asthma, AR, eczema, acute urticaria, and angioedema (questionnaire)	RA (based on physician diagnosis in rheumatology clinic)	5/40 RA patients vs. 9/40 control patients had one or more positive skin prick tests. Both groups had similar prevalence of five diseases which are commonly associated with atopy. Control patients had more asthma and allergic rhinitis; RA patients had more eczema.	No differences in the prevalence of atopy were found between RA patients and controls.	Sample size was too small. Limited statistical analysis Outdated study Inadequate statistical power Unsuitable study populations Imprecise definition of exposure and outcome
Hartung et al.[62], 2003	Hospital-based case-control study	Patients with RA (n=134) Controls (n=305)	Hay fever, allergy, house mite sensitivity, and asthma (physician-administered questionnaire)	RA (1987 American Rheumatism Association criteria)	No significant differences were identified between the groups concerning asthma (OR, 1.047; 95% CI, 0.558–1.964, p=0.887). Significantly lower occurrence of hay fever in patients with RA compared with controls (OR, 0.111; 95% CI, 0.036–0.339; p<0.0001) Significantly lower occurrence of house dust mite sensitivity (OR, 0.310; 95% CI, 0.121–0.793; p=0.003) Total IgE is lower in RA subjects (mean 51.44 IU/mL vs. 109.80 IU/mL, p<0.0001).	No significant difference in asthma status between RA patients and controls	Questionnaire based diagnosis of asthma; may have missed nonatopic forms of asthma. Total IgE levels were measured.

RA: rheumatoid arthritis; OA: osteoarthritis; ICD: International Classification of Diseases; CI: confidence interval; AR: allergic rhinitis; OR: odds ratio; RAST: radioallergosorbent test.

showed inverse associations between asthma and the risk of RA (Table 3): one cohort study[56], two case-control studies[57,58], and one cross-sectional study[59].

Tirosh et al.[56] conducted a cohort study using data from the Israeli Defense Force database in which they defined asthma by physician-diagnosis; however, they did not specify which criteria were used for RA[56]. They concluded that women with asthma had a significantly lower prevalence of type 1 DM, vasculitis, immune thrombocytopenic purpura, inflammatory bowel disease, and RA and that men with asthma had a lower prevalence of type 1 DM, vasculitis, and RA compared with those without asthma. The incidence of RA was higher in nonasthmatic versus asthmatic subjects with an unadjusted overall risk ratio of 2.21 (95% CI, 1.34–3.64; p=0.001). The main strength of this cohort study was that they included a large sample size of 37,641 asthma patients and 448,734 nonasthma subjects; however, their study is limited in that the age of the study population was too young (18–21 years) to develop RA, RA criteria were not clearly defined, temporality between asthma status and RA was not fully established, and the risk ratio was not adjusted for potential confounders and covariates. Thus, the nature of the association was unclear.

There are no population-based case-control studies showing inverse associations between asthma and the risk of RA. Case-control studies with the findings of inverse associations between asthma and risk of RA are all hospital-based studies[57,58] and included unsuitable controls as their controls were the patient's sister- or brother-in-law, neighbor, or friend[57] or were recruited from a different department of the same hospital[58]. For example, Hilliquin et al.[57] conducted a case-control study based on RA patients admitted to their hospital and defined atopic symptoms (i.e., asthma, hay fever, and atopic eczema) by using a standardized questionnaire and RA by using the 1987 ACR classification criteria[55]. Of 173 cases and 173 controls, the cumulative incidence of atopy was significantly lower in RA patients than in matched control subjects (7.5% vs. 18.8%; aOR, 0.39; 95% CI, 0.19–0.81; p<0.01). In this study, controls had a higher socioeconomic status than cases, which might result in a differential susceptibility bias (higher identification or detection of atopic conditions in controls). Their major limitations are potential unsuitability of cases and controls (and potential Berkson bias toward controls)[57,58], unreliable point prevalence of atopic conditions[57], the use of questionnaire for atopic diseases or asthma diagnosis[57,58], and relatively small sample sizes[57,58]. Thus, these case-control studies have significant limitations in addressing the relationship between asthma and the risk of RA.

The cross-sectional study conducted by Rudwaleit et al.[59] was based on RA patients who were followed-up at hospital outpatient clinics. They defined atopy including asthma, hay fever, and atopic dermatitis by questionnaire and RA by the 1987 ACR classification criteria[55]. The prevalence of any current (past 12 months) atopic disorder was 13.1% (64/487) in patients with RA and 20.7% (111/536) in controls (p=0.001). RA patients were less likely to have hay fever (42/487 [8.6%] vs. 82/536 [15.3%], p=0.001) and the proportion of patients with asthma (21/487 [4.3%] vs. 35/536 [6.5%], p>0.05) and atopic dermatitis (14/487 [2.9%] vs. 26/536 [4.9%], p>0.05) was decreased in the RA group versus controls; the results were not significant but consistent. Of note, among atopic patients with RA, the RA severity score was significantly lower in those who developed an atopic disorder before the onset of RA than in those who developed the first signs and/or symptoms of an atopic disorder at the time of or after the onset of RA (p=0.027). The major limitations are that they included control subjects from hospital staff, potentially resulting in a detection bias (higher likelihood of detecting atopic conditions). In addition, atopy was limited to the past 12 months only, thus eliminating patients who may have had asthma prior to the previous year. Asthma itself was not associated with the risk of RA in this study, while the overall atopy prevalence was.

These four epidemiological studies are in favor of the inverse association between asthma and the risk of RA. However, these studies are limited in that they used questionnaires to diagnose atopic diseases including asthma[57-59], unsuitable study populations (i.e., young adults[56], and hospital-based cases and controls[57,58]), unclear sampling frame[58], or inadequate adjustments[58]. The overall evidence for the inverse association between asthma and the risk of RA was weak and inconsistent.

3. No association between asthma and the risk of RA

There are five studies available in the literature which showed no association between asthma and the risk of RA (Table 4): one population-based retrospective cohort study[33], three case-control studies[60-62], and one cross-sectional study[63].

The population-based retrospective matched cohort study of 2,392 patients with asthma and 4,784 controls was conducted in Minnesota, USA by Yun et al.[33] where they used predetermined criteria for asthma[64] and RA[55]. They determined the association between asthma and proinflammatory diseases, such as irritable bowel disease, RA, DM, and CHD and found that asthma was associated with increased risks of DM (HR, 2.11; 95% CI, 1.43–3.13; p<0.001) and CHD (HR, 1.47; 95% CI, 1.05–2.06; p=0.02) but not with increased risks of irritable bowel disease or RA. Besides the cohort study design, the main strength of this study was that they assessed the association of asthma with other chronic inflammatory diseases along with RA and defined asthma status based on predetermined criteria for asthma instead of ICD codes or self-report; however, their study was significantly underpowered given the low incidence of RA and had inherent limitations as a retrospective study. In addition, approximately 45% of the study participants were less than 18 years old at the end of the follow-up, which might have reduced the statistical power in detecting any association between asthma and risk of RA because individuals usually develop RA in late adulthood.

Three case-control studies showing no association of asthma with risk of RA are all hospital-based studies[60-62]. The largest case-control study was performed by Olsson et al.[61] where they recruited RA patients from two hospitals in Sweden, and controls from the general population. Allergic diseases including asthma were established through a postal questionnaire, and RA by the 1987 ACR classification criteria[55]. They showed that RA was inversely, but nonsignificantly, associated with certain manifestations of rhinitis, but there was no association between RA and asthma and eczema, respectively. The major limitations are inadequate statistical power and imprecise definitions of exposure variables as they used a postal questionnaire to diagnose allergic diseases. In addition, the sample frame was often unclear.

The cross-sectional study was conducted by O'Driscoll et al.[63] where they conducted two sets of studies; the first set based on 266 atopic patients attending an allergy clinic, and the second set based on 40 RA patients recruited at a rheumatology clinic and 40 controls at a general hospital. They concluded that two patients of 266 atopic patients had RA (0.8%), a prevalence similar to that observed in the general population and that patients with RA had a prevalence of atopy and atopic diseases similar to that seen in the controls. Their major limitations are inadequate statistical power, unsuitable study populations (sampling from specialty clinic at a hospital), and imprecise definitions of exposure variables.

These five epidemiological studies are limited in that they are underpowered[60,63], used imprecise definitions of exposure variables[60-63], or recruited unsuitable study populations (e.g., inclusion of osteoarthritis patients as controls[60] or inclusion of young adult populations who are generally not susceptible to RA[33]). None of these studies reported statistical power to detect the effect size of interest. Therefore, overall, the evidence for supporting the null hypothesis in these five studies was weak.

In summary, while the existing literature concerning the association between asthma and the risk of RA is inconsistent, overall, in terms of consistency, biological coherence, and study quality, evidence supporting the positive association between asthma and the risk of RA is much stronger than that supporting otherwise. For example, while multiple cohort studies showed consistent and coherent findings backing the positive association of asthma with the risk of RA[47-49], only one cohort study looking at young military soldiers showed an inverse relationship[56]. Nonetheless, as previous epidemiological studies failed to recognize asthma as a disease with a potential systemic inflammatory feature, they did not perform analysis in a way that can provide an insight into heterogeneity and phenotypes of asthma in relation to the risk of RA and the potential coexistence of T_H2 and T_H1 conditions. For example, characterizing asthma in relation to the risk of RA has not been carefully analyzed (e.g., asthmatics with and without other atopic conditions, early- [or long-standing] vs. late-onset asthma, atopic vs. nonatopic asthma, eosinophilic vs. neutrophilic asthma, young vs. elderly asthma, and asthmatics with and without susceptibility to infections). The primary rationale for the lack of this further characterization of patients with asthma or the failure to address heterogeneity and phenotypes of asthma in the literature was that the conceptual framework for the hypothesis testing was mainly based on the counter-regulatory T_H1 versus T_H2 theory precluding other biological plausibility or mechanistic pathways underlying the relationship between asthma and the risk of RA, which is described in the next section.

Potential Mechanisms Underlying Association between Asthma and Increased Risk of Developing RA

The pathogeneses of asthma and RA entail ineffective tolerogenic immune responses to allergens and autoantigens, respectively. Immune effector cells (i.e., regulatory T cells, cytotoxic T cells, helper T cells, and B cells) play a crucial role in maintaining immune tolerance to allergens and autoantigens in both diseases, which leads one to infer that the two disease entities may share common pathogeneses. However, the complex immunogenetic mechanisms underlying the relationship between asthma and RA remain unclear. This is crucially important in understanding the nature of asthma, particularly with regard to the heterogeneity and phenotypes of asthma and optimization of asthma management as discussed in the Implication section.

1. Genetics

Asthma and RA are both diseases developed as the result of a complex interplay among aberrant regulatory T cell function or other mechanisms by which breakdown of immune tolerance ensues. In this regard, previous studies have suggested that immune tolerance is influenced by costimulatory molecules. A recent study looking at 200 cases of asthma, 184 cases of RA, and 182 healthy controls, reported that subjects with the T/T genotype of –3479T>G CD86 and the A/A genotype of –3458A>G CD40L were more likely to develop asthma and RA than those with the T/T genotype of –3479T>G CD86 and A/- genotype of –3458A>G CD40L, suggesting that a genetic interaction between CD86 and CD40L favored the development of both asthma and RA[65]. HLA-DRB1 and HLA-DQB1 genes were independently associated with asthma and its related traits in several candidate gene association studies[66], and HLA-DRB1 is the major determinant of the association with RA susceptibility[67]. Furthermore, a recent study found that patients with RA and valine at position 11 of HLA-DRB1 had the strongest association with radiological damage, higher all-cause mortality, and better response to tumor necrosis factor

https://doi.org/10.4046/trd.2017.80.2.113

inhibitor therapy[68]. Taken together, genetic factors associated with both asthma and RA may account—at least partially—for predisposition to both diseases. It is important to recognize the functional aspect of each involved gene for both asthma and RA and its functional studies of each gene might reveal the causal pathways of how genes and their biological functions determine the nature of the association between asthma and the risk of RA.

2. Environmental factors

It is possible that certain environmental factors predispose individuals to developing asthma and RA. For example, studies have suggested that smokers are at increased risk of developing asthma[69] and RA[70] independently. Furthermore, recent studies have reported insights into the molecular and cellular mechanisms which establish the pathogenesis of smoking-related RA[71,72]. Possible mechanisms are as follows: smoking commences chronic inflammatory process in the lungs, which induces the release of the enzymes, namely peptidylarginine deiminases 2 and 4 from smoke-activated, resident, and infiltrating pulmonary phagocytes. Peptidylarginine deiminases mediate conversion of diverse endogenous proteins to presumed citrullinated autoantigens. In genetically susceptible subjects who have the shared epitope (SE)-containing HLA-DRB1 alleles[71], this SE might provoke the generation of anti–cyclic citrullinated peptide (CCP) and pathogenic autoantibodies (anti-CCP antibodies), which play a critical role in initiating inflammatory responses in RA[72]. Accordingly, genetic studies have reported that the HLA-DRB1 SE alleles are particularly associated with anti-CCP–positive RA[73] and also influence the magnitude of the anti-CCP antibody production[74]. Therefore, gene-environmental interaction could be a potentially important pathway accounting for the association between asthma and RA.

3. Natural killer group 2D

Natural killer group 2D (NKG2D), a transmembrane protein expressed on natural killer (NK) cells, $CD8^+$ $\alpha\beta$ T cells, $\gamma\delta$ T cells, $CD4^+CD28^-$ T cells, and some $CD4^+$ T cells[75,76], may be important in the pathogeneses of both diseases. It is an activating receptor known to mediate the "stress surveillance" function of the cells, and recognizes ligands from the H60, MULT-1, and the Rae-1 families in mice, and MHC class I chain-related molecules (MICA or MICB) and UL16-binding proteins in humans, which are upregulated in response to DNA damage and on transformed cells[77,78]. Recent work by Farhadi et al.[79] determined the role of NKG2D and NK-cell effector functions mediated by granzyme B using house dust mite (HDM)–induced allergic inflammation murine models and found that allergic inflammation was significantly decreased after HDM exposures in NKG2D-deficient mice, and was restored in the mice by adoptive transfer of wild-type NK cells but not granzyme B deficient-NK cells. Therefore, they postulated that NK cell intrinsic expression of NKG2D is needed for allergic pulmonary inflammation following HDM allergen and that NK cells activate allergic pulmonary inflammation by the production of granzyme B. In clinical studies, it has been reported that high NK activity is observed in the peripheral blood sample of subjects with asthma[80-82]. Moreover, in severe asthma, NK cells display up-regulated expression of NKG2D, and expression levels of this surface molecule correspond well with the percentage of eosinophils in peripheral blood[83].

With regard to RA, patients often exhibit increased frequencies of highly differentiated effector $CD4^+CD28^-$ T cells in peripheral blood as compared with healthy controls[84-86]. These $CD4^+CD28^-$ T cells have proinflammatory and cytotoxic properties and may contribute to the development of typical RA signs and symptoms[87,88]. A recent study looking at 44 patients with RA reported that $CD4^+CD28^-$ T cells found in the synovial fluid of RA patients demonstrated additional effector functions such as interleukin 17 (IL-17) coproduction as compared to the same subset in the peripheral blood samples, indicating an important role for these cells in the continuation of inflammation in disease target organs in the subset of patients having a CD28 (null) population[89]. Furthermore, a significant proportion of $CD4^+CD28^-$ T cells from RA patients were reported to express NKG2D, which triggered autoreactive responses against synoviocytes expressing abnormally high NKG2D ligands MICA or MICB[88,90]. Collectively, we postulate that in a subset of asthmatics, enhanced NKG2D activity in immune cells may contribute towards generation of autoimmunity that facilitates development of RA.

4. T_H17 cells

T_H17 cells are a subgroup of T cells that produce various cytokines such as IL-17A, IL-17F, IL-22, and TNF-α. T_H17 cells are differentiated from naive T cells in the presence of IL-6 (increased expression associated with aging) and transforming growth factor β, which up-regulates the transcription factors retinoid acid–related orphan nuclear hormone receptor γt and signal transducer and activator of transcription 3[91]. T_H17 cells are regulated by IL-23, which is a cytokine to facilitate development of inflammation in many models of immune pathology. Previous mouse models of allergic asthma have demonstrated that IL-17A and IL-17F play a critical role in the development of airway inflammation, notably neutrophilic inflammation[92,93]; increase T_H2-associated eosinophilia[94]; and increase airway hyperresponsiveness and airway Mucin 5AC (MUC5AC) expression[95,96]. Studies have suggested that IL-17A and IL-17F are expressed in the airways of patients with asthma[97,98]. In addition to contributing to antigen induction process of airway inflammation, the IL-23–T_H17 axis is considered to be important in the host response reaction to respiratory tract bacterial and potentially viral infections[99]. Thus, it is plausible that T_H17 cells are engaged in the asthma exacerbation and in the pathogenesis of late-onset asthma following repeated respiratory tract infections.

The up-regulation of IL-17 is also known to play a role in the pathogenesis of RA. For instance, previous studies have reported that the IL-17 expression is found to be increased in RA patients compared with healthy subjects and that T_H17 cells isolated from RA patients can induce chronic destructive disorder and inflammation via a proinflammatory feedback loop mechanism in which T_H17 cells induce IL-6, IL-8, and inflammatory enzymes (i.e., matrix metalloproteinase-1 and -3) from the RA patients' synovial fibroblasts (RASFs) via IL-17A secretion and RASFs enhance IL-17A expression by T_H17 cells[100,101]. Therefore, upregulated T_H17 cells in asthma patients may induce chronic destructive disorder and inflammation of joints in the same patients later in life. In this respect, the current epidemiological studies are limited in testing the hypothesis whether asthma severity affects susceptibility to and severity of RA. This aspect needs to be addressed in future clinical studies.

5. Leukotrienes

Leukotrienes, a family of lipid mediators, are synthesized in the leukocytes from arachidonic acid via the actions of 5-lipoxygenase and are divided into two groups: leukotriene B4 (LTB4) and cysteinyl leukotrienes[102,103]. LTB4 and cysteinyl leukotrienes exert their biological effects by binding to cognate receptors, which belong to the G protein-coupled receptor superfamily[104]. LTB4 is thought to be a proinflammatory mediator engaged in the recruitment, activation, and survival of leukocytes, including neutrophils, macrophages, monocytes, eosinophils, and dendritic cells, whereas cysteinyl leukotrienes are robust bronchoconstrictors that have effects on airway remodeling[105-109]. Studies carried out in subjects with asthma have reported an important role for LTB4; for example, increased LTB4 levels are observed in sputum, bronchoalveolar lavage fluid, urine, exhaled breath condensate, and arterial blood samples from subjects with asthma[110-115]. Increased LTB4 synthesis by the up-regulation of 5-lipoxygenase and LTA4 hydrolase has been demonstrated in both adults[116] and pediatric subjects[117] with asthma. As an important determinant of LTB4 level, platelet-activating factor (PAF) has been considered a crucial inflammatory mediator responsible for airway hyperresponsiveness and airway inflammation through eosinophilic recruitment into lung in asthma[118,119]. PAF induces formation of leukotriene B4 from monocytes and leukotriene C4 from eosinophils[120]. PAF acetylhydrolase activity, which catalyzes PAF (removal of 2-actyl group) causing PAF degradation, is lower or deficient in patients with asthma[121-123]. Therefore, PAF in patients with asthma is sustained and further stimulate LTB4, which in turn results in causing inflammation in synovia as discussed below.

LTB4 levels have been reported to be significantly higher in the synovial fluid of RA subjects as compared with the levels in the synovial fluid of osteoarthritis subjects and that LTB4 levels significantly correlate with cell numbers in the synovial fluid from RA patients[124]. This study finding suggests that the increased level of this mediator in synovial fluid may contribute to perpetuation of inflammation and tissue destruction in RA[124]. This is not surprising given the nature of LTB4 as a powerful chemoattractant for neutrophils. For example, several studies suggest that LTB4 in the synovial fluid increases the influx of neutrophils into the joints, thus leading to the articular degradation by producing inflammatory cytokines and matrix metalloproteinases[125-127]. Apart from LTB4, LTC4, and LTD4 also contribute to inflammation in synovium as TNF-α secretion by human mast cells-1 was significantly increased when they were incubated with LTC4 and LTD4 and suppressed by CYsLT1R antagonist, montelukast[128]. The activated 5-lipoxygenase pathway in subjects with asthma may continue to induce chemotaxis, aggregation, and degranulation of neutrophils into the joints, ultimately causing the articular degradation by generating proinflammatory cytokines and matrix metalloproteinase. While the current CysLT1R antagonist (e.g., montelukast) blocks the effect of leukotriene C4 and D4 on CysLT1R during airway inflammation and improves asthma symptoms, as CYsLT1R is also expressed in synovial mast cells[129], CYsLT1R antagonist, montelukast, has shown to improve inflammation of RA in a mouse model[129]. Thus, patients with asthma who have RA might be potential candidates for treatment with CYsLT1R antagonist to alleviate their symptoms.

6. TNF-α

TNF-α is a pleiotropic cytokine that binds to the type 1 TNF receptor and is an important cytokine in the innate immune response. Upon activation, it promotes canonical stimulation of nuclear factor-κB (NF-κB). Previous studies have reported high expression of both TNF-α and NF-κB in adult patients with severe asthma[130-132] and children with moderate-to-severe asthma[133]. Furthermore, small, non–placebo-controlled studies of adults with corticosteroid-refractory asthma and increased TNF-α levels have shown clinical progress with TNF-α antagonist therapy[130,132].

TNF-α is abundantly present in RA patients' serum and arthritic synovium[134] and plays a key role in the pathogenesis of RA. Recent evidence has shown that TNF-α induced regulatory T (T_{reg}) cell dysfunction through the Ser418 dephosphorylation and TNF-α–induced T_{reg} dysfunction corresponded well with increased numbers of IL-17$^+$ and interferon-γ$^+$CD4$^+$T cells within the inflamed synovium of RA patients, suggesting that TNF-α controls the balance between T_{reg} cells and pathogenic T_H17 and T_H1 cells in the synovium of subjects with RA through FOXP3 dephosphorylation[135]. The activated TNF-α pathway in patients with severe or corticosteroid-refractory asthma may continue to impair T_{reg} function, which then results in an imbalance between T_{reg} cells and pathogenic T_H17 and T_H1 cells in the synovial cells, ultimately leading to the development of RA.

Implications

1. Research

Literature investigating asthma and an increased susceptibility to RA or other ARC is limited. The primary reason for this limitation is due to the limited conceptual understanding for the relationship between asthma and the risk of RA, which primarily focuses on the counter-regulatory T_H1/T_H2 theory. This theory may not be suitable for generalizing the counter-regulatory relationship between T_H1 versus T_H2 cells at an immunological level or for understanding the relationship between T_H1- versus T_H2-predominant clinical conditions at an epidemiological level as the development of human disease is much more complex than the pathways demonstrated at a cellular level. In addition, this simple conceptual framework precludes other potential biological mechanisms underlying the relationship between asthma and the risk of RA as described above, which, in turn, deters us from examining the positive relationship between asthma and the risk of RA.

Nonetheless, the main conceptual limitation of the current literature is a failure to recognize asthma "as a chronic inflammatory disease with systemic inflammatory features that go beyond the airway." Emerging evidence suggests that asthma poses a significant impact on immune dysfunction and dysregulation at a systemic level in both adults and children in a way that poses them at risk for significantly higher morbidity and mortality from ARC[23-29,32-42,47-54,56-63,136,137]. In this regard, the current literature suggests that asthma poses a significantly increased risk of RA in subjects with asthma. However, the underlying mechanisms remain unknown. In this review, we explored the potential mechanistic pathways underlying the positive association between asthma and the risk of RA. This mechanistic understanding is crucially important because the systemic impact of asthma on a broad range of common and serious communicable and noncommunicable diseases is largely unrecognized by clinicians and researchers. In addition, the knowledge on which subgroups of asthmatics are at higher risks is currently markedly limited despite the serious morbidity and mortality from ARC such as myocardial infarction, DM, and RA. The discovery of clinical and biological markers to identify subgroups of asthmatics at risk of serious ARC directly depends on the knowledge of the mechanistic underpinnings of the relationship between asthma and chronic proinflammatory diseases such as RA.

While there is important progress in characterizing patients with asthma in relation to endotypes and genotypes revealing potential pathways overlapping with ARC[46], there is still a long way to go in this research area as none of the previous cluster analyses or phenotypic characterization studies included ARC as a phenotype of asthma[138-154]. We believe that studying the mechanistic pathways underlying the association between asthma and the risk of RA or other ARC may advance our understanding of the nature of asthma and ARC, and it will ultimately benefit scientists and clinicians in understanding the nature of chronic proinflammatory diseases by providing insight into the diseases. Apart from the mechanistic studies discovering biomarkers to identify a subgroup of asthmatics at a high risk of developing ARC, clinical studies are needed to determine whether asthma control status, severity status, and medications affect the outcomes of ARC in terms of susceptibility and severity of ARC. In conjunction with these studies, clinical studies are warranted to determine clinical characteristics of a subgroup of asthmatics at a high risk of ARC, which will guide scientists to elucidate the mechanistic pathways and to discover suitable biomarkers to identify such asthmatics.

2. Patient management

Apart from the Centers for Disease Control and Prevention guidelines recommending a single dose of 23-valent pneumococcal polysaccharide vaccine to patients with asthma aged 19–64 years[155], the current asthma guidelines do not address the significance and management of ARC. Thus, no specific recommendations for management of RA among patients with asthma are available. At present, the systemic effect of asthma on susceptibility to and severity of a broad range of common and serious communicable and noncommunicable diseases such as RA is largely unrecognized by clinicians and researchers. For example, in recent years, while the respiratory morbidity due to poorly controlled asthma continues, the mortality directly related to the respiratory morbidity from poorly controlled asthma is relatively low because of the recent evidence-based guidelines and advanced asthma treatment. However, we speculate that ARC (e.g., invasive pneumococcal diseases or myocardial infarction) might pose a significant threat to the life of patients with asthma and unfortunately, these consequences of asthma are out of the clinical radar screen. The potential impact of poorly controlled asthma on the risk and severity of ARC has been rarely studied and recognized as clinicians primarily focus on respiratory morbidity. A few aspects can be considered for clinicians who manage patients with asthma.

First, it is important for clinicians to be cognizant of the increased risks of RA and other ARC among patients with asthma as this awareness by clinicians may enable early identification and intervention, thereby avoiding delay of therapeutic and preventive interventions. They need to have a low threshold for screening or evaluating ARC for asthmatics who present with ARC-related signs and symptoms. For example, patients with asthma who complain of mild joint stiffness and soreness need to be properly evaluated for RA and other inflammatory diseases as corticosteroids (e.g., high dose inhaled corticosteroid or systemic corticosteroid) administered to asthma patients might potentially mitigate their symptoms. Similarly, patients with asthma who have persistent chest pain should not be routinely considered as asthma-related symptoms because it could be an early manifestation of CHD. Second, clinicians should consider vaccinating patients with asthma with pneumococcal vaccines and other vaccines such as the zoster vaccine in order to reduce the risk of vaccine-preventable diseases. This is supported by recent studies by our group demonstrating a significantly increased risk of zoster among adults[24] and children[25,26] with asthma. Independent studies in England[28], Spain[29], and Taiwan[156] corroborated this finding. As zoster vaccine was approved for adults >50 years of age by the U.S. Food and Drug Administration, consideration for adults with asthma as a target group for the zoster vaccine should be granted. For children, as our study showed that the varicella vaccine reduces the risk of zoster[26], children with asthma should be vaccinated with two doses of the varicella vaccine. Patients who develop vaccine-preventable diseases should be carefully evaluated for their immune status, revaccinated with proper vaccines and checked to see if they have appropriate vaccine responses, and monitored carefully for ARC in the future. Third, specific treatment approaches for RA among patients with asthma can be considered. For example, in managing RA in patients with asthma, clinicians might consider administering CYsLT1R antagonist (e.g., montelukast) as another therapeutic option when treatment is being stepped up for asthma control and there is the need to follow these patients carefully[129]. Clinical trials are needed to address this issue. Finally, until we have a better understanding of ARC, regardless of asthma status, patients with asthma who develop ARC must undergo proper evaluations for its etiology. When we define the immunogenetic nature and underpinnings of ARC, routine and costly immunological investigations for patients with “certain (not all) ARC,” may not be indicated. For example, patients with asthma who have a history of frequent, but not serious respiratory infections (e.g., otitis media or *S. pyogenes* infection) may not need routine expensive immunological investigations. However, based on the current understanding and progress of research in this area, there is a lot of work to be done to reach this point.

3. Public health

Asthma is a common chronic condition, affecting 5.7% of the Korean population[4] and nearly 10% of the US population[5,6], with trends indicating the incidence will only continue to increase[7]. Asthma is not only common, but also costly; it is estimated that the total incremental cost of asthma on society in 2007 was $56 billion[157]. Management of asthma can cost $3,500 per patient per year which is a severe economic burden, especially for low-income patients[157]. RA also has a significant societal burden, affecting 0.27% (95% CI, 0.26–0.28) in the general population of Korea[158] and nearly 1% of the U.S. population[159]. Joint inflammation associated with RA can be very painful and can lead to work disability in conjunction with progressive physical disability. The cost of management is high, indicating further societal and economic burden[160]. Addressing the underlying risks associated with asthma may allow for better management of asthma and the ability to better predict and subsequently treat the onset of RA, ultimately reducing the economic and societal burden of these chronic conditions. Additionally, a better understanding of the relationship between asthma and RA may reveal new immunological mechanisms regarding the two disorders, leading to better treatment and management and reduction of societal burdens.

Specifically, at present, the effects of asthma epidemiology on RA epidemiology at a population level are unknown. A better understanding of the potential effects of asthma on the risk and epidemiology of chronic inflammatory diseases such as RA may not only provide an important basis for public health surveillance of these effects, but also lead to novel ways to identify a subgroup of patients with asthma who are at a risk of developing RA at a population level. Therefore, given the large proportion of individuals affected by asthma, surveillance of asthma epidemiology in relation to the epidemiology of ARC including RA has important public health implications. In this regard, our group showed that asthma affects vaccine-preventable diseases such as pneumococcal diseases, pertussis, and varicella. It is unknown the extent to which asthma affects the risk of vaccine-preventable diseases at a population level. Serious emerging and re-emerging outbreaks threatening public health have occurred throughout the world. A crucial question, which has not been addressed to date, is: whether asthma status and epidemiology in a given population affect the degree, timing, and duration of vaccine-preventable re-emerging outbreaks through primary and secondary vaccine failure and whether it is true for the emerging outbreaks. These questions call for further research into this area and deserve further public attention and support.

Conclusion

Asthma increases susceptibility to ARC such as RA and predisposes such patients to immune dysregulation, via mechanistic pathways caused by both genetic and environmental factors. The association of asthma with risk of RA suggests that asthma has systemic inflammatory features that go beyond a mere airway inflammation. There are many potential inflammatory pathways, which account for biological plausibility for

https://doi.org/10.4046/trd.2017.80.2.113

the association as discussed above. Unraveling the mechanistic underpinnings of ARC will be important not only for discovering potential therapeutics but also for diagnostics helping to identify asthmatics at a high risk for ARC. At present, while overall asthma mortality declines as asthma therapies and evidence-based guidelines improve, the impact of ARC on morbidity and mortality is largely overlooked by clinicians and researchers at individual and population levels. Therefore, it is clinically imperative to identify unrecognized phenotypes, endotypes, and genotypes for subgroups of asthmatics, who are at a high risk for ARC potentially, which will lead to early identification and treatment in order to prevent the ensuing (currently unrecognized) impact on morbidity and mortality. In this regard, future guidelines for asthma need to address this issue and others as summarized above. We hope this review provides an insight into the largely unrecognized impact of asthma on morbidity and mortality from common and serious communicable and noncommunicable diseases and the potential implications and interventions, which hopefully may help all individuals with asthma achieve the fullest health potential.

Conflicts of Interest

Dr. Juhn is the PI of the Innovative Methods to Improve Asthma Disease Management Award supported from Genentech, which has no relationship with the work presented in this manuscript. Otherwise, the study investigators have nothing to disclose that poses a conflict of interest.

Acknowledgments

We thank Ms. Kelly Okeson for administrative assistance. Also, we are indebted to Dr. Robert Varsallo in the Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic for his helpful and critical comments on this review paper. Dr. Young Juhn is supported by the NIH grants (R01 HL126667 and R21 AI116839) and Sanford Foundation grant.

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