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The mechanism underlying the association between ABO blood groups and allergic diseases: an evidence-based systematic review

Abdulrahman Salem Bahashwan*

Department of Basic Medical Sciences, College of Medicine, Taibah University, KSA

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Abstract
This systematic review investigates the connections between ABO blood groups and allergic diseases by analyzing the existing literature to uncover underlying immunological mechanisms. Our search of PubMed, Google Scholar, and the Cochrane Database identified 35 relevant studies, with 10 articles meeting our inclusion criteria. Results suggest that blood group antigens significantly influence immune responses through interactions with immunoglobulin E (IgE) and variations in cytokine profiles. This review highlights the impact of blood group antigens on IgE and cytokine profiles, the relationship between blood group types and allergic disease susceptibility, and the role of gut microbiota in allergy development. The evidence indicates that immunological mechanisms involving IgE antibodies and cytokine signaling play a crucial role in mediating the relationship between blood groups and allergies. Our findings underscore the importance of further research into the immunological pathways linking blood groups to allergic diseases, potentially informing the development of personalized treatments and preventative measures.

Introduction

Allergic disorders have become a significant health concern worldwide, with approximately 25% of the global population being afflicted. These conditions manifest as a variety of symptoms, from minor itch and sneeze to serious problems affecting the cardiovascular and respiratory systems.[1] This broad spectrum of manifestations highlights the complexity of allergic responses, which are essentially exaggerated reactions of the immune system to harmless substances.[2] There is a significant burden on healthcare systems because of the increasing frequency of allergies, highlighting the necessity for continuous research and enhanced management strategies.

In recent years, the study of blood groups has gained increased importance in the scientific community. Blood groups, determined by specific antigens on red blood cells, are crucial for blood transfusions and organ transplants. The four main blood types—A, B, AB, and O—have significant roles in medical practice because of these antigens.[3]

***Corresponding author:** Abdulrahman Salem Bahashwan, Department of Basic Medical Sciences, College of Medicine, Taibah University, KSA. *Email address*: asbahashwan@taibahu.edu.sa

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These antigens not only affect transfusion outcomes but also alter the morphology and function of blood membranes.[4] The latest research is establishing connections between blood group antigens and allergy reactions, indicating that these antigens may be more significant than only transfusion-related conditions.[5]

Scientific investigations have sought to understand the complex interactions between blood group antigens and the immune system in the context of allergic diseases. Studies[6,7] found a notable association between ABO blood groups and allergic disorders such as atopic dermatitis (AD), asthma, and allergic rhinitis (AR). The researchers unearthed a noteworthy propensity for individuals with blood group O to exhibit an augmented susceptibility to AR and asthma. Their findings suggested the presence of an intriguing link between this blood type and the increased likelihood of developing allergic conditions. On the contrary, findings obtained by Brachtel et al.[8] and Abid[9], revealed that non-O blood groups (namely, A and B) were linked to a higher proclivity for the development of AD. While these findings underscore the potential role of ABO blood groups as discernible risk factors in the realm of allergic diseases, the precise mechanistic underpinnings of this association remain unexplored.

Even during such scholarly revelations, there is a critical knowledge gap. This is because the exact mechanisms through which these correlations manifest are not comprehensively understood. The existence of this gap calls for further scientific exploration and scrutiny in the domains of immunology and allergy. The purpose of this systematic review article is to synthesize and critically analyze the existing literature, exploring the possible mechanistic pathways connecting blood groups to allergic diseases. We sought to elucidate the gaps in understanding and identify areas where further research is warranted. By amalgamating diverse strands of research, this systematic review will be carried out in such a manner so as to contribute to the evolving narrative on the intersection of blood groups and allergic diseases, with potential implications for future research directions and clinical practices. Following the advice of Okoli[10] the researcher aimed to perform a systematic review by following a logical investigation into the content of each article relative to the study objective. As such, the articles chosen for the systematic review helped address the research questions while simultaneously considering the methods used in each article and also the usefulness of each article in facilitating the synthesis of embodied information.

By compiling and examining existing studies, this review aimed to enhance the understanding of the interplay between blood group antigens and allergic reactions and to highlight areas requiring further investigation. The primary objective was to analyze current literature so as to clarify how blood groups influence allergic susceptibility. In addition, the study sought to explore and understand the mechanisms linking blood groups to allergies, with a particular emphasis on immune system functions and interactions.

This study was guided by the following research questions: (1) Is there a mechanism underlying the link between ABO blood groups and the prevalence or risk of allergic disorders? (2) What is the mechanism by which ABO blood groups predispose people to allergic diseases? (3) How does the ABO blood group affect the prevalence or risk of allergies?

Methods

Search strategy

A systematic review of the literature was done following the preferred reporting items for systematic reviews (PRISMA) guidelines (Figure 1). The study-types searched for included case-control studies, cross-sectional studies, prospective or retrospective cohort studies, and experimental studies. The Cochrane Database of Systematic Reviews, PubMed, and Google Scholar were systematically searched for relevant articles investigating the link between ABO blood grouping and allergic diseases, with a specific focus on the underlying immunological mechanisms.

The search was conducted using medical subject headings (MeSH) terms and keywords including ABO blood groups, A blood group, B blood group, AB blood group, O blood group, asthma, asthma attack, respiratory disease, lung disease, bronchial asthma, pulmonary disease, allergic rhinitis, atopic dermatitis, skin inflammation, skin allergy, rhinitis, dermatitis, eczema, hay fever, hypersensitivity, allergen, allergic diseases, food allergy, meat allergy, dust allergy, anaphylaxis, mechanism, immunology, cytokine profiles, gut microbiota, and immunological mechanisms.

Inclusion criteria

1. Database searched: Cochrane Database of Systematic Reviews, PubMed, and Google Scholar.
2. Study designs: Case-control studies, cross-sectional studies, prospective or retrospective cohort studies, and experimental studies.
3. Study participants: Human subjects with allergic diseases or individuals susceptible to allergic diseases.
4. Exposure variable: Human ABO blood type and allergies.
5. Primary Outcome: Immunological and mechanistic insights into ABO blood group impacting on allergic diseases.
6. Language: Studies published in the English language.

Exclusion criteria

1. Non-English studies: To ensure language consistency and accessibility.
2. Nonpeer-reviewed articles: Only peer reviewed literature was included for more reliability.
3. Irrelevant outcomes: Studies that do not specifically investigate the mechanistic association between ABO blood types and allergic diseases were excluded.
4. Gray literature: Conference presentations/abstracts, dissertations, and theses were excluded unless they were extremely essential for inclusion.
5. Animal studies: Nonhuman research including studies on Feline blood groups were excluded.
6. Duplicate articles: Similar studies were excluded to avoid redundancy in data extraction.

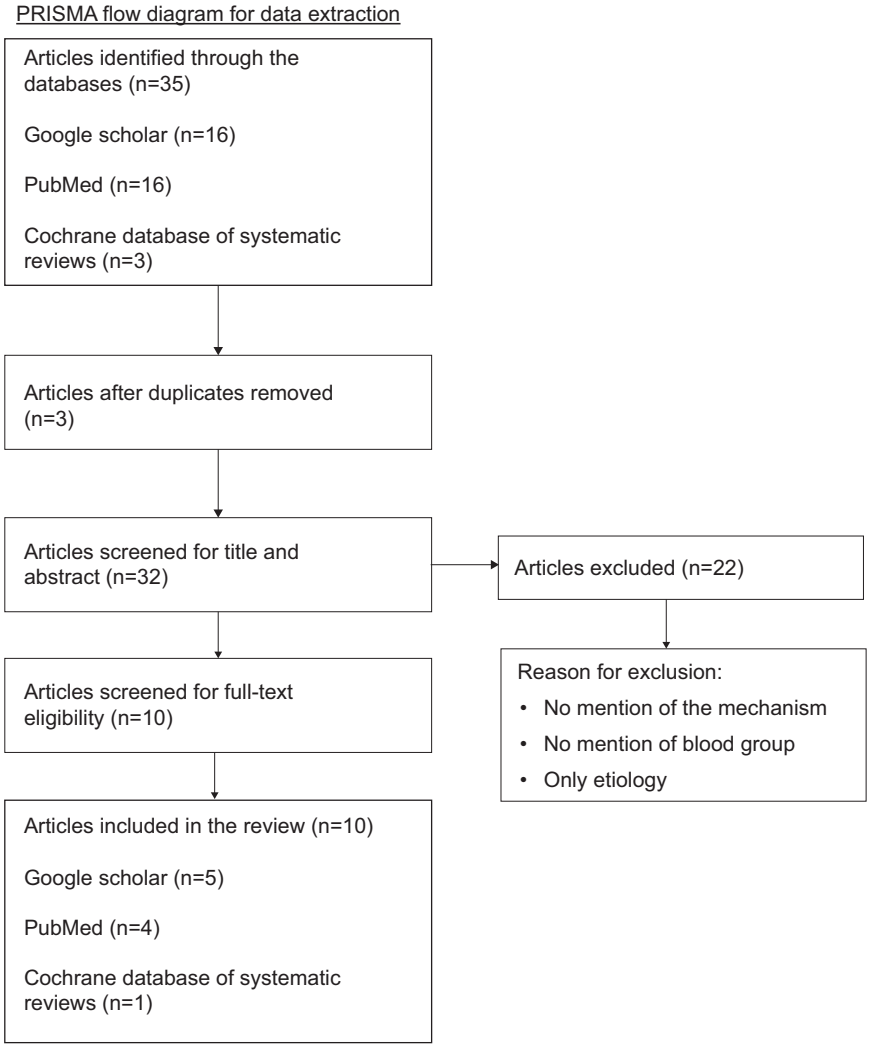

Figure 1 Prisma flow diagram.

Article screening process

A two-phase screening approach was employed. Initially, two independent reviewers screened article titles and abstracts to categorize them into include, exclude, or uncertain. Following that, full-text reviews of probable eligible studies were conducted. The final selection was based on a consensus. In case of disagreement, a third reviewer was included.

Extracted data included author names, publication year, study type, research aim/objective, methodology, exposure and outcome variables, cytokine profiles, and gut microbiota findings.

Risk of bias assessment

The risk of bias and study quality were evaluated using The Risk of Bias In Nonrandomized Studies–of Exposures (ROBINS-E) tool including critical key domains such as confounding, selection bias, missing data, measurement of outcomes, selection of reported results.[11]

Each study was classified as having low, moderate, or high risk of bias across these domains. Findings were systematically analyzed to identify common themes, mechanistic pathways, and inconsistencies among studies.

Data synthesis and analysis

Data obtained from the articles were evaluated quantitatively and qualitatively to generate significant insights to the association between ABO blood groups and allergic diseases. Contradictory results including population heterogeneity, study design differences, or confounding factors were also discussed. Consequently, data analysis and synthesis procedures were carried out with particular emphasis on attaining the study objective, which is to contribute to the evolving narrative on the intersection of blood groups and allergic diseases, with potential implications for future research directions and clinical practices. During the process, data analysis and synthesis of information from academic literature were carried out in such a manner so as to ensure that the observations

were assessed and merged to meet the overarching study objective.

It is reported that while carrying out data analysis and synthesis for the systematic reviews, it is fundamental to ensure that the entirety of the process adhered to the principle of impartiality.[10] Following this recommendation, the process was carried out in a methodological manner that, through impartiality considerations, guaranteed that conclusions generated from the study aligned with the need to utilize academic papers to investigate and generate themes related to the study objective.Further, the study conducted adhered to the suggestion provided by Bagias and colleagues[12] that systematic organization of information is essential in fostering the significance, relevance, and alignment of thematic analysis results to the goal of the research.

Results

Study selection

The systematic review encompassed a total of 35 articles, which were initially considered. Of these, 16 articles were sourced from Google Scholar, 16 from PubMed, and 3 from the Cochrane database. Three duplicate articles were removed during the first screening process, and 32 articles were screened based on the abstract and title. Moreover, 10 articles were screened for full-text eligibility while 22 articles were excluded for not meeting the inclusion criteria. Finally, 10 articles met the inclusion criteria and were analyzed (Table 1).

The risk of bias assessment using ROBINS-E

Low risk of bias was found in five of the selected studies[13,14,16,17,18] revealing robust methodologies and ensuring minimal bias across all domains.

On the other hand, moderate risk of bias was found in the remaining five included studies showing moderate risk because of incomplete control of confounders and/or limitations in exposure classification.[2,5,6,15,19]

Outcomes of the Thematic Analysis

The impact of blood group antigens on immunoglobulin dynamics

The link between blood group types and allergies has been widely reported in existing literature. Altaii and Al-Tae[2] investigated the association between blood group antigen interactions and IgE antibody production, indicating that IgE plays a fundamental role in allergic reactions. In the same context, Many studies observed that individuals with blood types A or O often produce higher IgE levels than those with blood type B.[20,21,22] This suggests that blood group antigens influence IgE production through immune cell interactions. Understanding these interactions can expand insights into immunological mechanistic pathways involved in allergic responses

Cytokine profile differences among blood groups

Allergic diseases and the underlying pathogenesis can be strongly influenced by cytokines signaling in inflammation and immune responses. Tamayo-Velasco and colleagues[23] highlighted that cytokine profile differs based on the blood group type, immune regulations, and cytokine profiles. Another study similarly reported that blood group antigens impact cytokine production associating it with allergy development.[22] Understanding these interactions might help in developing therapeutic interventions and addressing issues related to allergic disease dysregulation.

Gut microbiota and blood group-related allergies

Gut microbiota play a vital role in the development of allergic disease, particularly regarding blood group antigens. Abbas et al.,[13] demonstrated that gut microbiota impact allergy development and the composition of gut microbiota. In addition, Ewald and Sumner[19] revealed that blood group antigens could alter microbial populations influencing immune responses and the risk of allergy. The development of allergy is significantly influenced by the composition and functionalities the gut microbiota. Certain antigens linked to blood group specificity serve as binding sites and receptors that influence microbial gut communities.[16,22]

Discussion

The association between blood groups and allergies is increasingly recognized as a complex immunological interaction. Researchers highlighted the role of IgE production, ABO antigen glycosylation, microbiota gut composition, cytokine profiles, and the potency of immunological pathways in modulating allergic responses and susceptibility.[18,19,22] Akar-Ghibril and colleages[17] have shed light on the association noting that IgE serves as a fundamental mediator in allergy sensitization. In the same line, researchers showed a notable association between IgE levels and ABO blood group antigens, which impacts individuals' susceptibility to allergies.[2] These findings emphasize the genetic factors involved in the development of allergic disease.

Variations concerning the susceptibility to allergies between O and non-O blood groups persist as a significant topic of debate. Certain studies suggested that individuals with blood group O demonstrate an increased incidence of allergic diseases, possibly attributed to glycosylation changes of ABO antigens, resulting in modified immune recognition and IgE binding.[6,7,24] In contrast, other investigations indicated that non-O blood groups, especially A and B, demonstrate enhanced allergic susceptibility because of greater antigenic complexity and more robust interactions with IgE and immune cells.[8,9,25] These findings highlight the importance of additional mechanistic investigations to clarify the specific immunological pathways connecting blood group antigens to allergic sensitization.

On the other hand, cytokines dynamics should be considered in allergic pathogenesis. Th2 cytokines, including IL-4 and IL-13, which improve IgE production, have been shown to differ across various ABO phenotypes.[14,23]

Table 1 Retrieval characteristics of all included studies.

Author and Year	Study Type	Allergic Disorder	Sample Size	Main Findings
Abbas et al., 2019[13]	Cohort	Helicobacter pylori and Allergy association	214 individuals seropositive for H. pylori	The study demonstrated a higher incidence of H. pylori infection among patients with blood group O compared to the general population ($p < 0.001$), which may influence allergic responses via immune modulation.
Abo-Shanab et al., 2020[14]	Cohort	Bronchial hyper-responsiveness and acute bronchoconstriction	57 children with bronchial asthma	Results suggested that family history and genetic factors contributes to asthma susceptibility and severity. 66.67% of patients had allergic family history.
Ahluwalia et al., 2020[15]	Quantitative	Asthma and Streptococcus pneumoniae respiratory illnesses	2866 children with severe asthma exacerbations	The study investigated a genetic mechanism linking Asthma phenotypes with ABO-related immune responses. Children with non-O blood group have an increased risk of developing early childhood asthma, indicating involvement of A or B antigens in the incidence.
Altaii et al., 2022[2]	Quantitative correlational	Allergic asthma (AS), Allergic rhinitis (AR) and atopic dermatitis (AD)	38 patients with AS, 27 with AR and 46 with AD	The optimal total IgE values with the best discriminative accuracy: 77 IU/mL for AS and 81 IU/mL for AR and AD.
Apostolovic et al., 2018[5]	Cohort	Red meat allergy (Alpha-Gal Syndrome, AGS)	51 red meat-allergic patients, IgE-positive to α-Gal, alongside 102 healthy blood donors (A/O/B blood groups)	Anti-α-Gal IgE, IgG_1 and IgG_4 levels were significantly lower in blood group B individuals compared to A/O groups.
Cabezas-Cruz et al., 2017[16]	Cohort	ABO blood types and immune response to α-Gal-bearing pathogens	132 patients with malaria and tuberculosis	Findings suggested that blood group association with anti-α-Gal immunity influences susceptibility to vector-borne pathogens.
Akar-Ghibril et al., 2020[17]	Cohort	Allergic asthma phenotypes	Allergic asthma patients	Key biomarkers such as serum IgE, specific IgE tests, blood/sputum eosinophils, and distinguish allergic asthma patients.
Liumbruno and Franchini, 2013[18]	Retrospective case-control	Allergic and cardiovascular disorders	1,538 patients with allergic and cardiovascular disorders	ABO blood groups play a significant role in various human diseases, including cardiovascular, neoplastic, and infectious disorders.
Lai et al., 2023[6]	Retrospective case-control	Asthma and blood group–related antigens	475 patients with bronchial asthma	Findings emphasized the role of red cell antigens and their impact on allergic disease pathogenesis.
Ewald and Sumner, 2018[19]	Exploratory	Allergic diseases	Patients with intestinal and allergic diseases	The study highlighted the surprising role of blood group antigens in shaping allergic disease susceptibility.

Furthermore, pro-inflammatory cytokines TNF-α and IL-6, implicated in allergic inflammation, may exhibit differential regulation based on ABO antigen expression. Abo-Shanab et al.,[14] and Akar-Ghibril et al.,[17] highlighted the mechanism by which cytokines can affect personalized allergy prevention and treatment. Moreover, Altaii and Al-Tae[2] underscored a significant relationship linking individuals' blood group antigens and the onset and severity of allergies.

The composition of gut microbiota should also be considered alongside cytokines and the way they link to allergies associated with blood groups. The composition of gut microbiota significantly influences immune responses and is correlated to the development of allergies. The relationship between ABO blood groups and gut microbiota is a developing field, and studies demonstrated the significance of exploring the direct relationship between

ABO antigen expression and gut microbiota composition to discover innovative microbiota-based therapeutic approaches. [5,19,22]

Furthermore, future research should focus on investigations at the molecular level, specifically using genome-wide association studies (GWAS) and gene expression profile to explore the link between IgE production, ABO blood groups, genetic variations, and allergic susceptibility.

In addition, further studies should investigate the detailed mechanism associating cytokine profile associated with different ABO blood groups and various allergic diseases and reactions for a detailed understanding of the specific cytokine contributions toward the development and progression of allergic diseases. Longitudinal studies on gut microbiota alterations associated to ABO blood groups might offer novel insights into microbiota-based treatment of allergies.

The main limitation of the current study is the systematic review methodology. Since systematic reviews rely on secondary studies, the implication of this study is that the researcher had control over the existing study's findings.[26] As indicated by Cabezas-Cruz and colleagues[16,22] selection bias cannot be totally ruled out. The exclusion of review articles is an additional limitation of included studies.

Conclusion

This systematic review has established that a significant relationship exists between blood groups and allergies revealing intricate immune mechanisms underlying this correlation. The interplay between gut microbiota, IgE levels, and cytokine profiles involved in allergy susceptibility is based on the variations in blood grouping. The present study has provided fundamental insights regarding the underlying mechanisms and show insights in understanding allergic diseases linked to blood group-associated pathogenesis. These findings showed more efficient therapeutic approaches achievable through a thorough understanding of the role played by blood group variations in determining immune dysregulation. Future research should focus on detailed molecular and genetic mechanisms to enhance clinical approaches for allergy prevention and treatment.

Availability of Data and Materials

All data are present in the manuscript.

Ethical Approval

Not Applicable.

Author Contributions

The author confirms sole responsibility for study conception and design, data collection, analysis and interpretation of results, and the preparation of the manuscript.

Conflicts of Interest

The author declares no conflicts of interest with the present study.

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