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Biomarkers in allergic eczema

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Biomarkers in allergic eczema

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Editorial: Biomarkers in allergic eczema

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Editorial on the Research Topic
Biomarkers in allergic eczema

Eczema is a complex, heterogeneous inflammatory disease of the skin. Patients exhibit diverse immunopathological mechanisms and treatment responses, indicating the existence of multiple disease endotypes. Current therapies fail to achieve sustained disease control across all patient subgroups. Therefore, the identification of reliable biomarkers is essential for monitoring disease progression and therapeutic outcomes. This Research Topic- *Biomarkers in Allergic Eczema*- aims to elucidate the underlying immunological mechanisms, discover diagnostic, prognostic, and predictive biomarkers, and define their utility in patient stratification and assessment of treatment response. The development of clinically useful, cost-efficient, and non-invasive biomarkers for allergic eczema would greatly enhance personalized management strategies. These types of advances could transform clinical practice by enabling the early detection and accurate classification of disease endotypes, along with real-time monitoring of therapeutic responses.

Sargen et al. identified emerging diagnostic and prognostic biomarkers in allergic contact dermatitis (ACD), including *ADAM8, CD47, IL-37,* and *loricrin*. Sasaki et al. proposed neuroimmune mediators such as *IL-31* and *TRPV1* as therapeutic targets in ACD. Together, these reviews emphasize the importance of integrating skin and blood biomarker networks, multi-omics, and longitudinal cohort validation to advance the personalized management of allergic and inflammatory skin diseases in patients of all ages. Maskey et al. reported topical steroid withdrawal (TSW) as an emerging inflammatory syndrome following chronic corticosteroid use. They discussed the mechanisms involving nitric oxide–mediated vasodilation, epidermal cortisol dysregulation, microbiome imbalance, and cytokine rebound as prime drivers of TSW. The authors advocate clinical recognition, diagnostic refinement, and multidisciplinary management, including gradual tapering, skin barrier repair, and mental health support to reduce the occurrence of TSW. Song et al. explored the use of systemic inflammatory burden as a biomarker of eczema in 3,397 children and adolescents using the NHANES database. This study introduced the systemic inflammatory response index (SIRI) as a promising, easily measurable biomarker for systemic immune balance in allergic skin diseases. The authors demonstrated that higher SIRI levels are inversely associated with eczema prevalence, suggesting a potential protective

immunological balance. They also proposed that elevated SIRI levels may reflect stronger Th1 or regulatory *T* cell activity, which counteracts Th2-driven inflammation.

In a perspective article, Kataoka discussed the importance of biomarkers in personalizing healthcare to enable more effective treatment plan development in clinics, citing CCL17 as a key biomarker for atopic dermatitis and emphasizing its importance in the detection of subclinical manifestations of the disease. Early identification of subclinical inflammation enables proactive topical therapy and reduces unnecessary escalation to costly biologics or JAK inhibitors. Incorporating these biomarkers into precision medicine strategies can thus assist with improved disease control, cost-effective treatment options, and positive patient outcomes in an evolving era of advanced AD therapies. In another study, Chong et al. evaluated the clinical utility of strawberry- and tomato-specific IgE (S/T IgE) testing in 814 pediatric allergy cases, and found that only 2.2% (strawberry) and 5.4% (tomato) of tests aligned with clinically relevant outcomes, with severe allergy being rare. Conversely, the research group observed that exposure and reaction history (ERH) is a far stronger predictor of true allergy in comparison to systemic S/T IgE levels, offering high negative and low positive predictive value. These findings suggest that S/T IgE testing should be reserved for patients with a clear ERH, thereby reinforcing the importance of clinical history as the primary tool in diagnosis. Lazor et al. reviewed and outlined the current standards and emerging therapies for managing allergic eczema, ranging from emollients and topical corticosteroids to calcineurin inhibitors and systemic agents for severe cases, along with novel biologic therapeutic interventions, such as dupilumab and JAK inhibitors, which offer targeted and effective therapy. The multitude of therapeutic options in terms of both range and effectiveness, along with patient stratification, allows for personalized, proactive strategies and biomarker-driven approaches that reduce the financial and emotional burden of the disease on patients and their caregivers.

To investigate the function of mast cells in an *in situ* environment, Villanueva et al. investigated the use of intact human skin explant tissue to study human mast cell activation. Their Methods study describes the development and application of this full-thickness human skin specimen model. Spontaneous histamine release was investigated, along with induced FceR1 and MRGPRX2 activation. The use of acalabrutinib, QWF, and pertussis toxin to inhibit histamine release contributed to the verification of normal mast cell function. The use of "human skin punch biopsy discards" opens the way for *in situ* investigations of mast cell function and therapeutic inhibition.

Intake, metabolism, and use of vitamin B6 are important for brain function and the immune system. However, the role of vitamin B6 and its metabolites in eczema is understudied. Du and Li utilized data from the 2005–2006 National Health and Nutrition Examination Surveys (NHANES) to select 247 children and adolescents (aged 6–17) with eczema and 2009 without eczema. The active form of vitamin B6 (PLP), its inactive metabolite (4-PA), and the 4-PA/PLP ratio in serum were measured to determine their association with eczema. High levels of 4-PA and 4-PA/PLP were associated with eczema. No association was observed between dietary intake of vitamin B6 or serum PLP levels and eczema. These results suggest that the inclusion of vitamin B6 status in the screening of children may be of value for monitoring and perhaps predicting eczema.

In the future, integrating skin and blood biomarker networks, multi-omics, and longitudinal cohort validation will be pivotal in advancing the personalized management of allergic and inflammatory skin diseases across different age groups.

Author contributions

AM: Writing – original draft, Writing – review & editing. PB: Writing – original draft, Writing – review & editing. JG: Writing – original draft, Writing – review & editing.

Conflict of interest

PB is an employee of Boehringer Ingelheim Pharmaceuticals, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

ACD, allergic contact dermatitis; TSW, topical steroid withdrawal; SIRI, systemic inflammatory response index; ERH, exposure and reaction history; NHANES, National Health and Nutrition Examination Surveys.

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Fruitful or unfruitful: strawberry and tomato specific immunoglobulin E testing at a tertiary pediatric center

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Background: Suspected strawberry and tomato (S/T) food allergy (FA) can be evaluated using specific immunoglobulin E (sIgE) testing despite its low specificity and positive predictive value.
Objective: This study aims to understand ordering patterns for S/T sIgE testing and identify relevant factors to clinical decision-making.
Methods: We retrospectively reviewed 814 patients with sIgE testing available for strawberries (651), tomatoes (276), or both (113) from January 2012 to May 2022 at a tertiary pediatric hospital. Patient demographics, provider specialty, and reasons for testing were collected. Student's *t*-test and multiple regression analyses were performed to test the association between the S/T sIgE level and clinically relevant outcome (CRO) status. Fisher's exact test and general linear models were used to evaluate and compare potential predictive factors for CRO status.
Results: Allergy and immunology, gastroenterology, and general pediatrics ordered most S/T sIgE testing. Testing was ordered most frequently for non-IgE-mediated gastrointestinal symptoms, mild possible IgE-mediated reactions, and eczema. Testing was most often ordered for infants and school-age children. Mean sIgE levels were higher for S/T tests resulting in a CRO when controlling for other predictor variables ($p = 0.015$; $p = 0.002$ for S/T, respectively). Only 2.2% and 5.4% of tests resulted in a CRO for S/T, and severe allergy was rare. Testing for non-IgE-mediated GI symptoms or eczema, or in non-atopic patients, yielded no CROs. Exposure and reaction history of present illness (ERH) was associated with CROs ($p < 0.001$; $p = 0.04$) with a high negative predictive value (99.5%; 100%) and low positive predictive value (11.5%; 15.0%). ERH ($p < 0.001$, $\eta^2 = 0.073$; $p = 0.009$, $\eta^2 = 0.123$) was a more significant predictor than the sIgE level ($p = 0.002$, $\eta^2 = 0.037$; $p = 0.212$, $\eta^2 = 0.030$) for CRO status.
Conclusion: The diagnosis of S/T food allergy is made primarily based on clinical history. S/T sIgE testing for children and adolescents should be avoided for patients without an ERH and in the workup of non-IgE-mediated GI symptoms. Testing for eczema and non-atopic patients is likely low-yield.

KEYWORDS

food allergy, strawberry, tomato, immunoglobulin E, pediatric

Abbreviations
S/T, strawberry and tomato; FA, food allergy; sIgE, specific immunoglobulin E; CRO, clinically relevant outcome; US, United States; PFAS, pollen food allergy syndrome; A/I, allergy and immunology; GI, gastroenterology; GP, general pediatrics; ERH, exposure and reaction history of present illness; AD, atopic dermatitis.

Background

According to self-reported measures, food allergy (FA) is a major public health concern, affecting one in 13 children and one in 10 adults in the United States (US) (1, 2). Strawberry and tomato (S/T) are frequent suspects for FA as they are commonly consumed worldwide; however, these fruits may cause many non-allergic or local irritant reactions because they are highly acidic and may even cause pseudoallergic histamine release (3, 4). While accurate prevalence data are essential for developing effective strategies to prevent and manage FA, obtaining these measures is a complex and challenging task. The prevalence of strawberry allergy has been reported as 0.5%–4% in childhood (5); meanwhile, tomato allergy may account for 1.5% of FA in Northern Europe (6, 7). Severe reactions to S/T have rarely been described (8–10), and S/T allergy presents more often as pollen FA syndrome (PFAS), which is usually mild (11). A major mechanism of S/T PFAS is thought to involve cross-reactivity of strawberry Fra a 1 or tomato Sola l 4 to Bet v 1 in birch-pollen sensitized individuals, which may represent 8%–16% of Europe's population and more than 100 million persons globally (12–15).

Specific immunoglobulin E (sIgE) testing is often ordered in the FA workup but may not always be appropriately applied given its low specificity and positive predictive value (16, 17). While identifying FA is critical for preventing life-threatening reactions, overdiagnosis may result in physical, mental, and financial consequences for patients and their caregivers (18–22). For example, food avoidance can lead to nutritional problems or the development of FAs from a delayed introduction of allergenic foods (23–25). Meanwhile, patients and caregivers may suffer a worse quality of life due to the daily challenge of acquiring allergen-free foods, fear of accidental exposure, and bullying of food-allergic children (22, 26, 27). Further, unnecessary testing increases medical costs. Per food, sIgE testing costs $15–$35 in the US and £15–£100 in the United Kingdom (28). The need for special foods and epinephrine autoinjectors greatly magnifies the financial burden of FAs (21, 29, 30).

Given the significant consequences of FA misdiagnosis, highly predictive sIgE thresholds would be greatly beneficial. Some thresholds have been determined for the most common food allergens (i.e., milk, egg, and peanut), and component testing has further improved diagnostic accuracy, particularly for peanut allergy (20, 31, 32). However, sIgE testing for S/T remains poorly studied. Recently, a retrospective study conducted in Spain studied 43 children with a self-reported history of strawberry allergy. Among these children, 67% had positive strawberry allergy testing, but 94% tolerated the fruit, bringing into question the relevance of reported reactions and testing (33). A similar study for tomato allergy has not been reported. To improve quality and value in FA care, we aim to understand provider ordering patterns for S/T sIgE testing and identify clinically relevant factors to guide decision-making for these tests.

Methods

Specific immunoglobulin E testing specifications

All sIgE testing at our institution was performed on a Phadia 250 instrument (Thermo Fisher, Article #12-3900-01) using three positive controls (pooled human samples containing sIgE antibodies to house dust mite, common silver birch, or cat dander, respectively, for the high, medium, and low controls, all in 0.05% sodium azide) and one negative control (pooled human samples in 0.05% sodium azide without antibodies). The lower bound of testing was <0.35 kU/L prior to 2020 and <0.10 kU/L thereafter per manufacturer update. The upper bound was 100 kU/L for all samples.

Data collection

We retrospectively reviewed 814 patients who had sIgE testing performed for strawberry (651), tomato (276), or both (113) from January 2012 to May 2022 at Children's Hospital Los Angeles (CHLA). For patients with multiple S/T sIgE tests, the most recent test was used for analysis. Age at testing was grouped into one of five categories: infant (0–2 years old), preschool (3–6 years old), school age (6–12 years old), adolescence (13–17 years old), and adult (18 years old and over). Reasons for sending to S/T sIgE testing were determined from the ordering encounter note when available or the electronic test order form. We identified one or more testing reasons for each case using 10 categories: eczema, mild possible IgE-mediated reaction (i.e., hives, non-specific rash, and eye itching), severe possible IgE-mediated reaction (i.e., anaphylaxis), non-IgE-mediated gastrointestinal symptoms (i.e., abdominal pain, constipation, and diarrhea), PFAS (i.e., lip swelling and throat itching), unspecified reaction to S/T, previous positive S/T testing without a history of reaction, history of other food allergies, parental request otherwise not indicated, and unknown.

Data processing

Data were filtered systematically (**Figure 1**) for whether sIgE testing was for strawberry or tomato allergy, reliability of outcome data (i.e., a clear recommendation from any specialty regarding S/T following S/T sIgE testing), documentation of a final outcome (i.e., patient told to avoid the tested food or patient recommended/allowed to continue eating the food), availability of rationale, availability of the provider note from the ordering encounter, and availability of atopy data. For diagnostic yield analyses, we defined a clinically relevant outcome (CRO) as a definitive outcome where the patient was ultimately told to avoid S/T or consume cautiously due to PFAS. For analyses involving testing rationale, all reasons for

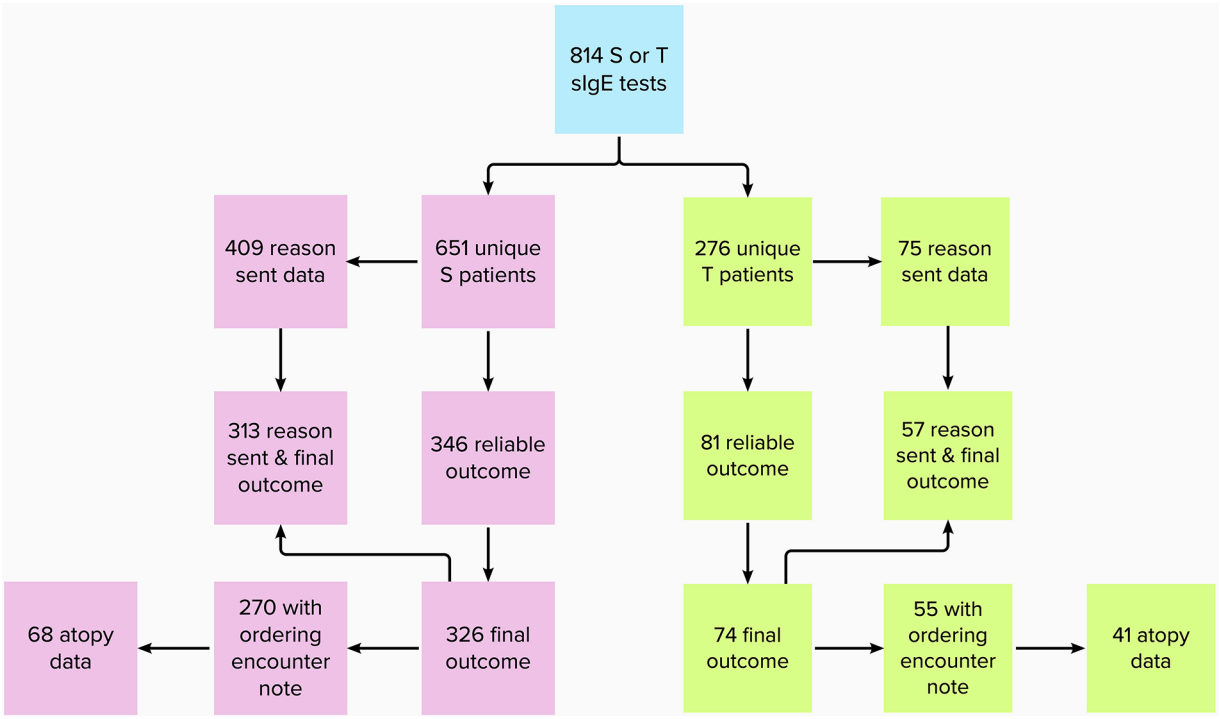

FIGURE 1
Flowchart of available data for each strawberry and tomato test.

sending a single test were considered to maximize fidelity; this was accomplished by treating each reason documented as a separate testing data point. To explore the relevance of an exposure and reaction history of present illness (ERH), patients were positive for ERH if the patient (themselves or via caregiver) reported an exposure to the specific food (ingestion or cutaneous contact) with a subsequent reaction during the ordering encounter (no specific time to reaction was required). Patients were considered atopic if they were diagnosed with eczema, asthma, and/or allergic rhinitis by an allergy and immunology (A/I) specialist at our hospital.

Statistical methods

Statistical analyses were conducted using SPSS (version 28, 2022) and Prism (version 9, 2022). Student's *t*-test was used to compare the mean sIgE levels between CRO and non-CRO groups for each food. ("<0.10" and "<0.35" were converted to "0.35" for quantitative analysis, given different minimum thresholds before and after 2020.) Multiple regression was then performed to compare mean sIgE levels between CRO and non-CRO groups while controlling for age at testing, sex, ethnicity, and ordering specialty. Fisher's exact test was used to evaluate associations between potential predictive factors (i.e., ERH and atopy) and having a CRO following S/T sIgE testing. A general linear model was employed to calculate partial eta-squared effect sizes for comparing the effect of ERH vs. S/T sIgE testing on CROs.

Results

Demographics

Our sample included 51.5% male participants for strawberry testing and 56.5% male participants for tomato testing. The mean age at testing was 7.7 ± 8.1 years for strawberry allergy and 8.8 ± 12.6 years for tomato allergy. Age distribution was bimodal, with the largest peak seen for infants (0–2 years old) (36.7%; 41.7%) and a second smaller peak observed for school-age children (6–12 years old) (27.0%; 23.6%) (Figure 2). Adults represented the smallest fraction for both S/T (4.1%; 9.4%) tests. Race/ethnicity for strawberry testing was 28.9% White, 4.3%

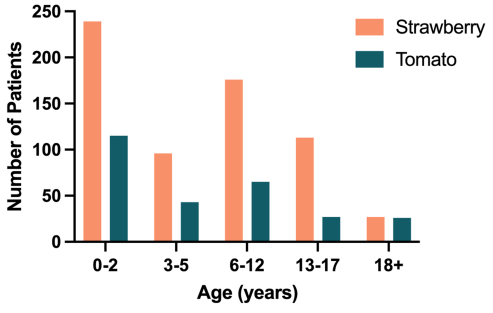

FIGURE 2
Number of patients in each age group with strawberry and tomato testing.

Black, 7.1% Hispanic/Latino, 6.0% Asian/Pacific Islander, 1.2% multiple, 20.1% other, and 32.4% unknown; for tomato testing, race/ethnicity was 22.8% White, 5.4% Black, 7.2% Hispanic/Latino, 5.8% Asian/Pacific Islander, 0.4% multiple, 22.5% other, and 35.9% unknown. Inpatients represented only 0.8% (5/651) and 1.4% (4/271) of S/T sIgE tests, respectively. Atopy was present in 60.6% (86/142) of patients tested for strawberry allergy and 61.2% (52/85) of patients tested for tomato allergy seen and with testing ordered by A/I specialists at CHLA.

Ordering provider specialties

The specialty of the ordering provider was available for 651 strawberry and 274 tomato tests (Figure 3). A/I, GI, and general pediatrics (GP) were the top ordering specialties, accounting for 97.8% and 98.2% of S/T sIgE tests, respectively. For strawberry allergy, GI (43.0%) ordered the most tests, followed by A/I (38.2%) and GP (16.6%). For tomato allergy, A/I (68.7%) ordered the most tests, followed by GP (23.7%) and GI (5.8%).

Reasons for testing

Reasons for sIgE testing were available for 409 strawberry and 75 tomato tests (Figure 4). Non-IgE-mediated gastrointestinal symptoms, mild possible IgE-mediated reactions, and eczema were the top reasons, accounting for 90.9% of strawberry and 66.7% of tomato tests. For strawberry allergy, non-IgE-mediated gastrointestinal symptoms (60.1%) were the most common reason for testing, followed by mild possible IgE-mediated reactions (24.7%) and eczema (6.1%). For tomato allergy, mild possible IgE-mediated reactions (32%) were the most common reason, followed by non-IgE-mediated gastrointestinal symptoms (20%) and eczema (14.7%). PFAS symptoms (4.2%; 9.3%) and a history of other food allergies (2.0%; 12%) were the next most common reasons for S/T testing, respectively.

CRO and epinephrine use

Final outcome data were available for 326 strawberry and 74 tomato cases. Of these, 2.15% (7/326) and 5.41% (4/74) of S/T sIgE tests resulted in a CRO. PFAS represented 42.9% (3/7) and 50% (2/4) of these CROs for S/T, respectively. For the four non-PFAS cases where the patient was ultimately told to avoid strawberries, reasons for avoidance included anaphylaxis, rash, unspecified acute reaction, and concern for strawberry allergy due to unspecified blueberry allergy. For the two non-PFAS tomato cases, rash (specifically eczema and hives) and unspecified acute reaction were the reasons for avoidance. Only one patient required epinephrine administration for strawberry allergy (0.3%, 1/326), and epinephrine was never required for tomato allergy (0/74).

sIgE levels and CRO

sIgE levels were available for all cases with final outcome data (7 and 4 with CROs and 319 and 70 without CROs for S/T,

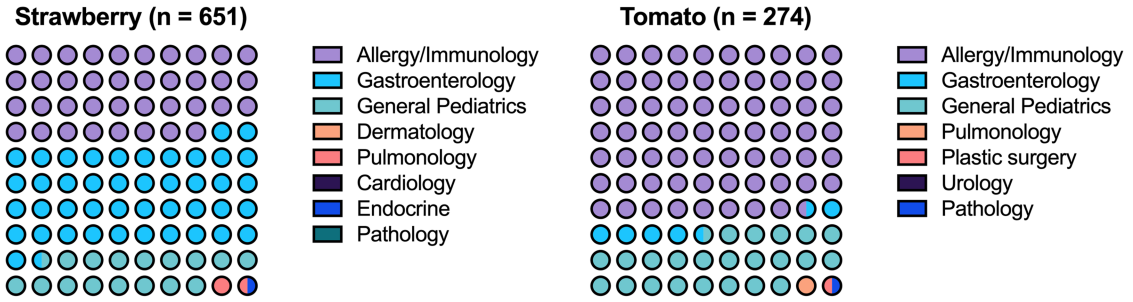

FIGURE 3
Specialty ordering strawberry and tomato testing.

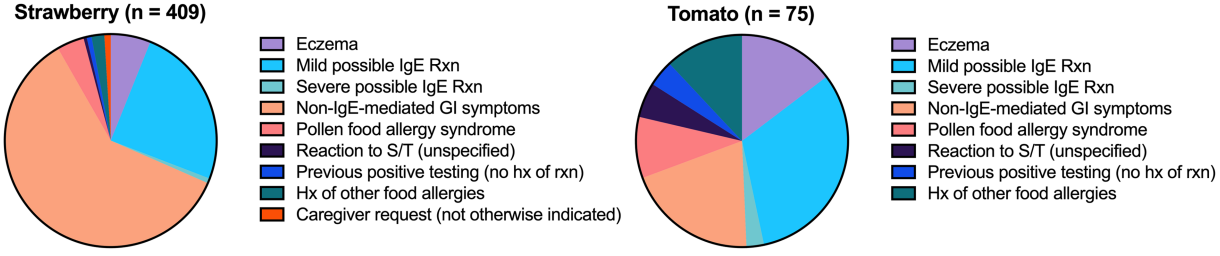

FIGURE 4
Reasons for strawberry and tomato testing.

respectively). The mean sIgE levels for S/T tests resulting in CROs were 5.5 ± 5.8 kU/L and 12.5 ± 1.7 kU/L, respectively. For tests without CROs, the mean sIgE levels were 0.9 ± 4.0 kU/L and 1.8 ± 3.7 kU/L, respectively. For both foods, the mean sIgE level was significantly higher among S/T tests resulting in CROs vs. no CROs ($p = 0.003$; $p < 0.001$ for S/T, respectively). Multiple linear regression models, including CRO status and other covariates, significantly predicted sIgE levels for strawberry [$F(5,320) = 3.730$, $p = 0.003$] and tomato [$F(5,68) = 2.633$, $p = 0.031$] allergy (**Supplementary Material A**). For strawberry allergy, CRO status ($p = 0.015$) and ordering specialty ($p = 0.015$) predicted sIgE levels, while for tomato allergy, only CRO status ($p = 0.002$) predicted sIgE levels.

Age and CRO

Age at testing was available for all cases with final outcome data. Following strawberry sIgE testing, CROs were observed for all age groups prior to adulthood: 2.3% (2/88) for infants, 4.3% (2/47) for preschool children, 1.0% (1/99) for school-age children, 2.4% (2/83) for adolescents, and 0% (0/9) for adults. One infant and two preschool children accounted for the three strawberry PFAS outcomes. Following tomato testing, CROs were observed for 7.1% (2/28) of school-age children and 18.2% (2/11) of adolescents but not for any other age group (0/17 for infants, 0/12 for preschool children, and 0/6 for adults). Adolescents accounted for the only two PFAS outcomes after tomato sIgE testing.

Reason to test and CRO yield

Filtering for cases with a documented reason to test and final outcome data resulted in 313 strawberry and 57 tomato cases (**Table 1**). S/T sIgE testing for non-IgE-mediated GI symptoms or eczema resulted in no CROs. Testing for PFAS symptoms yielded 21.4% and 40% CROs for S/T, respectively. Testing for mild and severe possible IgE-mediated reactions resulted in some CROs for strawberry allergy but none for tomato allergy.

Exposure and reaction history and CRO

An ordering encounter note and final outcome data were available for 270 strawberry and 55 tomato tests. ERH was significantly associated with a CRO following sIgE testing for S/T ($p < 0.001$; $p = 0.04$) with a high negative predictive value (99.5%; 100%) and a low positive predictive value (11.5%; 15.0%) (**Figure 5**). For strawberry cases, ERH significantly predicted CROs ($p < 0.001$) with a medium effect size ($\eta^2 = 0.073$), while sIgE levels also significantly predicted CROs ($p = 0.002$), albeit with a small effect size ($\eta^2 = 0.037$). For tomato cases, ERH significantly predicted CROs ($p = 0.009$) with a large effect size ($\eta^2 = 0.123$), while sIgE levels did not ($p = 0.212$, $\eta^2 = 0.030$).

Atopy and CRO

An ordering encounter note and final outcome data from A/I providers at our hospital were available for 68 strawberry and 41 tomato cases. Among this subgroup of cases, atopy was present in 75.0% (51/68) of strawberry and 78.0% (32/41) of tomato patients. None of the non-atopic S/T patients had a CRO following S/T sIgE testing (0/17; 0/9 for S/T, respectively). Meanwhile, 11.8% (6/51) and 9.4% (3/32) of atopic patients had a CRO following S/T testing, respectively. The association between atopic status and CRO following S/T sIgE testing was not statistically significant even when both were considered together ($p = 0.11$).

Discussion

Our study characterized the ordering patterns for more than 800 S/T sIgE tests at a tertiary pediatric hospital over 10 years and assessed factors that may influence diagnostic yield. S/T sIgE testing was most frequent for infants, reflecting caregiver and provider prioritization of establishing allergenic triggers with initial food introduction. Testing decreased for preschool children before increasing again for school-age children, which may reflect the increased risk of exposure to new foods with the start of school. At our hospital, S/T sIgE testing was almost

TABLE 1 CRO yield by reason for strawberry and tomato testing.

Reason for testing	Strawberry ($n = 313$)			Tomato ($n = 57$)		
	Number of patients	Number with CRO	CRO yield (%)	Number of patients	Number with CRO	CRO yield (%)
Eczema	17	0	0	10	0	0
Mild possible IgE reaction	78	3	4	16	0	0
Severe possible IgE reaction	3	1	33	2	0	0
Non-IgE-mediated gastrointestinal symptoms	188	0	0	12	0	0
Pollen food allergy syndrome	14	3	21	5	2	40
Reaction to S/T (unspecified)	1	1	100	3	1	33
Previous positive testing (no history of reaction)	3	0	0	2	0	0
History of other food allergies	5	1	20	7	0	0
Caregiver request (not otherwise indicated)	4	0	0	0	0	n/a

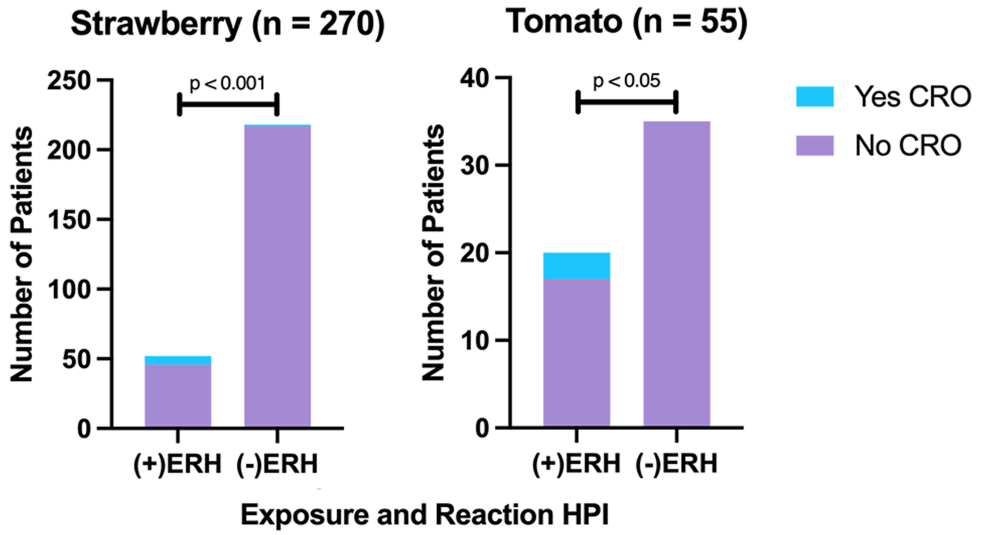

FIGURE 5
ERH was highly associated with CROs for strawberry and tomato testing.

exclusively used by A/I, GI, and general pediatrics and rarely by any other specialty. For both foods, mild possible IgE-mediated reactions, non-IgE-mediated gastrointestinal symptoms, and eczema were the most frequent reasons for testing.

Mean sIgE levels were significantly higher for S/T tests with a CRO, yet diagnostic yield was quite low, with only 2.2% (7/326) and 5.4% (4/74) of tests yielding a CRO. While the prevalence of S/T allergy was low in our sample, it is likely even lower in the general population. Patients in this study were suspected to have S/T allergy before testing and thus had an elevated pretest probability for a CRO. Further, atopy is associated with food allergy (34–37), and the presence of atopy in our sample was 2–8-fold higher than in the general population of developed countries (10%–30%) (38, 39). Perhaps expectedly, PFAS represented more than 40% of these CROs following S/T sIgE testing for both foods. Given the low CRO yields and rare S/T reactions in our cohort, more judicious testing for these foods should be considered.

Strikingly, non-IgE-mediated gastrointestinal symptoms accounted for more than 60% of strawberry tests despite no current evidence suggesting the benefit of sIgE testing for non-IgE-mediated gastrointestinal symptoms. Specialties other than A/I accounted for the majority of tests. Given that IgE testing for non-IgE-mediated gastrointestinal symptoms is contrary to known pathophysiology, it is unsurprising that none of the 188 strawberry sIgE tests sent for non-IgE-mediated gastrointestinal symptoms with final outcome data resulted in a CRO. This underscores the need for education on the situational value of IgE testing to specialties outside of A/I. Non-IgE-mediated gastrointestinal symptoms accounted for 20% of tomato tests. As with strawberry cases, this testing yielded no CROs. These findings highlight an opportunity to optimize ordering patterns by avoiding S/T sIgE testing for GI symptoms that are unlikely to be IgE-driven.

Atopic dermatitis (AD) is another condition for which S/T sIgE testing may not be helpful. Recent evidence suggests a limited role for sIgE testing (40) in AD management and mixed results from anti-IgE therapies (41). Of 17 strawberry and 10 tomato sIgE tests sent for "atopic dermatitis" or "eczema," none resulted in a CRO. These results support the current understanding that food is not the primary cause of AD (42) and that dietary elimination for AD has little benefit and more potential for harm (40). Meanwhile, patients with AD tend to have higher sIgE levels to many allergens, many of which may have no clinical relevance, which reduces any utility of sIgE testing in AD (43). In this context, our data support that S/T sIgE testing is not indicated in the evaluation of most eczema.

S/T testing for PFAS symptoms and strawberry testing for possible IgE-mediated reactions had some CROs. CROs were expected when testing for PFAS symptoms for S/T, given that fruits are common triggers of PFAS, which is IgE-mediated (44, 45). However, PFAS may be diagnosed from clinical history and testing for pollen sensitization and generally does not require testing for specific foods. Meanwhile, testing for mild and severe possible IgE-mediated reactions resulted in only a small number of CROs for strawberry allergy and none for tomato allergy, suggesting that S/T infrequently cause IgE-mediated allergy beyond PFAS.

From an age standpoint, tomato sIgE testing resulted in no CROs for children under 11 years old (0/29), suggesting that tomato sIgE testing may not be of value for infants and preschool children. Furthermore, tomato sIgE resulted in PFAS only with the start of adolescence, consistent with previous observations that PFAS is less common in younger children (45). These trends were not observed for strawberry allergy, for which CROs were found for all age groups prior to adulthood and PFAS was found in patients under 6 years old and even in infants.

We also evaluated the potential relevance of an ERH or atopy in the decision to order S/T testing. Interestingly, the absence of an

ERH made a CRO following S/T sIgE testing statistically unlikely, with high negative predictive values for both strawberry (99.5%) and tomato (100%) fruits. Alternatively, the presence of an ERH could not reliably predict a CRO with low positive predictive values for both strawberry (11.5%) and tomato (15.0%) fruits. Thus, a negative ERH may largely rule out S/T allergy. Furthermore, results showed that ERH rather than sIgE testing had a greater bearing on CRO status, revealing the importance of taking a good clinical history and that, in many cases, sIgE testing may not affect management. Regarding atopy, non-atopic patients were never found to have a CRO following testing (0/26). While this is consistent with increased atopy with FA, our study was underpowered to evaluate this association due to a lack of relevant data.

Limitations

Our report had several limitations. Owing to the retrospective nature of this study and our relatively strict systematic approach to analysis, data were not always available. Racial/ethnic composition was also unclear in many instances. Regarding the reasons for testing analysis, since multiple reasons could be provided for a single sIgE test, we could not ascertain which of these reasons was linked to CROs in these cases. Finally, since our sample was largely pediatric, extrapolation of these findings to the adult population is limited.

Conclusion

At a large tertiary pediatric center, S/T sIgE testing was predominately ordered by A/I, GI, and GP, mostly for infants and school-age children. Clinical history rather than serological testing was the primary determinant of CRO status. ERH had a very high negative predictive value but a poor positive predictive value for CROs. Although mean sIgE levels were higher for S/T tests resulting in CROs, the overall yield was quite low. A large number of strawberry tests were sent for non-IgE-mediated gastrointestinal symptoms with no CROs. Further, S/T tests may have minimal yield for patients without atopy and in the workup of most eczema, although larger studies are needed to confirm these additional findings. Taken together, the threshold for ordering sIgE testing for S/T may need to be re-evaluated.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Children's Hospital Los Angeles IRB. The studies were conducted in accordance with local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AC: Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original draft, Visualization. NI: Conceptualization, Methodology, Data Curation, Writing – Review & editing, Resources. WC: Methodology, Formal Analysis, Writing – Review & editing. JT: Conceptualization, Methodology, Writing – Review & editing, Resources, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/falgy.2023.1277631/full#supplementary-material

SUPPLEMENTARY TABLE S1
Specific immunoglobulin E level regression models.

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Functional human skin explants as tools for assessing mast cell activation and inhibition

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Mast cells are activated through a variety of different receptors to release preformed granules and mediators synthesized *de novo*. However, the physiology and function of mast cells are not fully understood. Traditional studies of mast cell activation in humans have utilized cultures of tissue-derived mast cells including CD34+ progenitor cells or well-characterized commercially available cell lines. One limitation of these methods is that mast cells are no longer in a natural state. Therefore, their applicability to human skin disorders may be limited. Human skin explant models have been utilized to investigate the short-term effects of cell mediators, drugs, and irritants on skin while avoiding the ethical concerns surrounding *in vivo* stimulation studies with non-approved agents. Nonetheless, few studies have utilized intact human tissue to study mast cell degranulation. This "Methods" paper describes the development and application of an intact skin explant model to study human mast cell activation. In this manuscript, we share our protocol for setting up *ex vivo* human skin explants and describe the results of stimulation experiments and techniques to minimize trauma-induced histamine release. Skin explants were generated using de-identified, full-thickness, non-diseased skin specimens from plastic and reconstructive surgeries. Results were reproducible and demonstrated FcεRI- and MRGPRX2-induced mediator release which was inhibited with the use of a BTK inhibitor and QWF, respectively. Thus, this explant model provides a quick and accessible method of assessing human skin mast cell activation and inhibition.

KEYWORDS

mast cell, histamine, explant, IgE, BTK, MRGPRX2

Introduction

Mast cell activation is implicated in a diverse range of allergic disorders and innate immune processes (1). FcεRI-IgE binding is perhaps one of the most well-known pathways for mast cell activation. FcεRI is a high-affinity heterotetramer receptor for IgE containing one α-, one β-, and a γ-chain homodimer (αβγ2). The α-chain subunit facilitates the IgE binding. Meanwhile, the β-chain and γ-chain subunits allow for the downstream signaling cascade via Lyn inducing transphosphorylation of immunoreceptor

Abbreviations
ACP-196, acalabrutinib; BTK, Bruton's tyrosine kinase; HR, histamine release; NDRI, national disease research interchange; PAG, PIPES-albumin-glucose; PAGCM, PIPES-albumin-glucose-calcium-magnesium; PIPES, Piperazine-N,N′-bis(2-ethanesulfonic acid); PTX, pertussis toxin; RH, residual histamine; SCF, Stem cell factor; SHR, spontaneous histamine release; TSHC, total skin histamine content.

tyrosine-based activation motifs (ITAMs) that are attached to both chain subunits (2). In addition to Lyn, the FcεRI pathway features multiple downstream kinases including Syk, BTK, Fyn, and PI3K (3). Notably, inhibition of BTK, Syk, or PI3K broadly prevents IgE-mediated degranulation and cytokine production in primary human mast cells (3–7). The function of BTK in mast cells was further delineated in a study by Kawakami et al. (8). The BTK inhibitor acalabrutinib was shown to prevent anaphylaxis completely in a humanized mouse model and in most peanut allergic individuals during an oral food challenge (3, 9).

A more recently discovered pathway for activating mast cell degranulation is via Mas-related G protein-coupled receptor member X2 (MRGPRX2) (10). Like FcεRI, MRGPRX2 signals through pertussis toxin (PTX)-sensitive G_i proteins that control exocytosis (11, 12). MRGPRX2 is expressed at high levels in human skin mast cells and synovial mast cells, but not in lung mast cells (13). However, unlike FcεRI, MRGPRX2 is a low-affinity, "universal" receptor for both endogenous and exogenous ligands with shared properties of cationic molecules and amphipathic peptides (10, 14). In addition, McNeil et al. demonstrated that high concentrations of MRGPRX2 ligands induced swelling and anaphylaxis in mice via the murine orthologue Mrgprb2 (15).

Through these and other pathways, mast cells are activated to rapidly release preformed granules containing proteases, biogenic amines, and cytokines- all of which are vital in inflammatory responses (7, 16, 17). Such preformed granules include tryptase, histamine, and Tumor necrosis alpha (TNF-α). Tryptase activates protease activated receptors (PARs) on a variety of cell types including sensory neurons. Histamine enables the clinical features of allergic reactions. TNF-α stimulates the expression of adhesion molecules, which attract and bind leukocytes to the inflamed site (7, 17, 18). Synthesized mediators such as leukotrienes and prostaglandin D_2 can potentiate the vasodilatory effects of histamine and serve to recruit and activate leukocytes. Therefore, activation of mast cells can lead to degranulation and generation of mediators implicated in angioedema, atopic dermatitis, anaphylaxis, asthma, rosacea, and chronic urticaria (19). Thus, inhibition of mast cell activation is a viable target for treatment (7, 20–22).

Traditional studies of mast cell activation in humans have utilized cultures of mast cells derived from tissue or CD34+ progenitor cells, or well-characterized commercially available cell lines.[12] Umbilical cord blood, peripheral blood mononuclear cells (PBMCs), or bone marrow mononuclear cells (BMMCs) have been essential for procuring CD34+ progenitor cells to generate human mast cells (23). However, the process of generating mast cell cultures from skin homogenates or CD34+ progenitors can be costly and take 4 weeks and 6 weeks, respectively (24). An advantage of utilizing commercially available cell lines is that they can be utilized immediately for the study of immunological responses via mast cell stimulation. Available mast cell lines include HuMCs (human mast cells cultured from CD34+ progenitor cells), LAD2 (Laboratory of allergic diseases 2) mast cells, and the HMC1 (Human Mast Cell 1) line. Compared to human skin mast cells, both LAD2 and HMC1 mast cells have significantly lower levels of tryptase and chymase (25). HuMCs and LAD2 cells both have a slow growth rate thus limiting their expansion (26). A universal limitation of all of these methods is that mast cells are no longer in a natural state. Therefore, their applicability to human skin disorders may be limited.

An alternative method for assessing mast cell activation is microdialysis. Skin microdialysis is a technique used to recover soluble endogenous and exogenous molecules from the interstitial space in human skin (27). This type of procedure can be performed *in vivo* or *ex vivo*. It involves the insertion of thin tubular dialysis membranes into the dermis or the subcutaneous tissue which are then perfused at a low speed with a physiological solution. Due to its invasive nature, a local anesthetic is generally required to ease discomfort from probe insertion (27). Soluble molecules present in the extracellular fluid diffuse into the microdialysis tube which are then collected for analysis. Appropriate controls are required to determine whether sampled molecules are truly related to the disease state under investigation or have been generated as part of the skin response to probe implantation (27). Microdialysis has been utilized to assess mast cell MRGPRX2-mediated activation in chronic prurigo as well as pre- and post-treatment levels of histamine and eicosanoids in atopic dermatitis (28, 29). However, microdialysis does not assess the total tissue concentration of histamine or other mediators. In live human volunteers, microdialysis is limited to the use of only approved drugs and agents. Additional limitations are that commercially available microdialysis equipment is expensive and lacks flexibility in its application (30).

The human skin explant model has been utilized to investigate the short-term effects of cytokines and irritants on skin while avoiding the ethical problems of *in vivo* stimulation studies with non-approved agents (31). Under appropriate conditions, skin explants may remain viable for 14 days at 37 °C (32). Intact skin explants generated from biopsies have been utilized to examine the role of cytokines in the non-histaminergic pruritus pathway induced by TRPV1-, TRPA1-and PAR2-agonists (33). In a study by Tausk and Undem, human skin fragments of various sizes were utilized to examine histamine release induced by substance *p* and stem cell factor (SCF) (34). Though, the applicability of the findings of these 2 studies to other mast cell activation pathways remained unknown. Another study sought to investigate histamine release in response to FcεRI, and MRGPRX2 activation. However, the method of skin processing induced high levels of spontaneous histamine release (35). These results suggest that intact skin explants could serve as an alternative method for assessing mast cell activation.

This "Methods" paper describes the development and application of an intact skin explant model to study human skin mast cell activation. In brief, discarded surgical skin specimens were exposed to various conditions to measure spontaneous histamine release. Subsequently, the specimens were stimulated with well-characterized ligands and inhibitors of FcεRI and MRGPRX2 signaling. Residual histamine (RH) content was quantified in specimens incubated overnight in 1.6% perchloric acid. Finally, total skin histamine content (TSHC) was determined by adding spontaneous, stimulated, and residual histamine. Among the benefits of this method are the limited

processing of skin specimens and relatively short time to completion (less than 24 h).

Materials and equipments

Skin specimens

- De-identified, non-diseased human skin tissue without adipose layer from abdominal or breast surgeries was provided by the National Disease Research Interchange (NDRI) (Figure 1). Samples were provided from only adult individuals without a history of cancer or history of chemotherapy or radiation within the previous 5 years.
- De-identified, non-diseased human skin tissue was provided from adult plastic and reconstructive surgeries at Johns Hopkins Bayview Medical Center. Occasionally, these samples included the adipose layer which was removed prior to performing biopsies. These samples were not prescreened for cancer or radiation history, and age and gender were not provided.
- Consent was obtained by surgeons for the use of tissue for research.
- This study was determined to be IRB-exempt using their questionnaire because it fell within the category of "Not Human Subjects Research (NHSR)/Quality Improvement (QI)." Proof of this exemption was formally obtained from the IRB in the form of a letter as required by NDRI before shipping skin.

Skin procedure

- Sterilized fine splinter forceps 4.5 in. forceps (Medline)
- Sterile smooth, straight, stainless steel 5-1/2 in. scissors (Skylar Instruments)
- Sterile disposable OR Grade 2.5 mm and 4 mm punches (Acuderm)
- 6-well culture plate (Costar® 6-well Clear TC-treated Multiple Well Plates, Individually Wrapped, Sterile)
- Microcentrifuge tubes 1.5 ml
- Eppendorf Pipettes 10 µl, 100 µl, 1,000 µl
- TipOne pipette tips 10 µl, 100 µl, 1,000 µl
- Nitrile gloves
- Incubator
- Micro-Centrifuge (Labnet Prism C2500-R)
- Histamine autoanalyzer
- Autoanalyzer sample cups
- Orbital shaker
- Sharps Container
- Ethanol 70%

Reagents

- Ultrapure water, Cayman Chemical
- Polyclonal goat anti-IgE, courtesy of Dr. Robert Hamilton, DACI Laboratory, Baltimore, MD
- Acalabrutinib (ACP-196), Cayman Chemical

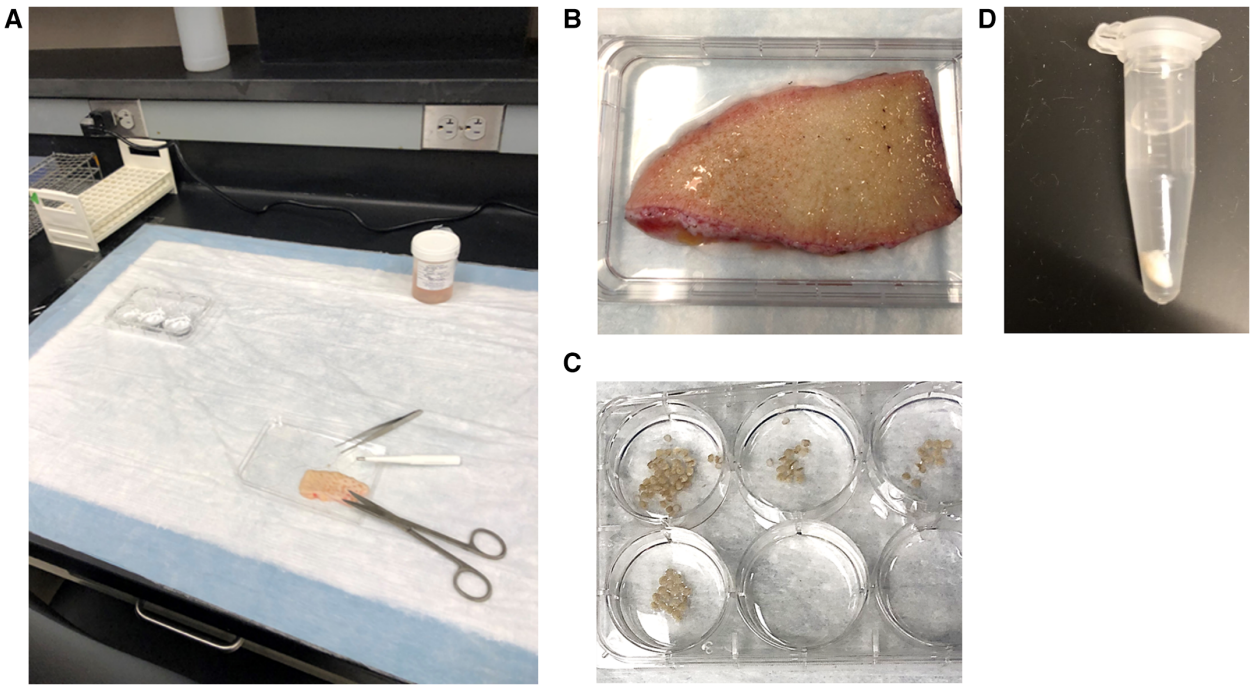

FIGURE 1
(**A**) bench set up for skin explant experiments. (**B**) Skin is placed on inverted lid of a 6-well culture plate which allows for the collection of any buffer that is released from the skin and provides a stable surface for the performance of punch biopsies. (**C**) Punch biopsies are immediately placed in wells containing PAG before being transferred to microcentrifuge tubes filled with PAGCM and/or inhibitors. (**D**) Following stimulation, biopsies are transferred to perchloric acid. Shown here is a 4 mm punch in 1 ml of 1.6% perchloric acid.

- Compound 48/80, Sigma-Aldrich
- QWF [Boc-Gln-D-Trp(Formyl)-Phe-OBzl], TOCRIS
- Pertussis Toxin (PTX), Sigma-Aldrich
- PIPES-albumin-glucose (PAG) buffer, prepared in-house. PAG consists of 25 mM PIPES [Piperazine-N,N′-bis(2-ethanesulfonic acid)], 110 mM NaCl, 5 mM KCl, 0.1% glucose, and 0.003% human serum albumin (HSA)
- PAGCM, prepared in-house. PAGCM consists of PAG supplemented with 1 mM $CaCl_2$ and 1 mM $MgCl_2$.
- PAG-EDTA, prepared in-house. PAG-EDTA consists of PAG supplemented with 0.1 mM EDTA (ethylenediamine N, N, N′, N′- tetraacetic acid)
- Perchloric acid ($HCLO_4$) 1.6%, prepared in-house on the day of the experiment by diluting stock supply ($HCLO_4$ 61%) with deionized water.

Stepwise procedures

Preparation of reagents

- PAG and PAGCM were removed from fridge and allowed to come to room temperature (RT). The incubator was warmed to 37 °C.
- Reconstitute stimuli and inhibitors if necessary. *Note:* Compound 48/80 powder was reconstituted to a concentration of 10 mg/ml using ultrapure water. All other commercial reagents were reconstituted per manufacturer instructions. Stock concentrations of all reagents were further diluted in PAGCM.
- Microcentrifuge tubes were filled with PAGCM (with or without inhibitors) as indicated below, and placed in the incubator to warm. *Note:* Explants used for inhibition conditions are exposed to the inhibitors during the spontaneous HR incubation and stimulation.
- The total volume of buffer in which explants were incubated was 100 µl for anti-IgE and its inhibitors, 75 µl for compound 48/80 and its inhibitors, and 75 µl for experiments that examined anti-IgE and compound 48/80 responses in the same donor.
- For each stimulus and inhibitor, prepare [2×] concentration (working concentration). This will be combined with an equal amount of buffer (or another reagent) in each microcentrifuge tube to create the final concentration at the appropriate volume. For example, 50 µl of 6 ug/ml [2×] anti-IgE was added to 50 µl of PAGCM to make 100 µl of 3 µg/ml [1×] anti-IgE.
  - For inhibition experiments, the same approach was taken. For example, 50 ul of 5 µg/ml [2×] acalabrutinib was added to 50 µl of 6 µg/ml [2×] anti-IgE to make 100 µl of 2.5 µg/ml [1×] acalabrutinib + 3 µg/ml [1×] anti-IgE.
- All HR incubations were performed in duplicate or triplicate. Separate tubes were designated for PGD_2 measurement in duplicate.
- Prepare microcentrifuge tubes for spontaneous histamine release before processing the skin/performing biopsies.
- Prepare stimulation tubes while explants are incubating for spontaneous histamine release.
- All prepared microcentrifuge tubes were pre-warmed to help maintain consistent temperature of specimens.

Skin stimulation procedures

- An overview of the explant stimulation and inhibition procedure is provided in Figure 2.
- NDRI skin segments, which were a minimum of 5 × 5 cm, arrived within 24 h of harvest on an ice pack in a sterile specimen container filled with phosphate buffered saline (PBS) and antibiotics.
- Specimen container was removed from shipping box or refrigerator and set on benchtop for 1 h to allow skin to reach RT.
- Specimens were divided into equal size samples using skin biopsy punches. *Note:* Experiments were initially conducted using both 2.5 mm punches and 4 mm punches. It was felt that using two 2.5 mm punches in each microcentrifuge tube produced more consistent results between duplicate and triplicate conditions.
- Wells of a 6-well culture plate were filled with RT PAG. Skin was set on the lid from 6-well culture plate for stabilization. Specimens were biopsied using a 2.5 mm or 4 mm punch. Care was taken to avoid taking biopsies from stretch marks. Biopsies were transferred to wells containing RT PAG as they were obtained to prevent specimens from drying out.
- Punch biopsies were placed in pre-warmed microcentrifuge tubes containing PAGCM with/without inhibitors.
- Biopsies were incubated at 37 °C for 1 h to assess spontaneous HR. In the case of QWF and PTX, the spontaneous HR incubation time was the same as the duration of pretreatment with the inhibitor (60 min). This incubation was shortened to 30 min for experiments involving acalabrutinib. Thus, for anti-IgE experiments that involved acalabrutinib, spontaneous HR was measured after 30 min for all samples.
- Following the spontaneous HR incubation, biopsies were transferred to stimulation tubes using designated forceps for each experimental condition to avoid cross-contamination (i.e., using inhibitor forceps on stimulation-only samples).
- Spontaneous HR buffer was transferred to histamine cups and brought to a volume of 1 ml with PAGCM. This was frozen (−20 °C) for later spontaneous histamine release assessment.
- Stimulation tubes were returned to incubator for 1 h to assess stimulated histamine release (see Results section for data supporting the decision to use a stimulation time of 1 h). Following stimulation, biopsies were transferred to designated tubes filled with 1 ml of RT 1.6% perchloric acid. Stimulation HR buffer was transferred to histamine cups and brought to a volume of 1 ml with PAGCM before being frozen (−20 °C).
- Following overnight incubation in perchloric acid at 4 °C, samples were centrifuged at 12,000 rpm for 4 min and the supernatant was harvested for histamine release. Residual histamine (RH) in samples was either analyzed immediately

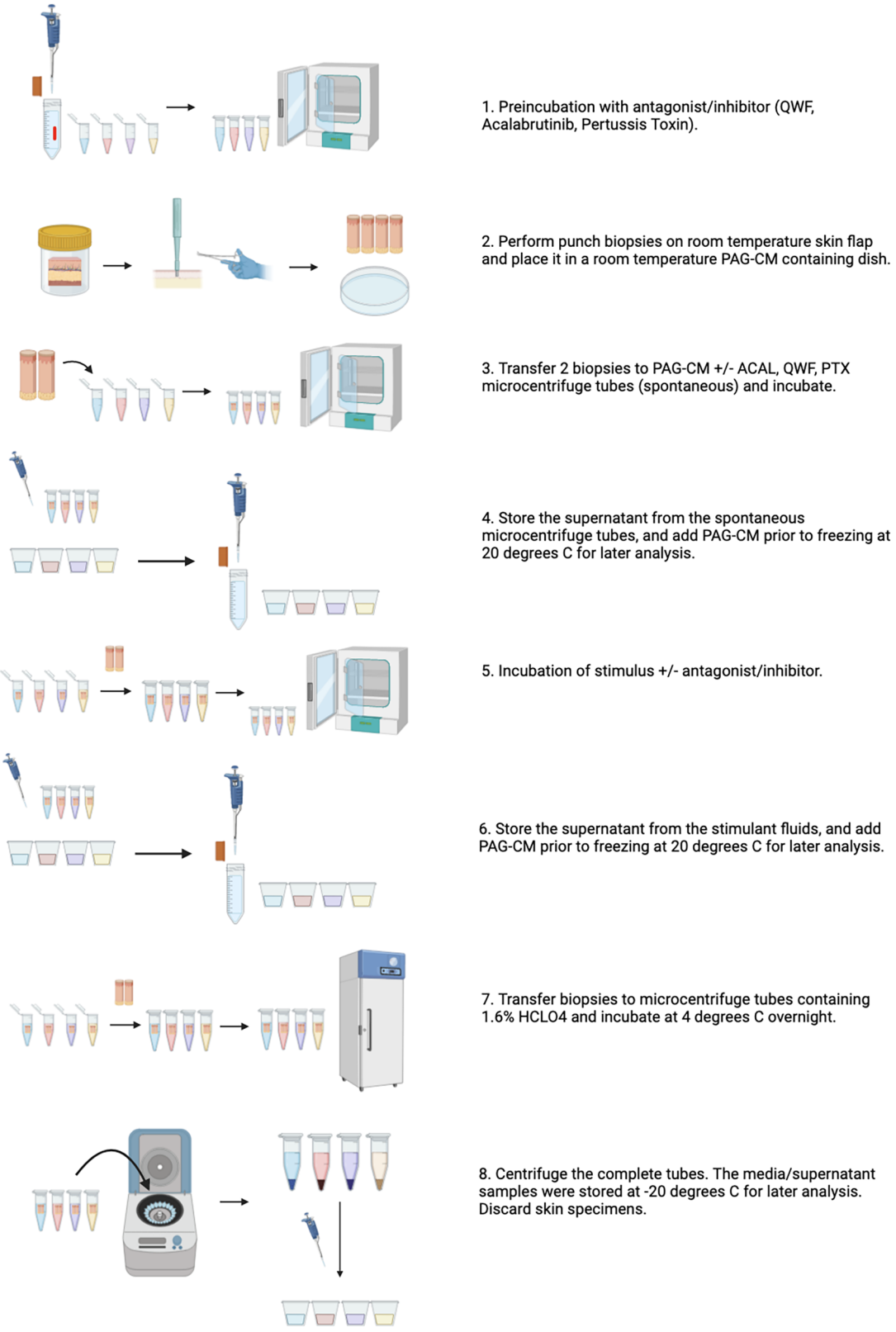

FIGURE 2
Overview of the skin explant model to study mast cell activation and inhibition. Created in Biorender.com.

(along with stored stimulated and spontaneous histamine release samples from the day before) or stored at −20 °C until later analyzed.

Processing and stimulation of fresh surgical skin specimens

- Fresh surgical skin specimens, approximately 2 × 2 cm, were provided by JHBMC, within 2–4 h of surgery, in a sterile specimen container at room temperature without buffer or media.
- Specimens were placed in RT PAG for one hour or washed in EDTA (followed by increasing concentrations of calcium) at the start of the experiment. For the EDTA wash, the intact surgical specimen was placed in PAG/0.1 mM EDTA for 20 min, then transferred to PAG for 20 min, then a 1:1 mix of PAG + PAGCM (0.5 mM $CaCl_2$) for 20 min, then PAGCM (1 mM $CaCl_2$) for 15 min. Each wash was performed in a 6-well plate on an orbital shaker (65 rpm) in a volume of 3 ml. Following the final wash, 2.5 mm punch biopsies were obtained and assessed for spontaneous, stimulated, and residual histamine as described above.

Mediator quantification

We measured spontaneous, stimulated, and residual histamine (RH) of 2.5 mm biopsy pairs or single 4 mm biopsies using a fluorometric autoanalyzer (36). Spontaneous histamine release (HR) was assessed following incubation in buffer alone for 1 h at 37 °C. Stimulated HR was determined for various concentrations of MC stimuli ± their respective inhibitors or antagonists at various time points at 37 °C. Inhibitors and antagonists were added during the spontaneous incubation and again during the incubation with the stimuli. RH content was extracted by incubating biopsies overnight at 4 °C in 1.6% perchloric acid. Total skin histamine content (TSHC) was calculated by adding HR and RH content for each biopsy pair. All results were expressed as a percentage of TSHC. Prostaglandin D_2 (PGD_2) was assessed using a Cayman Chemical prostaglandin D_2 ELISA (Item No. 512031).

Statistical analysis

All summary data are presented as mean ± SD. Statistical analyses were performed with GraphPad Prism (version 10.1.2) using Wilcoxon signed rank test or Mann Whitney test for paired and unpaired samples, respectively. A Spearman rank correlation test was used to assess the relationship between 2 variables. A Kruskal-Wallis test or an analysis of variance (ANOVA) with Tukey's multiple comparison test was performed to determine whether there was significant variation between 3 or more variables. A p value <0.05 was considered significant.

Results

Total skin histamine content

We determined the total skin histamine content of 2.5 mm biopsy pairs (Figure 3) and single 4 mm biopsies (Supplementary Figure S1) by adding the spontaneous, stimulated, and residual histamine of each sample. For both conditions, we observed that the total skin histamine content of biopsies varied between and within individual donors. A strong correlation was found between tissue weight, which also varied, and total skin histamine content; however, variance in total skin histamine content was still observed after histamine content was corrected for tissue weight (Supplementary Figure S1). In a prior study by Eady et al, light microscopy revealed wide variations in mast cell counts between different sections from the same biopsy specimen, confirming that mast cells are unevenly distributed even within the same biopsy specimen (37). Therefore, we hypothesize that differences in weight and mast cell distribution between biopsies are responsible for the variance that we observed in total skin histamine content. There were few studies to draw upon as a guide for the expected total histamine content of skin. One study reported that the histamine content of healthy skin was 15.7 ± 3 (mean ± 2 SEM) ng/mg. Notably, that study used a process of boiling minced skin for 5 min to extract tissue histamine (38). Using overnight perchloric acid digestion at 4 °C to extract residual histamine, we found that the total histamine content of most of our skin biopsies (when adjusted for weight) fell within this range while others exceeded this range.

Spontaneous histamine release

We observed variability in net spontaneous histamine release between subjects and within subjects. The highest levels of

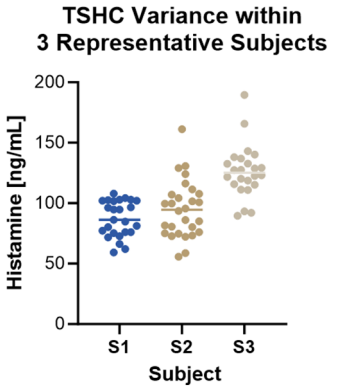

FIGURE 3
Total skin histamine content varied between and within individual donors. Data is shown for 3 subjects. Each circle represents a pair of 2.5 mm punch biopsies. Mean THSC was 87.12 ± 14.8 ng/ml, 94.80 ± 23.73 ng/ml, and 126.1 ± 1.69 ng/ml for subjects S1, S2, and S3, respectively. Kruskal-Wallis test, $p < 0.0001$.

spontaneous histamine release were noted initially following the skin biopsy procedure and values decreased over time (Figure 4). To further understand the variability in raw spontaneous histamine release between samples, we examined the relationship between spontaneous histamine release and total skin histamine content. We observed that spontaneous histamine release was directly correlated with total skin histamine content (Figure 5, Supplementary Figure S2). Despite the variability in raw histamine release, the initial spontaneous histamine release for NDRI skin specimens as a percentage remained low, only exceeding 2% of total skin histamine content on rare occasions. To standardize our results, we report histamine release as a percentage of total histamine content in the sections that follow.

Stimulated mediator release

We established the kinetics of IgE-mediated histamine release for this model by quantifying histamine release at 2, 5, 10, 20, 30, 60, and 120 min in triplicate (not shown). While histamine release could be detected as soon as 5 min in response to the highest concentration of anti-IgE, it was not observed in all replicates. This may have been due to variation in the diffusion of anti-IgE into the tissue during these shorter time periods as well as mast cell distribution. Results of anti-IgE mediated histamine release were more consistent for the 30-, 60-, and 120-min stimulation periods (Figure 6A). It was previously reported that, depending on the donor, optimal histamine release for purified skin mast cells was obtained using an anti-IgE concentration of either 1 µg/ml or 3 µg/ml (39). We found no significant difference between the results for these concentrations. Using 4 mm punches, we confirmed the ability to detect mast cell-derived PGD_2 following anti-IgE stimulation (Figure 6B).

To determine whether anti-IgE mediated histamine release could be inhibited by a specific inhibitor of IgE signaling, we pretreated samples with the BTK inhibitor acalabrutinib. We found that the optimal inhibitory concentration of acalabrutinib in this model was 2.5 µg/ml (Figure 6C). Pertussis toxin also inhibited anti-IgE-mediated histamine release (Supplementary Figure S3). Our results are in line with a prior study which showed that incubation with pertussis toxin for 4 h at 37 °C inhibited anti-IgE mediated histamine release from dispersed human skin mast cell cultures by 63.3 ± 8.2% (40). In contrast, an earlier study demonstrated that pertussis toxin failed to inhibit anti-IgE (3 µg/ml) mediated histamine release from dispersed human skin mast cells (41).

Based on our anti-IgE results, we next examined the kinetics of compound 48/80-mediated histamine release at 30, 60, and 120 min. Results were similar across these 3 time points (Figure 7A). To determine whether compound 48/80-mediated histamine release could be inhibited in our model, we pretreated samples with QWF (Figure 6B) or pertussis toxin (Figure 6C). Although MRGPRX2 antagonists have been developed for clinical use and are in phase I and phase II trials, we did not have access to these agents. Therefore, we utilized QWF which has been reported to be an antagonist of MRGPRX2 (42). QWF and pertussis toxin have been shown to inhibit compound 48/80-mediated degranulation in human mast cell lines (26, 42) and human cord blood-derived mast cells (43), and we observed that these agents inhibited histamine release in our explant model.

After establishing the kinetics of histamine release, we examined anti-IgE- and compound 48/80-mediated histamine release in the same donors. Utilizing a stimulation period of 1 h, we found greater histamine release in response to compound 48/80 than with anti-IgE (Figure 8). Our results are in contrast with previous studies which showed that cultured skin-derived MCs

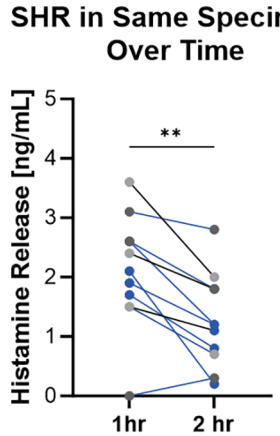

FIGURE 4
Spontaneous histamine release varied over time and between donors. Pairs of 2.5 mm punches were incubated at 37 °C. Buffer was harvested and replaced at 1 h and 2 h. Data shown are histamine release during those time periods from 3 donors with number of samples per donor ranging from 2 to 4. Wilcoxon paired sign rank test, $p = 0.0029$.

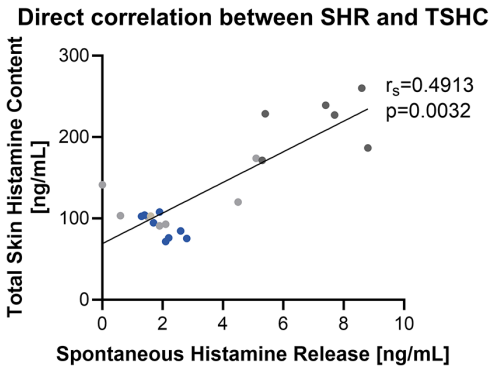

FIGURE 5
Spontaneous histamine release is directly correlated with total skin histamine content at physiologic temperature. Data shown are histamine release during those time periods from 3 donors with number of samples per donor ranging from 6 to 10 paired 2.5 mm punches. Each color represents a different donor.

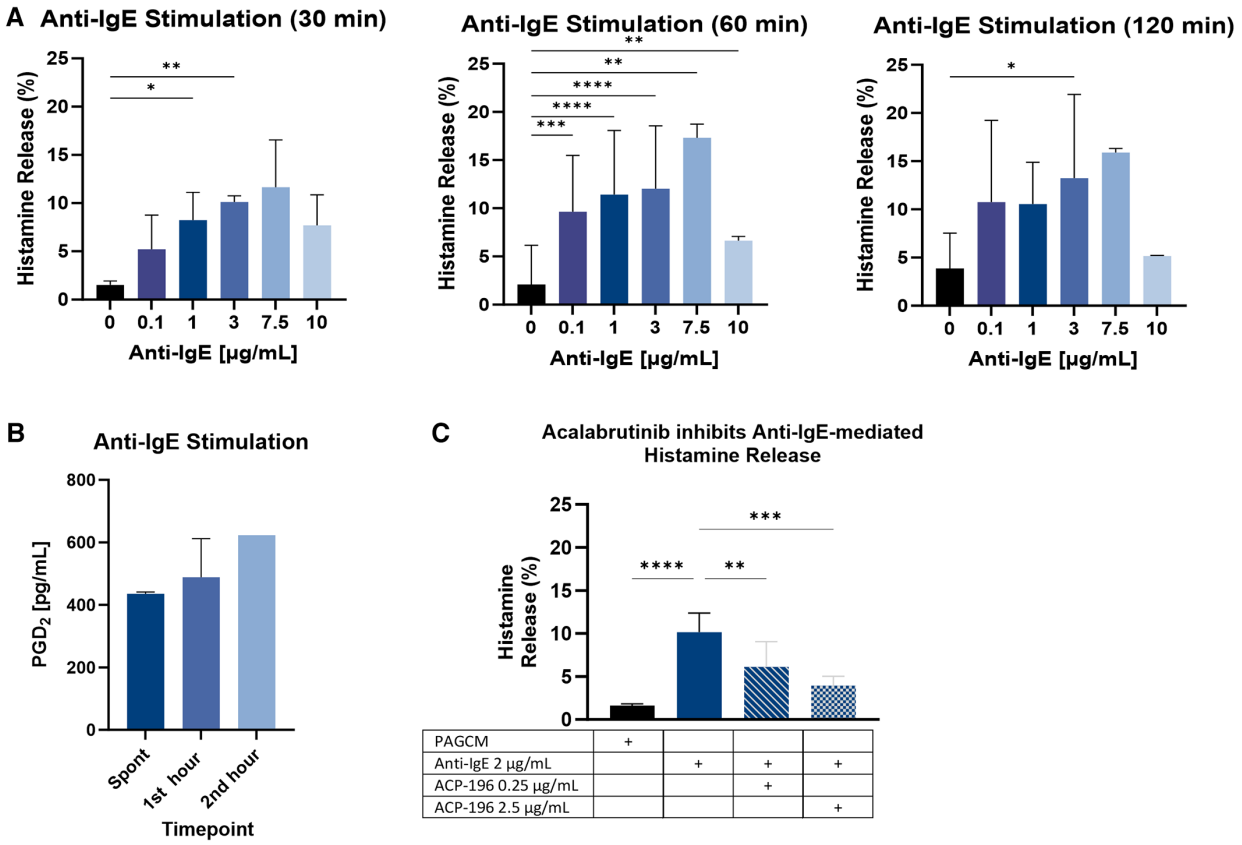

FIGURE 6
IgE-mediated mediator release. (A) The kinetics of explant histamine release following stimulation with polyclonal goat anti-IgE are shown for 30 min, 60 min, and 120 min. Paired 2.5 mm punches were examined in triplicate. Data is shown for the same 3 donors for each time point. (B) PGD_2 production was measured from 4 mm punches from 2 subjects at baseline (1 h before stimulation) and at 60 min and 120 min following stimulation with 1 µg/ml anti-IgE (note: results reflect PGD_2 produced during the 1st and 2nd hour following stimulation, not cumulative production). (C) Inhibition of IgE-mediated histamine release by acalabrutinib is shown for 3 donors. Paired 2.5 mm punches were examined in duplicate. Samples were incubated with acalabrutinib (ACP-196) for 30 min before stimulation and again during stimulation with anti-IgE. Results for histamine kinetics and acalabrutinib inhibition were analyzed using ANOVA with Tukey's multiple comparison test. Only significant p values are shown. *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$, ****$p < 0.0001$.

were less responsive to MRGPRX2 activation than FcεRI-aggregation due to both acute and chronic inhibition by SCF in the culture media (44, 45). Furthermore, skin mast cells in culture undergo several non-synchronized modulations. For instance, tryptase and chymase expression strongly decline over time (46). There is also a marked increase in FcεRI surface expression and FcεRI-mediated histamine release (increasing from ≈15.5% to ≈60%) during the culture period (46).

Results from fresh surgical specimens

We examined histamine release from fresh surgical specimens obtained on the same day and noted that spontaneous histamine release was markedly elevated. In some cases, spontaneous histamine release exceeded 60% within the first hour following biopsy, but this decreased over time in the same specimens (Supplementary Figure S4). We questioned whether the trauma of the procedure or skin processing caused this steep rise in spontaneous histamine release. We found that warming of the skin did not have an appreciable impact on spontaneous histamine release. Elevated spontaneous histamine release also occurred despite incubating specimens at room temperature in PBS/1% BSA instead of a high calcium-containing buffer (Supplementary Figure S4). Thus, we hypothesized that the combination of trauma and existing calcium in the skin contributed to high spontaneous histamine release. Incubating the skin specimen in EDTA and washing in increasing concentrations of calcium reduced spontaneous histamine release to 1.03 ± 0.37% while allowing detection of histamine release via anti-IgE and compound 48/80 (Figure 9).

Discussion

This "Methods" paper describes the development and application of an intact skin explant model to study human mast cell activation. This method allows for the comparison of dose

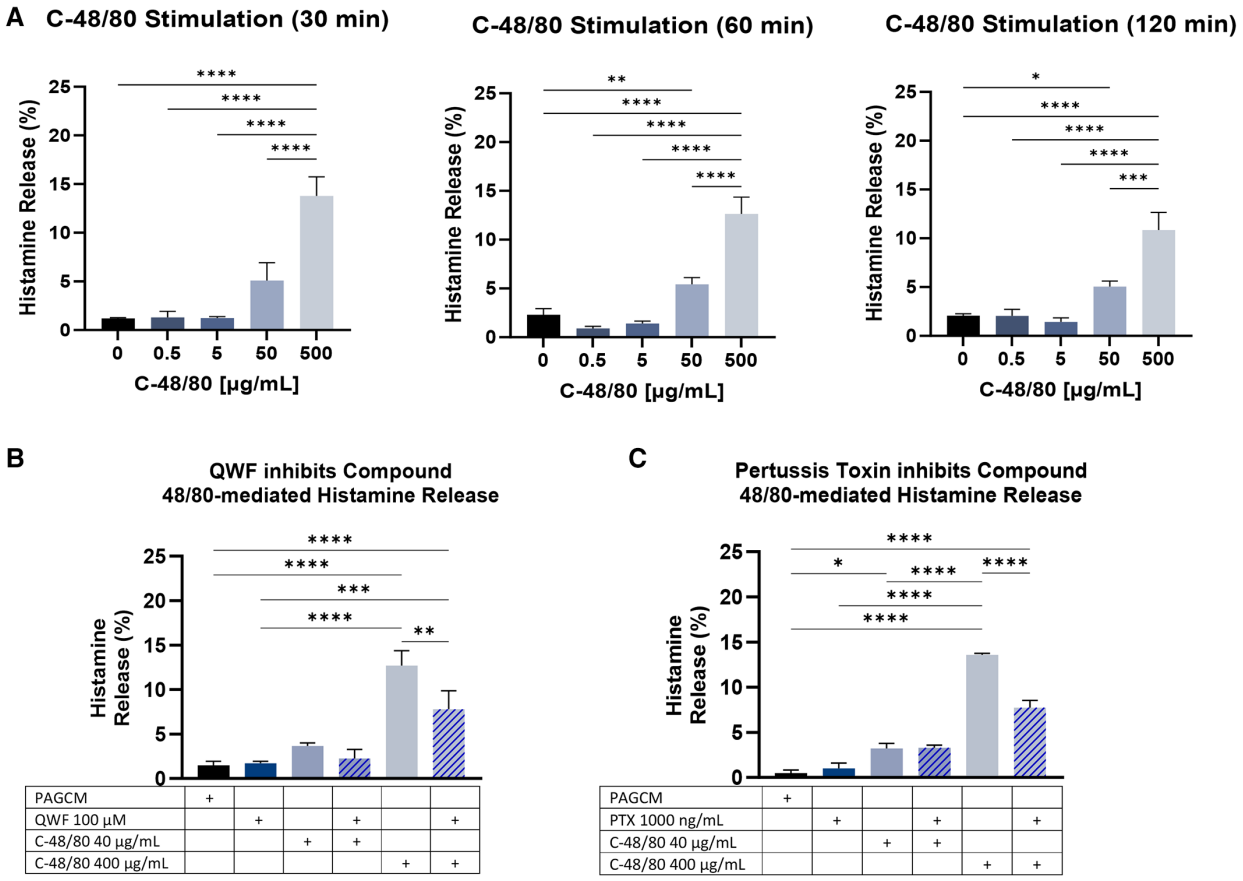

FIGURE 7
Compound 48/80-mediated histamine release. (**A**) The kinetics of explant histamine release following stimulation with compound 48/80 (C-48/80) are shown for 30 min, 60 min, and 120 min. Paired 2.5 mm punches were examined in duplicate. Data is shown for the same 3 donors for each time point. (**B**) QWF at 100 µM concentration shows inhibition of compound 48/80 mediated histamine release. Data from 2 donors in duplicate (paired 2.5 mm punches). (**C**) Inhibition of compound 48/80 mediated.

responses to distinct mast cell stimuli and their antagonists or inhibitors even between different donors.

Prior studies of mast cell activation in humans have utilized well-characterized commercially available cell lines, mast cell cultures derived from tissue or CD34+ progenitor cells, *in vivo* skin testing, skin chambers, and microdialysis. However, each of these methods has drawbacks. The applicability of cell cultures to human skin disorders may be limited as mast cells are no longer in a natural state. The process of generating mast cell cultures from tissue or progenitor cells can be costly and time consuming. *In vivo* skin testing assesses visible wheal and erythema formation in response to stimuli, but alone does not provide a means for direct sampling of released mediators. In contrast, skin chamber studies and microdialysis can assess levels of endogenous as well as exogenous substances or drugs administered to patients. Traditional skin chamber studies have a long time course for blister formation (up to 2 h), a tendency for blisters to coalesce, and occasional ecchymoses (47). Newer negative pressure devices have a shorter time course of blister formation due to the combination of heat and higher pressure. Mediator assessment is still limited by the number of blisters that can be formed and the size of the collection chambers used (48). *In vivo* microdialysis studies require the use of topical anesthetics to limit discomfort while *ex vivo* studies require access to large sections of tissue. In addition, financial cost may limit widespread use of microdialysis for both *in vivo* and *ex vivo* studies. Both *in vivo* microdialysis and skin chamber studies are also limited to the use of only approved pharmacologic therapies in inhibition studies.

The advantages of our skin explant model include: the avoidance of regulatory and safety issues with studies of live patients, the use of small skin samples to assess mast cell responses, and a quick turnaround time for experiments. Another benefit of this skin explant model is no processing or manipulation of the skin allowing receptors and granules to remain intact. Compared to culturing and cloning HMC1 and LAD2 cells, this skin procedure takes less than 2 days to complete and involves less manipulation. Although the HMC1 cell line may have a faster growth rate than other cell lines, it is inadequate in studying degranulation of mast cells (26). Our

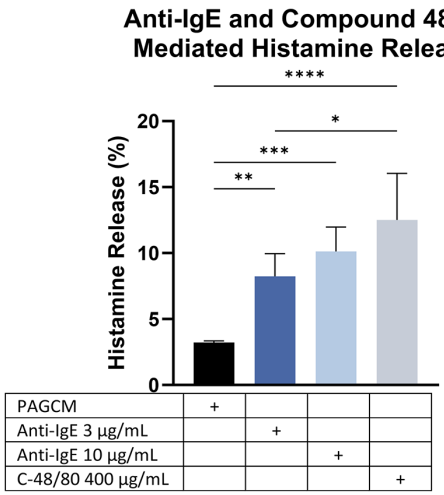

FIGURE 8
Comparison of IgE-mediated and compound 48/80-mediated histamine release within the same individuals. Data are shown for 3 donors. Paired 2.5 mm punches were examined in duplicate. ANOVA with Tukey's multiple comparison test. *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$, ****$p < 0.0001$.

method provides the advantage of closely mimicking the *in vivo* immunological mast cell response.

Given the variability in histamine content of biopsies between and within the same donors, our model requires analysis of histamine release as a percent of the total histamine content for each sample. Using designated specimens to serve as "representative" specimens for spontaneous release or total histamine content for an entire experiment could result in misleading results (mistaking spontaneous release for stimulated release). We encountered this problem when we began to develop this model as the first specimens that we received were from fresh surgical specimens which initially had a high level of spontaneous histamine release at baseline.

Moreover, beta-hexosaminidase assays are commonly performed in place of histamine assays in determining degranulation in mast cells. Although we did not measure beta-hexosaminidase in our study, we anticipate that our model can produce similar beta-hexosaminidase results based on prior studies that demonstrate a correlation between beta-hexosaminidase and histamine assays (15, 29, 49, 50).

In the development of this explant model, efforts were made to minimize spontaneous histamine release. It is important to distinguish the receptor-mediated mast cell histamine release from spontaneous degranulation. Due to the high level of spontaneous histamine release from fresh surgical samples initially, we were initially unable to distinguish stimulated release from spontaneous release during the stimulated period (Supplementary Figure S4). However, the protocol we developed for fresh same-day specimens reduced spontaneous release while maintaining the ability to detect stimulated release (Figure 9).

Using this model, the magnitude of stimulated histamine release may vary depending on the agent used or pathway interrogated. We found that compound 48/80 produced higher histamine release than anti-IgE activation (Figure 7). Our results are in contrast with previous studies which showed that cultured skin-derived mast cells were less responsive to MRGPRX2

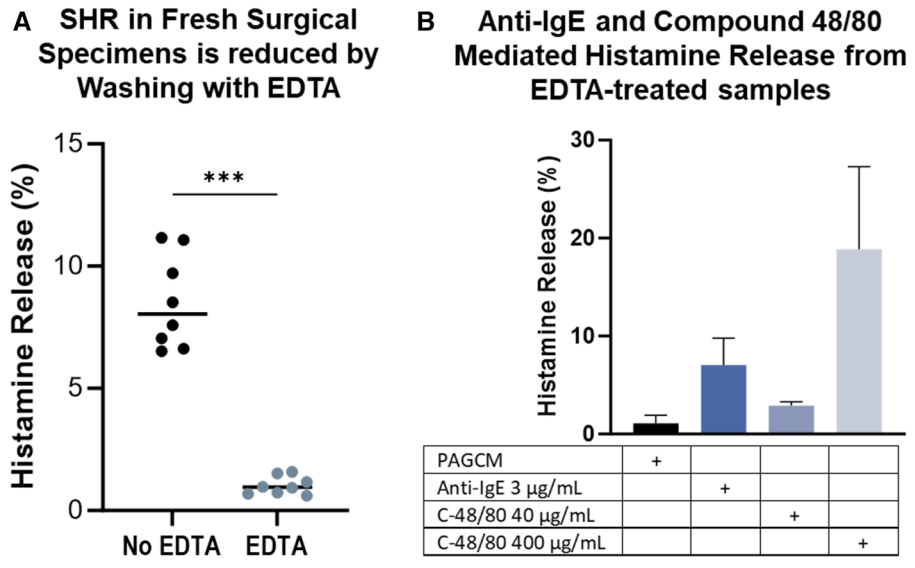

FIGURE 9
EDTA treatment minimizes spontaneous histamine release from specimens stimulated the same day as surgery while preserving stimulated release. Data is shown for 2.5 mm biopsy pairs from the same donor, same surgery day. (A) Spontaneous histamine release is reduced by EDTA. Mann Whitney test, $p = 0.0002$. (B) Samples were washed in EDTA followed by increasing concentrations of calcium at room temperature before assessing spontaneous and stimulated histamine release. Data shown for the same subject in duplicate.

activation than FcεRI-aggregation due to both acute and chronic inhibition by SCF (44, 45). SCF has also been shown to acutely enhance FcεRI-mediated mast cell degranulation while chronic exposure may reduce FcεRI-mediated degranulation (51). In one study, skin mast cell FcεRI-mediated histamine release was shown to increase nearly fourfold when mast cells were cultured in SCF + IL-4 for up to 16 weeks (46). There was also a corresponding increase in FcεRIα surface expression, which the authors speculated was due to constant exposure to IL-4. Thus, an advantage of our model is that the response to FcεRI and MRGPRX2 activation may be more consistent with the natural state as our method does not require addition of SCF or cytokines for culture.

As expected, the kinetics for stimulated histamine release in our explant model were notably longer than for isolated cell suspensions and tissue homogenates. For instance, in one study, anti-IgE-mediated histamine release from mast cells in skin tissue homogenates reached 14.2% for normal controls following 20 min incubation with the optimal dose of anti-IgE (52). In our model, median stimulated histamine release for 1 µg/ml anti-IgE was only 4.66% at 20 min, but rose to 15.75% at 1 h with this same dose (one donor, in triplicate). Thus, our results are in line with those of skin homogenates when a longer stimulation period is conducted. Our work demonstrates that, under optimal conditions, intact explants may serve as a useful model for assessing human skin mast cell function without enzymatic digestion or mincing the skin.

High levels of spontaneous histamine release have been observed in studies utilizing tissue homogenates. Veien et al. utilized dispersed mast cell suspensions isolated from neonatal foreskins to understand the mechanisms of histamine and tryptase release induced by vancomycin, morphine, and atracurium (53). They found that these drugs caused the release of both histamine and tryptase, and that this activation could be inhibited by blocking phospholipase C and phospholipase A2. However, data was excluded from samples with spontaneous histamine release exceeding 15%, which the authors attributed to cell lysis during processing (53). In another study, Ruzicka and Gluck compared mast cell responses in atopic dermatitis skin lesions and healthy control skin using tissue homogenates which were generated by mincing fresh biopsies approximately 0.5 cm^2 in size (54). The authors found that atopic skin released twice as much histamine in response to anti-IgE than healthy skin whereas compound 48/80-mediated release was almost identical between the two groups. However, the mean spontaneous histamine release was markedly elevated at 31.6% ± 4.2% (mean ± SEM) for healthy controls and 25.9% ± 4.0% for the patients with atopic dermatitis (54). The authors postulated that the preparation of sections of the firm skin tissue led to the damage of mast cells. If this were indeed the cause, it is possible that these high levels of spontaneous histamine release could have been avoided with our intact skin explant model.

A study by Clegg et al. sought to characterize histamine release from fresh human foreskin slices in response to anti-IgE, compound 48/80, and other synthetic secretagogues, as well as the inhibitory effects of salbutamol and sodium cromoglycate (35). The authors utilized a tissue chopper to generate 200 µm thick fresh foreskin slices which were then washed in 2 ml of Hanks' Balanced Salt Solution (HBSS) before the experiment. With this preparation method, the authors noted that spontaneous histamine release was high (ranging from 10 to 30%). The authors attempted to reduce spontaneous histamine release by washing the slices twice in a larger volume of HBSS (5 ml), allowing the slices to rest for 1 h, then washing for a third time before challenge. This washing procedure reduced spontaneous histamine release to 7.5 ± 0.5% but also reduced the skin slices' stimulated response to all secretagogues and increased the number of specimens failing to release any histamine during stimulation (35). In our model, we found that incubating fresh skin specimens in EDTA and washing in increasing concentrations of calcium reduced spontaneous histamine release while allowing detection of stimulated histamine release via anti-IgE and compound 48/80.

To date, few studies have utilized intact human tissue to study *ex vivo* mast cell degranulation. Of these studies, most have involved the use of microdialysis on large skin explants. *Ex vivo* microdialysis allows the use of nonapproved agents, however cost and access to large enough tissue limit its widespread use. Alternatively, Tausk and Undem examined net histamine release, induced by the MRGPRX2 ligand substance *p* and SCF, from small human neonatal foreskin and adult face and back skin fragments weighing between 9 and 48 mg. They found that large concentrations of substance *p* induce histamine release from skin mast cells, and that it was unlikely that these concentrations are reached physiologically during sensory nerve stimulation with capsaicin (34). Our model builds on this work and provides a more convenient and accessible alternative to microdialysis.

As our study entailed the use of de-identified surgical specimens, it is unknown whether donor characteristics influenced our results. These factors include atopic history and other medical history, medications administered before and during surgery, and age. With the exception of one NDRI donor, all skin specimens were from female donors. Thus, we were unable to assess whether there were sex differences in mast cell responses in this model. As our NDRI samples were exclusively either breast or abdomen, it is also unclear how our results would have differed had other body sites been evaluated.

Occasionally, there were NDRI surgical resections from which no appreciable histamine release could be elicited with anti-IgE or compound 48/80. We considered several possibilities for this finding including whether these individuals had received treatment with a drug that inhibited their mast cell activation. We also questioned whether these individuals had impaired mast cell responses at baseline. In a subset of the general population, basophil nonresponders or nonreleasers are well-described. In such individuals, blood basophils have poor histamine release in response to IgE-crosslinking with a polyclonal IgG antibody while other activation pathways remain intact (55). While this nonreleasing phenotype has also been observed in Syk-deficient human lung mast cells (56), this functional phenotype has not been described in human skin mast cells. Another possibility considered for the poor histamine response of these explants is

that their mast cells perhaps degranulated in transit. However, analysis of the residual histamine content in these skin samples was comparable to that of those individuals who had demonstrable histamine release via FcεRI and MRGPRX2 in our study. Nevertheless, given the wide variability in total skin histamine content between donors, we cannot conclude that nonresponsive specimens had not been partially depleted of histamine before arrival.

Our model specifically evaluated MRGPRX2 and FcεRI function of skin mast cells in discarded surgical skin specimens using well-studied reagents. The use of this explant model to investigate other agents could be limited by the diffusion capability of reagents in the skin. It is also possible that this model may not be applicable to the evaluation of mast cell histamine release from skin punch biopsies obtained directly from patients due to the inhibitory effects of lidocaine and epinephrine on IgE- and 48/80-induced mast cell histamine release (57–59). Additional work is required to optimize this model for fresh punch biopsies from patients.

The viability of skin mast cells is another potential limitation of this model. While other studies have reported skin viability up to 14 days (32), it is unclear whether mast cell responses will remain intact for that period of time. Data presented in this methods paper are from experiments performed on skin either the same day as or one day after surgery (NDRI). We have observed that histamine release can be detected 2 days after surgery in specimens stored in PBS+ antibiotics and 3 days after surgery in specimens stored in RPMI+ antibiotics (data not shown). Further investigations are required to determine the effect of time on mast cell viability and releasability in this model.

Our study characterized the kinetics of histamine release induced by anti-IgE and compound 48/80 in skin explants and the ability of acalabrutinib, QWF, and pertussis toxin to inhibit histamine release. Potential applications of our model include investigations of allergic diseases and evaluation of therapeutics under development to block these processes. This model can be also extended to examine levels of other mast cell mediators including tryptase, eicosanoids, and cytokines in response to activation of these pathways and whether other agents can effectively inhibit their release. However, this model has limitations when it comes to measuring cytokines and eicosanoids due to the production of these mediators of other cell types found in the skin. In addition, this model is not suited for interrogation of signaling pathways or molecular analysis requiring single cell suspension.

Conclusion

The protocol reported here describes our methodology to successfully model human mast cell activation using intact skin biopsies. This model provides reproducible results and serves as an option to study possible stimuli and inhibitors for mast cell activation. In the future, this model may be extended to study altered mast cell function in various disease states, including primary mast cell disorders and chronic urticaria.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The requirement of ethical approval was waived by Johns Hopkins Hospital Institutional Review Board for the studies on humans because it fell within the category of "Not Human Subjects Research (NHSR)/Quality Improvement (QI)". The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry.

Author contributions

CV: Writing – original draft, Writing – review & editing, Formal Analysis, Investigation. KB: Formal Analysis, Investigation, Writing – review & editing, Methodology. TO: Investigation, Writing – review & editing. DB: Investigation, Writing – review & editing. KC: Investigation, Writing – review & editing, Methodology. SS: Writing – review & editing, Methodology, Resources. EO: Conceptualization, Resources, Writing – review & editing, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/falgy.2024.1373511/full#supplementary-material

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Thymus and activation-regulated chemokine (CCL17) as a clinical biomarker in atopic dermatitis: significance and limitations in the new treatment era

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Thymus and activation-regulated chemokine (TARC; CCL17) is a T-helper-2 chemokine that reflects atopic dermatitis (AD) disease activity. Since 2008, serum TARC levels have been commercially measured in Japan, and clinical experience has shown the usefulness of TARC. The fallacy that eczema is always visible often hinders successful treatment, when there is subclinical inflammation which is inferable from the TARC level. AD treatment has entered a new era with higher therapeutic efficacy. TARC has a different meaning than it did previously, and its significance and limitations are discussed. First, a more appropriate topical therapy monitoring TARC would be useful in selecting truly necessitated patients for expensive new therapies. Dupilumab quickly lowers serum TARC before clinical improvement, and its normalization is not a criterion for dose reduction. However, in some severe cases, TARC may help determine whether to continue treatment. During treatment with JAK inhibitors, serum TARC levels are often elevated and may be abnormally high, leading to the exacerbation of dermatitis. Prurigo nodularis is divided into two types associated with elevated and normal TARC levels, which may aid in the selection of therapeutic agents. In this new era, TARC remains a useful biomarker for more accurate drug selection and the determination of therapeutic efficacy; Currently, in clinical trials of AD, all outcome measurements depend on the clinical score; however the use of a biomarker, such as TARC, as a secondary outcome measure will clarify the characteristics of each drug and the pathophysiological conditions for which it is expected to be effective.

KEYWORDS

atopic dermatitis, monitoring biomarker, thymus and activation-regulated chemokine, biologics, JAK inhibitors, topical corticosteroid

1 Introduction

Atopic dermatitis (AD), a chronic pruritic dermatosis, confers a significant disease burden. In the past decade, increased availability of many molecular-targeted therapies, with remarkably improved therapeutic outcomes. In this era of novel, expensive therapies, precision medicine requires biomarkers for classifying and identifying patients for whom specific therapies are suitable (1, 2). For monitoring disease activity, the thymus and activation-regulated chemokine (TARC; also known as CCL17) is the most supported biomarker (3), because of its T helper 2 cell-mediated chemotactic activity (4). Type 2 inflammatory cells play a crucial role in AD pathogenesis (5). Although serum TARC

levels are closely related to AD clinical disease activity (6, 7) their usefulness is not widely recognized because of the need for laboratory-based measurement. In Japan, serum TARC measurements have been commercially available since 2008, which, we realized, improves AD treatment outcomes (8). In AD treatment, the recent introduction of many biological agents and JAK inhibitors (JAKIs) has induced changes in TARC levels that differ from those during conventional topical therapy and may warrant an understanding of the different underlying mechanisms. Based on the 15-year clinical experience with TARC monitoring in Japan, we discuss the significance of TARC as a monitoring marker, before and after the introduction of molecular-targeted therapies. In this article serum TARC levels were measured by a chemiluminescent enzyme immunoassay using the HISCL® system (Sysmex, Hyogo, Japan) and a TARC Assay Kit (Shionogi, Osaka, Japan) whose detection scope is 10–30,000 pg/mL.

2 Case description which implies key learning points from TARC monitoring during conventional treatment of AD

A 10-year-old girl, originally from a European country, presented to our hospital with generalized dermatitis that had persisted since early infancy. For marked, refractory lesions, she was prescribed whole-body application of emollient, twice a day, and a 5-day course of very-high-potency topical corticosteroids (TCS) and showed transient improvement. However, within a few days of switching to only emollient or moderate TCS, AD flared up, with nocturnal pruritus that disturbed sleep. On her first visit to our department, she presented with generalized erythema, excoriations, and a serum TARC level of 2,175 pg/mL, for which she was prescribed whole-body (excluding the face) high-potency TCS application for 1 month that resulted in symptom disappearance and normalization of the serum TARC to 262 pg/mL. The patient was instructed on TCS weaning off before leaving for her country. Upon her return to Japan 4 months later, she had no skin lesions on semi-weekly proactive TCS treatment, with the TARC level maintained at 250 pg/mL. At the 1-year follow-up, all skin lesions, except for a small lesion, had cleared up with weekly TCS application, with normal TARC level (379 pg/mL). The patient was extremely grateful that her skin had remained normal for a year, without any problems in her daily life, and was hopeful about her future.

Despite using similar drugs, differences in treatment methods can frequently alter the outcomes drastically, even among Japanese residents. Figure 1 shows the changes in the biomarkers in a representative case. The treatment methods differ depending on whether the TCS dosage was guided by TARC monitoring.

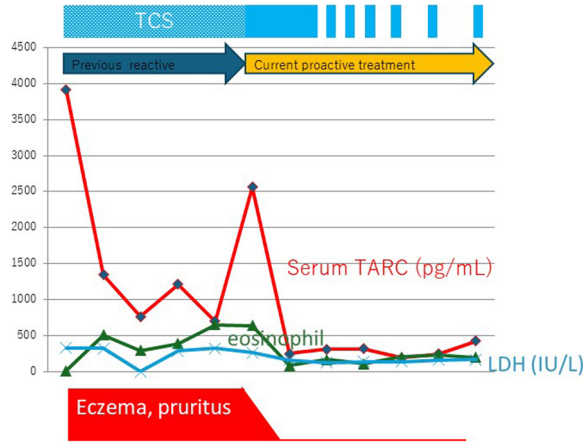


FIGURE 1
The truth of waning and waxing atopic dermatitis. A representative case of adult atopic dermatitis after successful proactive topical corticosteroid treatment. Changes in the serum thymus and activation-regulated chemokine (TARC) levels indicate that an appropriate method of application is important for achieving successful outcomes. Eo, eosinophils; IgE, immunoglobulin E; LDH, lactate dehydrogenase; TCS, topical corticosteroid.

2.1 Truth of waning and waxing (flare-ups) AD

Both physicians and patients believe that AD is a chronic disease with recurrent exacerbations; however, in many cases, these exacerbations are iatrogenic and caused by high or low drug doses.

2.2 Accurate proactive treatment for better outcome

A meta-analysis demonstrated the robust superiority of proactive treatment (9), although the preliminary findings are too nascent for clinical implementation, given the diverse disease severities and dermatitis disease activities among AD patients. Nonetheless, a precise treatment plan based on these two factors will improve outcomes. Abnormally high TARC levels indicate accelerated type 2 inflammation wherein early intensive therapy for rapid mitigation of inflammation predicts a better prognosis with careful drug/dose reduction to prevent flare-ups. Objective improvement and Patient Reported outcome (PRO) are insufficient to determine whether the current treatment adequately controls inflammation. The sustained normalization of TARC levels indicates good long-term control (10) and validates AD treatment. However, a weak or insufficient TCS regimen that does not reduce TARC levels (11), and short-term treatment will cause repeated flare-ups. Residual inflammation, even if occult, will inevitably flare-up after treatment discontinuation. Long-term control can be achieved by controlling residual subclinical inflammation (12).

2.3 Re-recognition of the importance of topical therapy

With accurate proactive treatment and TARC-monitoring-based tight control, good control of type 2 inflammation is achievable with

topical therapy alone in a significant proportion of patients, with long-term remission maintained by administering minimal, safe doses of topical drugs. However, in cases with TARC levels refractory to initial intensive TCS or an increase in TARC levels with post-stabilization TCS reduction, local therapy alone is potentially ineffective, and systemic therapy should be considered.

2.4 Goal of AD treatment and patient adherence

Unlike in other countries, in Japan, the AD guidelines clearly state the treatment goal: "The goal of treatment is to reach and maintain a state in which symptoms are absent or mild with minimum drug. Even when this goal is not attained, the objective is to maintain a clinical state with mild symptoms and without rapid exacerbations that affect daily activities" (13). These guidelines were developed to mitigate the confusion regarding AD treatment in Japan in the 1990s (14) that significantly reduced the quality of life of many patients. Then, TCS was considered merely a symptomatic treatment, with a lack of clear physician-led guidance on the dosage or cessation of topical application, which was left to the patient's discretion and, consequently, many patients experienced repeated flare-ups despite TCS usage. Misleading media reports about adverse effects rapidly increased the number of patients with steroid avoidance-induced severe dermatitis and led to significant reduction in the quality of life. This social problem was mediated not only by patients' anxiety about side effects, but also a discordance between patients and physicians regarding treatment goals, as patients did not want reactive management of recurrent flares with TCS but aimed to achieve long-term control. However, at that time, many dermatologists did not believe that this goal was achievable and considered flare management as the primary objective of pharmacotherapy. In Japan, since 2008, TARC monitoring aided precise disease control, and the number of steroid-phobic patients has decreased. For the successful treatment of chronic disease, both the physician's treatment strategy and the patient's adherence are essential, and TARC monitoring provides a numerical treatment goal to aid both (7).

3 Significance of serum TARC monitoring with newer AD treatments

3.1 Biologics

In patients who are appropriately treated with conventional therapies, the serum TARC level normalizes, and the treatment goal can be achieved by maintaining normal TARC levels when tapering pharmacotherapy. Newer molecular-targeted drugs alter serum TARC levels differently: dupilumab (15), tralokinumab (16), and lebrikizumab (17) decrease serum TARC, and dupilumab has potent TARC-normalizing capability whereby TARC levels normalize within a few months of initiation. During early treatment, despite normal TARC levels, many patients may have decreased but persistent subjective and objective clinical symptoms. Therefore, TARC normalization precedes clinical improvement, and does not necessarily imply the disappearance of subclinical inflammation. Alternatively, in some refractory cases, TARC levels decline after starting dupilumab although TARC normalization may require continued treatment for a few years. In real-world settings, although good control is often achieved with extended-dosing intervals of dupilumab (18), early dosing-interval extension in severe cases confers a risk of relapse; in such cases, TARC monitoring may aid decision-making (Figure 2). Although abnormally high TARC levels despite prolonged dupilumab treatment may indicate dupilumab resistance, TARC is not a predictor of the response to dupilumab (19).

Nemolizumab, an IL31RA antibody, has proven efficacy in AD-induced pruritus, but may increase serum TARC levels. In clinical trials, TARC elevation was unassociated with changes in the EASI scores (20). However, in some patients, nemolizumab is associated with severe new-onset or worsening dermatitis, with abnormally high TARC levels, that warrants TCS intensification or nemolizumab discontinuation.

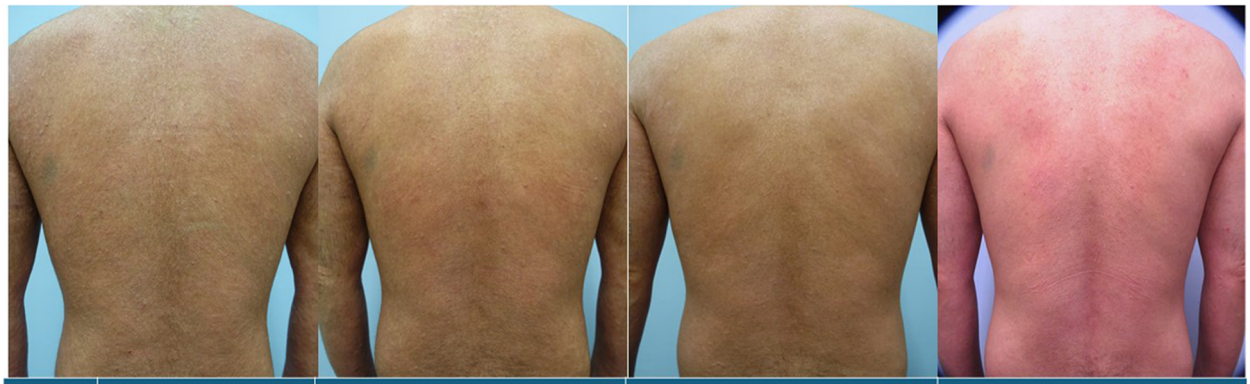
3.2 JAKIs

Three JAKIs—baricitinib, upadacitinib, and abrocitinib—are currently used for systemic treatment of AD and, despite a good clinical response, increase TARC levels during prolonged treatment (>6 months) (21), which detracts from TARC's value as a clinical biomarker (22). Nevertheless, this phenomenon is noteworthy because of the parallel increases in serum immunoglobulin E and TARC levels that suggest enhanced type 2 inflammation.

4 Discussion

Approximately 55% of adults with moderate-to-severe AD have inadequate disease control (23). TARC aids efficacy maximization and identification of the limitations of conventional therapies; however, newer therapies may be unsuitable for some patients with moderate-to-severe disease, and conventional treatments should be optimized before initiating expensive newer therapies (24) that some patients would not prefer. In some countries, national financial allocations preclude the provision of expensive drugs. It is imperative to prevent the denial of appropriate medical care to poor patients. The high cost of AD treatment is an important social cost, and a clinical study to identify patients who would benefit from cyclosporine has been planned (25). Serum TARC monitoring facilitates optimization of inexpensive conventional therapies and patient selection for new therapies.

Although a systematic review confirmed the importance of remission induction and maintenance (11), the extent of posttreatment remission is unclear. The suppression of inflammation induces not only symptomatic improvement but also TARC reduction and decreased type 2 inflammation, which could theoretically indicate normalization. Although yet unsupported by clinical evidence, based on numerous clinical



	0M	4M	12M	36M
EASI	42.9	16.8	2.3	1.2
POEM	14	5	6	2
PPNRS	6	2	2	1

		0M	4M	8M	12M	20M	24M	32M	36M
TARC	pg/mL	9414	1122	1667	983	922	819	595	360
LDH	U/L	574	303	297	235	222	202	189	181
Eosinophils	count/μl	370	820	540	500	420	520	270	230
IgE	IU/mL	40468	19403	14669	9098	4524	5516	4226	3100

FIGURE 2
Usefulness of TARC monitoring during dupilumab treatment in patients with severe AD. Dupilumab treatment was initiated for a middle-aged patient with severe refractory AD and, because dupilumab strongly suppresses type 2 inflammation, serum TARC levels decreased rapidly and significantly within 4 months but remained abnormal. TARC levels increased, at the 8th month since dupilumab initiation, after cessation of cyclosporine treatment following improvements in subjective and objective symptoms, which suggests that cyclosporine levels should be tapered after confirming the effect of dupilumab in patients with severe disease who were previously treated with cyclosporine. At the 12th month, the subjective and objective symptoms had improved, but the TARC level was abnormal. Despite dupilumab's ability to suppress type 2 inflammation, presumably, the inflammation persisted as indicated by the higher-than-normal TARC levels. After confirming TARC normalization at the 32nd month, the dosing interval was extended to 3 weeks, and the skin recovered to an almost normal state without relapse, despite the longer inter-dose interval.

experiences, it is recommended that the serum TARC levels should be maintained below 600 pg/mL in patients who are older than 6 years. Recently, steroid withdrawal has become a problem in Europe and the U.S. (26, 27). By rejecting the dogma that AD is incurable, physicians and patients can establish treatment goals based on objective targets defined by numerical data.

The dissociation of TARC changes from skin manifestations during biologic or JAKI treatment is a remarkable phenomenon. Recently, in Japan, there have been several cases, albeit unpublished, of clinical secondary ineffectiveness indicated by preceding elevated TARC levels during continuous JAKI administration. Proteomics of lesional skin revealed decreased levels of various chemokines, including TARC, soon after administration (28). It is unclear whether local and systemic responses differ or long-term administration induces different changes; however, elevated serum TARC levels are potentially associated with subsequent worsening of AD. Studies examining real-world biomarkers over time have significant implications, and follow-up rates are 70% for dupilumab; 21% for tralokinumab; and 19%, 35%, and 19% for baricitinib, upadacitinib, and abrocitinib (21), respectively. A detailed comparison of the evolution of TARC and clinical scores, including dropout cases, may help stratify real-world responders.

Prurigo nodularis (PN) is a refractory chronic skin disease, with a high disease burden on conventional treatment. New therapies have been developed based on PN pathophysiology, which mainly involves type 2 inflammation, pruritic neurotransmission, epidermal thickening, and dermal fibrosis (29). The efficacy of dupilumab (30) against type 2 inflammation and nemolizumab (31) against IL31, which mediates itch transmission, has been confirmed in clinical trials. The association of PN with atopy in a subset of patients fosters an assumption that PN is an AD subtype, whereas PN can occur without atopy. Important disease-specific differences between PN and AD have recently been reported (32, 33). Nemolizumab demonstrated clear efficacy in PN and rapidly improved pruritus, although one of its most common adverse events was AD (28). IL31 may have unique effects on the immune and nervous systems (34), including negative regulation of TH2 cells or CGRP-mediated activation of immunoregulatory pathways in sensory neurons. Distinguishing between classical PN without AD which is super-responder to nemolizumab and PN + AD could facilitate the selection of an effective treatment without worsening AD. Serum TARC levels are nearly normal in classical PN without dermatitis, whereas it is frequently elevated in AD-associated PN. Thus, TARC may constitute a pretreatment

stratification marker, such as for dupilumab in patients with PN and high serum TARC, because of potentially enhanced type 2 inflammation, and selection of nemolizumab in patients with PN and normal serum TARC.

To evaluate the efficacy and stability of novel therapeutics over time based on biological mechanisms, TARC and other biomarkers are good tools. Currently for clinical trials, Harmonizing Outcome Measures for Eczema (HOME) recommends four core outcome measures: EASI for clinical signs, POEM and PPNRS as subjective symptoms, DLQI for quality of life, and ADCT or RECAP (35) for long-term control. However, the current practice of using expensive drugs without predicting their efficacy must be changed, possibly by disclosing biomarker trends as secondary outcomes in clinical trials, with stratified biomarker analyses, wherein serum TARC is a leading candidate for monitoring type 2 inflammation.

Drug breakthroughs have ushered in a paradigm shift in the therapeutic goals for several chronic inflammatory diseases, led by rheumatoid arthritis (RA). Highly effective biologics have redefined the goals and strategies of RA therapy whereby patient outcomes have improved dramatically. Furthermore, in RA, not only novel drug development but also treatment strategy reevaluation has improved outcomes. A review of Treat to Target (T2T) studies for RA revealed the superiority of a tight control strategy over a specific drug to control RA. A T2T approach targeting remission or low disease activity is achievable in early RA with less expensive, rather than newer, drugs (36). Adjunctive serum TARC monitoring, with clinical findings, enables precision medicine for tight control. However, in many cases, iatrogenic symptom relapse secondary to dosage reduction based on inaccurate judgments may occur because biomarkers are not monitored. Thus, even with the same drug, there is a possibility that treatment efficacy can be improved by revising treatment strategies.

Recently, remission has been also included as a treatment goal for asthma, which reflects a paradigm shift from short-term symptom control to long-term symptom prevention. An international expert panel presented a framework for complete remission in asthma patients, on and off treatment. Complete remission is defined as clinical remission plus objective resolution of asthma-related inflammation, including biomarker monitoring (37). For AD, a T2T-based conceptual approach was recently proposed (38–40), and recommended that patient satisfaction, with minimal impact on the quality of life and clear/almost-clear skin with no or minimal itching, should be the ultimate treatment goal in AD. Unfortunately, clinical remission, complete remission, and strategies to achieve these outcomes have not been described. Serum TARC is a potential candidate marker for objectively ascertaining the resolution of AD-related inflammation during AD remission. Currently, the target achievement for T2T in AD is limited to clinical scores and PROs. The addition of biomarkers will brighten the goal landscape.

5 Limitations

TARC elevations occur in various autoimmune (41), skin diseases (8, 42) and Hodgkin's lymphoma (43). Thus, TARC is not a diagnostic marker for AD alone. Some patients with persistent lichenified lesions have relatively low serum TARC levels. TARC levels were generally higher in younger children (13). The recommendation for targeting TARC levels is empirical and not based on randomized controlled trial evidence.

6 Conclusion

In the new era of AD treatment, clinical and complete remission should be defined, and a consensus on the goals of AD treatment and strategies to achieve them should be established. To evaluate the effectiveness of a drug, objective and precise measurements, including biomarkers, should be considered, besides conventional evaluations. When selecting an expensive new treatment in clinical practice, monitoring biomarkers, such as TARC, optimizes conventional treatment and patient selection and facilitates the evaluation of therapeutic efficacy in the context of the patient's pathology.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Osaka Habikino Medical Center Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YK: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Biomarkers to aid in diagnosis of allergic contact dermatitis

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Allergic contact dermatitis (ACD) is an increasingly common skin condition characterized by itchy rashes in response to allergens. The most common diagnostic test involves patch testing (PT), but despite the efficacy of PT for identifying and guiding patients toward avoidance of allergens, PT alone does not elucidate the underlying biomechanistic changes which may be useful for sub-categorizing ACD further. In addition, some patients may never be able to identify their causative allergens unless they go to highly specialized ACD centers. Accordingly, this mini review attempts to summarize biomarkers that may help with identifying and sub-categorizing cases of ACD for appropriate diagnosis, especially in patients with difficult-to-identify allergens.

KEYWORDS

allergic contact dermatitis, biomarkers, haptens, pathophysiology, diagnosis

1 Introduction

1.1 Epidemiology of ACD

Recent epidemiologic studies predict that upwards of 20% of children and adults may be affected by acute or chronic ACD with significant impairments in quality of life (1). One older study has even suggested that 55% of patients studied exhibited signs of ACD to at least one allergen, and the prevalence seems to be increasing (2). The most common allergens in patients with ACD are nickel and other metals, fragrances, and preservatives (3). Additionally, another important allergen associated specifically with ACD is latex, a natural rubber compound found in many products (especially latex gloves). The substance in particular which is believed to be involved in the sensitization of latex are the so-called vulcanization accelerants which polymerize the latex into sheets which can be made into industrial products (4). In one study, between 5.4% and 7.6% of the general population were found to be sensitized to latex (5). This number increases to 10%–20% when healthcare workers are studied independently (5). Even though ACD to latex is common, it must be distinguished from irritant contact dermatitis, which may be even more common than ACD in occupational settings (6). ACD is also twice as likely to occur in women and can often be seen in children and adolescents (3). Occupational contact dermatitis is, in many countries, the leading occupational disease, with an estimated incidence rate around 0.5–1.9 cases per 1,000 full-time workers per year (7). Although common in all groups, genes, age, sex, and ethnicity are among the main risk factors for susceptibility for ACD (3).

1.2 Clinical presentation of ACD

Most often, the clinical presentation of ACD begins as an eczematous process characterized by pruritus, erythema, edema, vesicles, and crusting. In some patients, however, a non-eczematous subtype may be present characterized by predominantly urticarial, granulomatous, acneiform, lichen planus-like, or dry, hyperkeratotic lesions (8). These different clinical presentations may make it difficult for some clinicians to differentiate between ACD and similar skin conditions such as atopic dermatitis and irritant contact dermatitis—a similar process to ACD, but without an allergic immune response. However, more attention is being brought to the different variations of eczema and eczema-like skin conditions such as ACD, yielding helpful results for the differentiation of each condition.

1.3 Pathophysiology of contact dermatitis

Despite classically being defined as a Type IV hypersensitivity reaction, both Type I and Type IV hypersensitivity reactions can be seen in ACD cases, sometimes simultaneously and sometimes sequentially (9).

Sensitization to an allergen begins with conversion of pro-haptens to haptens, a process which depends on keratinocytes for enzymes to facilitate the conversion (10). Immunologically active haptens are then formed after inactive haptens penetrate the stratum corneum and covalently bind to endogenous proteins and trigger an immune response (10, 11) (Figure 1C). It is thought that pre-existing skin barrier dysfunction is necessary for antigens to penetrate the stratum corneum and thus trigger sensitization (10) (Figures 1A,B). Once the process of sensitization has begun, keratinocytes encountering the now-immunogenic antigen triggers keratinocyte release of inflammatory molecules which are responsible for the classical symptoms associated with ACD (10).

Following the innate immune response, local antigen-presenting cells (mainly Langerhans cells, but dendritic cells as well) migrate to regional lymph nodes and activate antigen-specific T-cells (Figures 1D,E); the predominant activation of T-helper 1 (T_H1) cells results in the classic Type IV hypersensitivity reactions associated with ACD (12) (Figure 1F). These antigen-specific T-cells now enter the circulation and the site of original exposure, such that re-exposure to the antigen triggers activation of T-cells via cytokines and induces an inflammatory response (12) (Figure 1F).

1.4 Current measures for diagnosis and screening

ACD is usually first suspected in patients who have rashes in distributions that would be suggestive of frequent contact with allergens (12). One commonly seen distribution is on the lower abdomen due to frequent contact with nickel belt buckles. Other areas which are common distributions of ACD include hands, feet, face, and eyelid, as well as unilateral presentations (12). Another indication by which patients should undergo PT is those who present with rashes and work in occupations with frequent use of chemicals or irritants that are commonly linked to ACD (12). Currently, a diagnosis of ACD is made by screening through a complete history that leads clinicians to suspect ACD followed by confirmatory PT.

PT is done by occluding allergens at concentrations below what would typically be irritating for patients without ACD on the patient's skin for 2 days, allowing it time to develop an immune response that can be seen and measured, while also allowing enough time for transient inflammatory responses to subside in patients without ACD (12, 13). However, even after an unremarkable 48-h incubation, re-testing or delaying reading by an additional 24–48 h may be necessary in some patients (12). Many patients may struggle with itching at the sites of PT, and it may also be difficult for some patients to avoid getting the testing sites wet for the 48-h incubation period.

2 Biomarkers for diagnosis

Current screening and diagnostic measures for ACD may be unreliable and can sometimes be unable to distinguish between equally common conditions that may appear similar, such as atopic dermatitis and irritant contact dermatitis. To find more objective measures that can lead clinicians to identify and diagnose ACD, we have compiled biomarkers present in patients with ACD for this purpose.

Biomarkers that can be used to distinguish ACD from other similar skin conditions for diagnostic purposes can be divided into four categories: indicators of skin barrier dysfunction, biomarkers indicating that immunologically active haptens are being formed, cytokines and other inflammatory markers, and genetic markers that may make individuals susceptible to sensitization. In the following sections, we will discuss these biomarkers within their corresponding categories.

2.1 Skin barrier dysfunction

The first step in sensitization usually involves dysfunction of the skin barrier such that it cannot prevent antigens from penetrating the stratum corneum. Skin barrier integrity often becomes compromised in the context of skin microflora dysbiosis. Commensal bacteria on the surface of the skin provide a protective benefit by secreting antimicrobial peptides (14). Loss of these bacteria on the surface of the skin results in withdrawal of the protective antimicrobial peptides, which then allows *Staphylococcus aureus* to colonize the surface of the skin (14) (Figure 1B). Recent studies have shown that *S. aureus* colonization causes aberrant epidermal lipid compositions, which in turn results in skin barrier dysfunction (15). Changes in lipid composition involve accumulation of shorter length fatty acids by

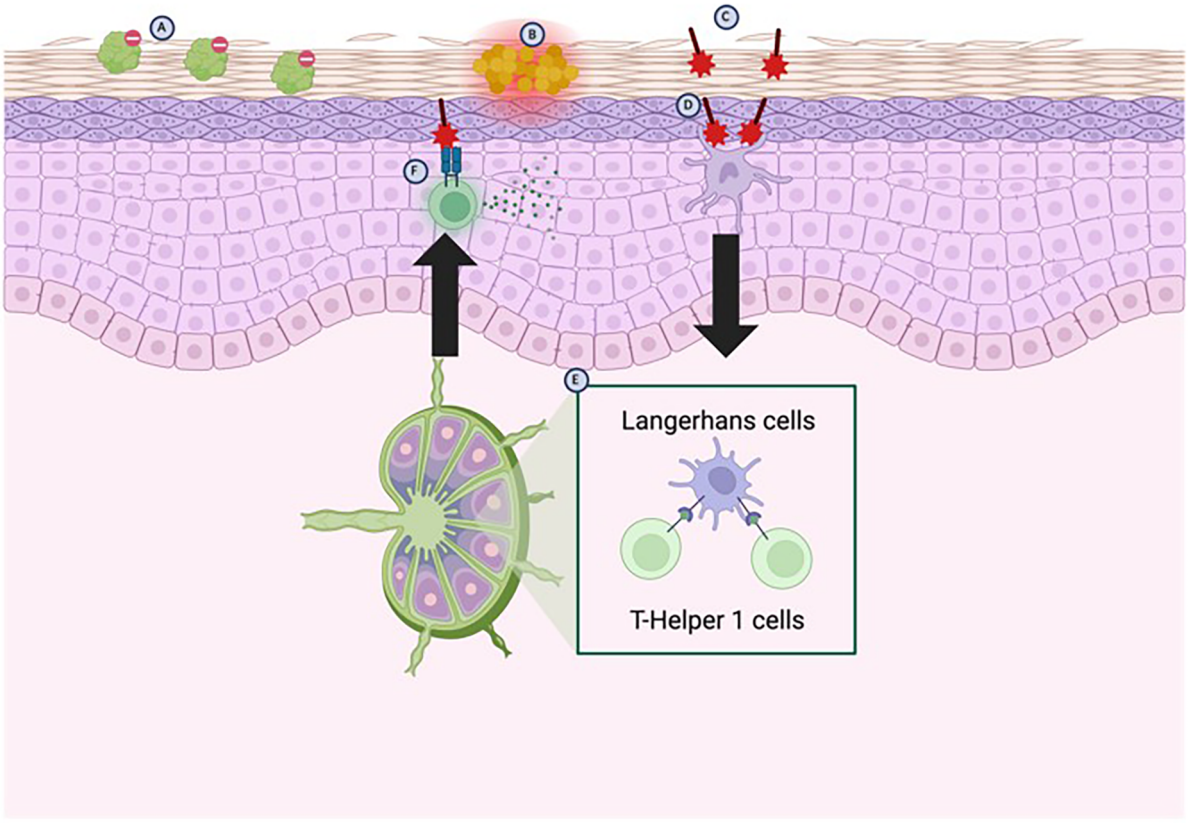

FIGURE 1
Pathophysiology of ACD. Genetic absence or loss-of-function mutations in the FLG (filaggrin) gene predisposes patients to a disrupted skin barrier **(A)** The weakened skin barrier is then susceptible to colonization by *Staphylococcus aureus* **(B)** displaces commensal skin bacteria, which further weakens the skin barrier by releasing products which inhibit fatty acid elongation, leading to an accumulation of shortened fatty acids. The further weakened skin barrier then allows for haptens to enter and bind to endogenous proteins in the skin **(C)** which are then detected mainly by Langerhans cells, but to some degree by resident dendritic cells **(D)** The Langerhans cells migrate to local lymph nodes where they activate T-Helper 1 cells **(E)** T-Helper 1 cells then migrate back to local tissues and upon re-exposure to the antigens trigger release of pro-inflammatory cytokines **(F)** (created with BioRender).

downregulating the enzymes responsible for creating longer fatty acid chains—known as elongases (15). Accumulation of 16–18 carbon long fatty acids is most associated with skin barrier dysfunction resulting from *S. aureus* colonization and these lipid changes are especially significant when the skin is colonized by MRSA strains (15). As a result of these changes, lipid analysis suggests a fatty acid shortening on the skin as well as cultures positive for *S. aureus* may be indicative of ACD but may also include other differentials.

2.2 Indicators of hapten formation and activation

Protein-hapten binding occurs after protein-reactive chemicals act as sensitizers through a process known as haptenation (16) (Figure 1C). Theoretically, protein-bound haptens could be isolated and identified. However, this is not currently done for ACD *in vivo* besides for research purposes despite protein-hapten binding being an integral part of the pathogenesis of ACD. In addition to protein-bound haptens being identified *in vivo*, certain molecules such as glutathione may also provide some basis for suspecting protein-bound haptens in the skin. In one study, 13/14 sensitizers were able to bind glutathione due to its thiol group and, moreover, glutathione is a common endogenous peptide which is used for detoxification (16). As a result of its detoxifying effect and ability to bind haptens, glutathione can be depleted and in patients with ACD a lower concentration of glutathione may be expected than in unaffected skin (16).

2.3 Cytokines and other inflammatory markers

The most clinically impactful biomarkers for ACD are likely to be cytokines and other inflammatory markers associated with the disease. In fact, the symptomatology of ACD is unlikely to occur without the downstream effects of these inflammatory molecules secreted by the activated immune system. Once sensitization has occurred at the local level, alarmins and cytokines are secreted by the keratinocytes activated by protein-bound haptens. Alarmins have downstream effects to activate toll-like receptors (TLRs)

such as TLR2 and TLR4; TLR2 and TLR4 have further effects to activate nuclear factor-κB-dependent proinflammatory cytokines such as IL-1a, IL-1b, TNF-α, granulocyte-macrophage colony-stimulating factor, IL-8 and IL-18 (10). IL-1a is mainly responsible for the induction of skin sensitization to antigen, whereas IL-1b is required for Langerhans cell migration (Figure 1D). The products of the keratinocytes subsequently act to activate innate immunity and activate the T-cell response characteristic of Type IV hypersensitivity reactions (Figures 1E, F). Some cytokines associated with downstream pathways of ACD may also be helpful in identifying ACD lesions. One study, for instance, identified that IL-31—a cytokine associated released by activated T_H2 cells—was present in skin lesions of patients with atopic dermatitis and ACD, but not psoriasis (17). Despite the strong association of these inflammatory markers with ACD, however, they remain non-specific markers present in other atopic conditions such as atopic dermatitis and so they may not be helpful in aiding diagnosis of ACD exclusively (10, 12, 17).

2.4 Genetic biomarkers

Polymorphisms in the FLG gene—the gene coding for the filaggrin protein—have been shown to predispose patients to having a dysfunctional skin barrier that may allow for sensitization by chemicals and antigens (17) (Figure 1A). Indeed, a loss-of-function mutation or deficiency in the FLG gene has been well-characterized as the strongest known genetic risk factor for skin barrier dysfunction in atopic dermatitis (14). Lack of integrity of the skin barrier due to lack of functional copies of filaggrin allow haptens to penetrate the stratum corneum and lead to sensitization of the skin towards the antigen while also providing a point of entry for *S. aureus* to colonize the skin and potentiate the inflammatory response in response to the antigen.

In some rare cases of ACD, some antigens may directly sensitize the skin, bypassing the innate immune response. One of the proposed mechanisms by which these so-called contact sensitizers produce an ACD response is by covalently binding to cysteine residues on a cytosolic protein called Keap1. This protein is typically a sensor for oxidative and electrophilic stress, which degrades Nrf2—an intracellular transcription factor—by proteasomal degradation, but these covalent modifications prevent it Keap1 from ubiquitinylating Nrf2. Nrf2 is then free to transcriptionally promote antioxidant changes in the cell, protecting them from inflammatory effects. Knockout studies in mice without Nrf2 have shown that mice lacking Nrf2 become sensitized with antigens that typically do not sensitize in wild-type mice (10), indicating a possible genetic basis for susceptibility for ACD to develop.

Other studies have suggested polymorphisms and mutations in genes coding for interleukins may predispose some patients to developing ACD, but these have not been well-characterized and may require more research before they can be used for diagnostic purposes. One study identified an association between IL-16 polymorphisms and ACD in patients who are sensitized to one or more allergens (18). However, in-depth analyses of interleukins and polymorphisms that may be responsible for a genetic basis of ACD, are not diagnostic on their own since there is an overlap with other atopic conditions.

3 Discussion

ACD is generally felt to be underdiagnosed for several reasons, including difficulty with correctly diagnosing and differentiating it from similar conditions such as atopic dermatitis, lichen planus, or angioedema (19). Other obstacles for diagnosis of ACD include low proportion of patients seeing clinicians who can provide them with a diagnosis since many patients opt to forego treatment for dermatologic conditions (19). The most important distinguishing feature between ACD and atopic dermatitis is the presence of symptomatic skin at sites which may come in contact with allergens. However, systemic absorption of allergen and movement of allergens from one part of the body to another may result in ACD rashes on distant sites which may be difficult to identify as ACD over atopic dermatitis (19). While eczematous lesions on the skin are the most common symptom of ACD, some patients may experience distinct manifestations which are not commonly associated with atopic dermatitis, such as: erythema multiforme, lichen planus, eruptive rashes, and pigment changes (19).

Currently, there are gaps in our knowledge of the pathogenesis of ACD and how it may differ from other allergic conditions and other skin conditions such as atopic dermatitis and psoriasis. Because of this, it is difficult to use biomarkers to differentiate skin lesions as ACD from other similar-appearing conditions which may be prone to irritation by PT. As a result, we conclude that there needs to be more research done to fill in the gaps when it comes to biomarkers that may be pathognomonic for ACD. One example discussed in this paper is how skin barrier dysfunction is usually considered a prerequisite for ACD to develop, but it is also a non-specific process that has been tied to several other conditions. Indeed, skin barrier dysfunction has been linked with atopic dermatitis, childhood asthma, food allergy, and allergic rhinosinusitis (17). As a result of this, while we have examined some biomarkers suggesting skin barrier dysfunction in patients with ACD, we do not expect biomarkers of skin barrier dysfunction alone to provide a basis for the diagnosis of ACD.

PT may remain the gold standard for identification of ACD and the allergen causing the reactions. However, given the general trend towards more molecular assays in identifying disease, it would not be unrealistic to assume that isolation of protein-bound haptens in active ACD lesions may provide the highest sensitivity test to diagnose ACD. Furthermore, it may also be useful in cases where the causative agent cannot be identified through PT alone and may be beneficial in narrowing the selection of antigens a clinician should test. Ideally, more research should be done on this subject so that identification of certain biomarkers on a blood test could provide physicians with a definitive diagnosis of ACD, but the overlap between ACD and other common conditions makes this unlikely.

Author contributions

MS: Writing – original draft, Writing – review & editing. AS: Writing – original draft, Writing – review & editing. AM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. X-ML: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Scratching the surface: biomarkers and neurobiomarkers for improved allergic contact dermatitis management

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Allergic contact dermatitis (ACD), also known as allergic eczema, is a common inflammatory skin disorder that affects millions of Americans and imposes significant physical, psychological, and economic burdens. Differentiating ACD from other forms of dermatitis remains a challenge, with patch testing as the gold standard. Despite its utility, patch testing can lack diagnostic accuracy, highlighting the importance of molecular biomarkers to refine diagnosis and treatment. Advances in transcriptomics and machine-learning have enabled the identification of biomarkers involved in ACD, such as loricrin (LOR), ADAM8, CD47, BATF, SELE, and IL-37. Moreover, biomarkers such as LOR, NMF, and TEWL, may have prognostic value in evaluating therapeutic response. Emerging neurological biomarkers (neurobiomarkers), including IL-31 and TRPV1, target pathways involved in the pruritic and inflammatory responses, offering novel therapeutic targets as well. This mini review summarizes current ACD treatments, biomarkers for targeted therapies, and emphasizes the role of neurobiomarkers in ACD treatment. Additional research on the validity of the therapeutic potential of these biomarkers is necessary to improve ACD treatment and outcomes.

KEYWORDS

neurobiomarkers, pruritus, inflammation, IL-31, allergic contact dermatitis

1 Introduction

Allergic contact dermatitis (ACD) or allergic eczema, is a prevalent inflammatory skin disorder characterized by pruritus, erythema, vesicles, and scaling of the skin in response to allergen exposure (1). It is a type IV delayed hypersensitivity reaction that affects millions of Americans and accounts for a substantial proportion of dermatological consultations, with some studies estimating a prevalence of 20% in the general population (1). ACD can result in notable physical disabilities and lost workdays, contributing to significant reductions in quality of life and increased financial burdens (2).

Despite advancements in understanding ACD, differentiating it from irritant contact dermatitis (ICD), a nonallergic skin reaction that does not involve sensitization or immunological memory, and other types of dermatitis, remains a challenge (3). Current diagnosis of ACD relies on patch testing as the gold standard, complemented by an assessment of clinical presentation and exposure history (2, 3). Despite its clinical utility in identifying allergens, patch testing is reliant on subjective interpretations and may be insufficient in differentiating ACD and ICD due to overlapping clinical presentations (2).

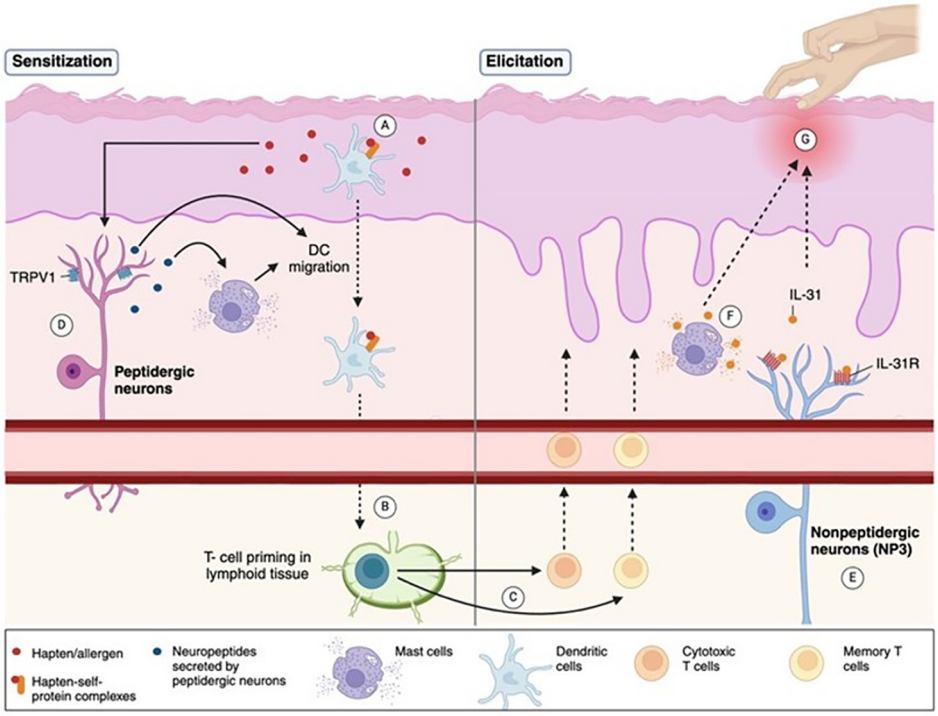

FIGURE 1
Pathophysiology of ACD and associated neuro biomarkers. The pathophysiology of ACD involves a two-phase immune response. **(A)** In the sensitization phase, allergens/haptens penetrate the skin, form hapten-self-protein complexes, and are processed by dendritic cells (DCs), promoting T-cell priming in lymphoid tissue. **(B,C)** The elicitation phase occurs upon re-exposure to the allergen, activating effector and memory T-cells that migrate to the skin, causing inflammation, erythema, or spongiosis. **(D)** Peptidergic neurons sustain inflammation by releasing neuropeptides that activate mast cells, promote DC migration, and enhance T-cell priming. TRPV1, an ion channel expressed on peptidergic neurons, contributes to inflammatory signaling. **(E)** Nonpeptidergic neurons, especially the NP3 subset, express the IL-31 receptor (IL-31R) complex, and are activated during allergen re-exposure to maintain itch perception. **(F)** IL-31, a pruritogenic cytokine, is secreted by activated T-cells and mast cells, amplifying itch and inflammation. **(G)** The combined immune and neural pathways drive the clinical features of ACD, namely chronic itch. (Created with BioRender).

Furthermore, while ACD and ICD act through different mechanistic pathways, treatment is approached similarly. Management emphasizes allergen or irritant avoidance with supplemental topical treatments, corticosteroids, phototherapy, and systemic immunosuppressants for severe cases (3). Consequently, there is a need for molecular biomarkers to distinguish ACD from ICD to provide targeted therapies.

This review explores current treatment approaches to ACD, discusses their limitations, and examines emerging biomarkers with therapeutic potential. In addition, given the limited scientific literature on neurological biomarkers (neurobiomarkers) involved in ACD-related pruritus, this review highlights some potential neurobiomarker targets for precision therapy in improving outcomes for patients with ACD.

2 Pathophysiology of ACD

The pathophysiology of ACD involves a complex interplay between immune mechanisms, epidermal barrier dysfunction, and neuroimmune interactions. ACD is classified as a delayed type IV hypersensitivity reaction following topical exposure to sensitizing agents (2). It is mediated by the activation of allergen-specific T cells (1) and involves of both the innate and acquired immune responses (3). The immune response to ACD involves two phases. The first phase is the sensitization phase, in which the immune system is primed by the allergen. During this phase, allergens penetrate the skin and lead to the formation of hapten-self-protein complexes and are processed by dendritic cells (DC) (Figure 1A), leading to T- cell priming in lymphoid tissue (Figure 1B) (3). The subsequent elicitation phase is triggered by re-exposure to the allergen, in which antigen-specific effector and memory T- cells migrate to the skin (Figure 1C), inducing inflammation and resultant erythema, spongiosis, or vesicle formation (Figure 1G) (3). While ACD is typically associated with an increased production of T helper (Th)1- like cytokines (4), previous research has demonstrated an increased production of both Th1- and Th2- like cytokines in the peripheral blood mononuclear cells (PBMC) of allergic patients (5).

In addition to immune dysfunction, alterations in the epidermal barrier also play a crucial role in ACD disease progression. Structural proteins of the cornified envelope, such as loricrin (LOR), are essential in maintaining the skin barrier (6). Reduced LOR expression has been demonstrated in tape-strips

isolated from ACD patients, suggesting that loss of epidermal integrity may promote ACD progression (7).

Neuroimmune interactions involving two types of skin-resident sensory neurons, peptidergic and nonpeptidergic, further amplify inflammatory reactions and pruritus in ACD. Peptidergic neurons initiate and maintain the inflammatory response by secreting neuropeptides that activate mast cells and promote DC migration and Th2 priming (Figure 1D) (8). On the other hand, nonpeptidergic neurons respond to inflammatory signals upon allergen re-exposure sustaining itch perception (Figure 1E) (8). These interactions form a feedback loop in which continual scratching allows deeper penetration of allergens and sustained inflammation. Understanding these mechanisms is crucial to developing multifaceted therapies that target both immune and neural pathways that govern ACD pathogenesis.

3 Current treatments for ACD and limitations

The management of ACD primarily emphasizes allergen avoidance and symptom relief, with avoidance strategies serving as the cornerstone of therapy (1, 3). Lack of skin clearance in response to allergen avoidance for 6–8 weeks should be followed up to evaluate potential exposures and enhance patient education regarding allergen identification and avoidance (3). Topical corticosteroids are commonly prescribed as first-line adjunctive therapy for reducing inflammation in all types of contact dermatitis (CD) (1, 3). Although calcineurin inhibitors such as tacrolimus and pimecrolimus are an off-label use for ACD (3), they offer steroid-sparing alternatives for sensitive areas like the face and eyelids (1). Recalcitrant or severe ACD that is unresponsive to topical therapy may be treated with phototherapy or systemic corticosteroids (3). A limitation of topical treatments is that ACD can occur to the medication's active ingredient or excipients (3).

Recent advances have introduced biologic therapies targeting specific inflammatory pathways. For example, Dupilumab is an IL-4 receptor α- inhibitor that prevents activation of the IL-4/IL-13 signaling cascade, halting the Th2 inflammatory response (9). Though it has been approved for moderate-to-severe atopic dermatitis (AD), the effects on ACD are unclear, with some patients demonstrating ACD improvement on Dupilumab (4, 9). However, despite these innovations, high costs remain a barrier to treatment (10).

4 Role of biomarkers in the characterization of ACD patients

4.1 Diagnostic biomarkers

Biomarkers hold promise in improving the diagnosis and management of ACD. Although patch testing, the diagnostic gold standard for ACD, does not provide clear distinction from ICD (2), diagnostic biomarkers have been investigated to differentiate the two entities based on immune cell profiles and gene expression signatures. Previous studies of punch biopsies using leukocyte deconvolution algorithms to analyze immune cell composition demonstrated that ACD is characterized by an accumulation of M1 macrophages, natural killer cells, and activated mast cells, while ICD is characterized by increased monocytes and T cells with fewer resting mast cells (2). Functional gene analyses revealed that ADAM8 and CD47 were of greatest importance in differentiating ACD from ICD, which are involved in inflammation and T cell migration, respectively (2). Additionally, the biomarkers CD47, BATF, FASLG, SELE, and IL37 were found to be of diagnostic and therapeutic value in a supervised machine-learning-based approach (2). The roles of these diagnostic biomarkers are summarized in Table 1. Although both ACD and ICD are approached similarly with allergen or irritant avoidance and the use of adjunctive therapies such as corticosteroids, these diagnostic markers must be studied more extensively as they may provide insight into targeted therapies for ACD.

4.2 Prognostic biomarkers

Potential prognostic biomarkers for ACD, including loricrin (LOR) transcript levels, natural moisturizing factor (NMF), and transepidermal water loss (TEWL) offer insights into disease severity and progression. These biomarkers are summarized in Table 1 but are elaborated herein.

TABLE 1 Biomarkers implicated in ACD and their role in pathogenesis.

Biomarker	Involvement in ACD pathogenesis
ADAM8[a]	• Involved in inflammatory cell recruitment and activation (2)
CD47[a]	• Transmembrane protein that is widely expressed, notably in NK cells (2) • Differentiation of effector cytotoxic T lymphocytes (CTLs) (2)
BATF[a]	• Differentiation of effector CTLs and Th17 cells in ACD (2)
FASLG[a]	• Cell death induction through FAS-FASL interactions promoting immune cell mediated apoptosis of haptenized keratinocytes in ACD (2)
SELE[a]	• Encodes E-selectin (2). Important in T cell rolling and homing (2)
IL37[a]	• Immunoregulatory cytokine expressed by effector memory T cells and inhibits innate immune signaling (2)
LOR[a,b]	• Key structural protein in the skin involved in skin barrier integrity (6) • Reductions in LOR mRNA have been demonstrated in tape strips of ACD patients (7)
NMF[b]	• Hygroscopic, low molecular weight compounds that promote skin hydration and barrier integrity (6). • Reductions in NMF are correlated with AD disease progression and *S. aureus* infection (6) • Role in ACD is less clear, with some allergens leading to NMF reductions, and others having no effect (13)
TEWL[b]	• Measures passive water flux across the stratum corneum and is positively correlated with skin barrier damage (6) • Can be used to assess the damaging effects of allergens on the epidermis, and monitor response to therapy (6)

[a]Biomarkers with potential diagnostic value.
[b]Biomarkers with potential prognostic value.

LOR is a cornified envelope protein that is implicated in the mechanical and barrier integrity of the skin (6). A previous study by Tam et al. demonstrated reduced LOR mRNA expression in tape strips collected from individuals with ACD compared to healthy skin and ICD- affected skin, highlighting its diagnostic potential (7). Given its function in preserving skin integrity, LOR may also serve as a prognostic biomarker in evaluating inflammation severity, disease progression, and response to therapy.

Other biomarkers such as NMF also play a potential prognostic role in ACD. NMF is composed of hygroscopic, low- molecular weight compounds derived from the enzymatic breakdown of filaggrin, a key structural protein in the in the stratum corneum (6, 11). Decreased NMF levels are a surrogate marker for loss of function mutations in the filaggrin (FLG) gene, which are strongly correlated with AD and impaired epidermal barrier function (6, 11). Additionally, Th2- mediated inflammation has been shown to downregulate FLG expression, leading to subsequent reductions in NMF (6). Clinically low NMF levels may predispose patients to colonization by *Staphylococcus aureus*, which adheres more readily to corneocytes in NMF-depleted skin (12). While studies have demonstrated that reduced NMF levels are correlated with AD severity, the role of NMF in ACD remains unclear. Some allergens have elicited reductions in NMF, whereas others appear to have no effect (13). Notably, several studies have linked NMF depletion to irritants or ICD rather than contact allergens or ACD; however, the irritant properties of certain allergens may contribute to these inconsistent findings (6). Despite these discrepancies, NMF's well-established role in assessing skin barrier integrity and disease severity in AD, coupled with evidence linking low NMF levels to increased susceptibility to *S. aureus* infection, underscore the need for further research in determining NMF's potential as a biomarker for ACD progression and therapeutic monitoring.

Lastly, TEWL is a commonly used biophysical biomarker in dermatological research for its ability to assess skin barrier function. It measures the passive movement of water across the stratum corneum and is positively correlated with skin barrier damage (6). It is also used to assess response to interventions in occupational settings and can thus be a useful in assessing damage to the stratum corneum triggered by ACD and response to therapy (6).

5 Neuroimmune interactions and biomarkers involved in ACD-related itch

Neuroimmune interactions contribute significantly to itch in allergic eczema. Interleukin-31 (IL-31) and transient receptor potential vanilloid 1 (TRPV1) appear to be potential neurobiomarkers in ACD, playing essential roles in modulating itch and inflammation (8).

IL-31 is a pruritogenic cytokine produced by activated T cells (14) and mast cells in response to immunogenic stimuli (Figure 1F) (8). NP3 neurons, a subset of nonpeptidergic neurons involved in pruritus, are defined by the expression of the IL-31 receptor (IL-31 R) complex, comprised of IL-31RA and the oncostatin M receptor (OSMR)(Figure 1E) (8). IL-31 signaling activates the JAK/STAT pathway and activates NP3 neurons to secrete brain natriuretic peptide (BNP), a pruritogen that stimulates spinal dorsal horn neurons to propagate itch sensations in AD and ACD (8). Itch is a predominant complaint of ACD that can negatively impact patients' quality of life (15). As such, great attention has been focused on IL-31R inhibition, with inhibitors such as the antibody nemolizumab greatly relieving itch and rash severity in AD studies (8). Given the similar neuroimmune mechanisms of IL-31 in AD and ACD, further studies on the applicability of IL-31 as a marker of ACD- related itch, and its inhibition in therapeutic applications should be investigated.

Additionally, TRPV1, an ion channel expressed on peptidergic neurons (Figure 1D), has been implicated in ACD-related itch in response to allergens such as squaric acid dibutyl ester (8). Interestingly, a newly developed topical TRPV1 selective antagonist, PAC-14028, has demonstrated statistically significant improvements in physician-evaluated IGA (Investigator's Global Assessment) scores in patients with AD, with lower scores indicating greater skin improvement (16). Moreover, although not statistically significant due to limited study sample size, PAC-14028 was also associated with slight improvements in pruritus, SCORAD (Scoring Atopic Dermatitis), EASI 75/90 (Eczema Area and Severity Index), and sleep disturbance scores (16). TRPV1's role in ACD-related itch may thus make it a promising target in alleviating pruritis.

6 Discussion

The integration of biomarkers and neuroimmune targets into precision medicine offers new opportunities to better diagnose and treat ACD. Transcriptomic analysis and machine-learning models enable patient stratification, allowing for the identification of biomarkers such as ADAM8, CD47, BATF, SELE, IL-37 that may aid in diagnosis and differentiating ACD from other forms of dermatitis (2). Additionally, LOR (6, 7), NMF (13), and TEWL (6) have been studied as key indicators of skin barrier integrity in ACD and similar conditions like AD. Therapies targeting neurobiomarkers of ACD, including IL-31 and TRPV1 also show promise in reducing ACD- associated pruritus (8).

ACD imposes a great psychological impact on patients, with a reduced quality of life. This can manifest as occupational and non-occupational effects such as anxiety, depression, disabilities that result in inability to perform work activities, sleep disturbances, and limitations in personal, family, and leisurely activities (15). While research on the biomarkers and neurobiomarkers involved in ACD is still nascent, future research should focus on biomarker validation through use of advanced preclinical models (17) and larger clinical trials to better understand their clinical utility and use as potential targets. Future developments may thus allow for multi-targeted approaches that address both immune and neurogenic therapies that enhance long-term ACD control, especially in refractory cases, and lead to the development of personalized care that provides symptom relief.

Author contributions

AS: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing. AM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Breaking the cycle: a comprehensive exploration of topical steroid addiction and withdrawal

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Topical steroid withdrawal (TSW) is a skin condition characterized by red burning, itchy, painful skin lesions, often accompanied by peeling, and cracking. Patients experience sleep disturbances due to intense itching, significantly impacting their quality of life. A majority of affected individuals develop secondary bacterial infection, marked by heavy colonization of *Staphylococcus aureus (S. aureus)* and alterations in the skin microbiome. TSW is described as a rebound effect following discontinuation of prolonged use of mid-to-high-potency topical corticosteroids. There exist no definitive diagnostic criteria for this entity, and it is often misdiagnosed as a flare-up of an underlying condition or a contact allergy. Despite numerous personal reports and experiences shared on online platforms, studies on TSW remain scarce in scientific literature. Recognizing and effectively managing this condition is critical for healthcare providers seeking to develop comprehensive management plans. These plans typically include supportive therapy for both physical and psychological symptoms, as well as the gradual tapering of corticosteroid use before complete discontinuation. This review aims to consolidate the existing knowledge on TSW, providing a comprehensive resource for its identification, management, and treatment. By enhancing understanding of TSW, this review seeks to support healthcare providers in implementing optimal management strategies and improving patient outcomes.

KEYWORDS

topical steroid withdrawal, topical steroid addiction, corticosteroids, atopic dermatitis, treatment and management

1 Introduction

Atopic dermatitis (AD), a prevalent inflammatory skin disorder, affects an estimated 17% of children and 7% of adults in the United States (1). Redness, swelling, cracking, crusting, scaling due to intense itching and pruritus are key hallmarks of AD, Topical corticosteroids (TCS, or TS) have been the mainstays in managing AD for more than 40 years and are endorsed as the first-line anti-inflammatory treatment for eczema and other atopic conditions in international guidelines (1, 2). Despite their demonstrated safety and efficacy in both short-term daily use and long-term intermittent application,

concerns have surfaced regarding the cumulative effects of prolonged TCS use, specifically regarding topical steroid addiction (TSA) and withdrawal (TSW) (3), with numerous websites and patient blogs warning against these potential risks (4).

TSA and TSW are adverse outcomes associated with inappropriate or prolonged TCS use. Even though TCS has been used for AD for more than 40-years, and despite the term "steroid addiction" being introduced in 1979 (5), TSA and TSW have only recently gained attention on online platforms. TSA tends to precede TSW (6) and is defined as physical dependence on TCS with prolonged use (5). Patients with TSA typically present with increasing resistance and may require more potent steroids or frequent applications to prevent flares (7, 8). Furthermore, TSA is also characterized by the exacerbation of dermatological conditions following TCS withdrawal compared to pre- application (9, 10). This cycle of increasing dependency on TSA is often referred to as "steroid addiction syndrome" (4, 8). On the other hand, TSW, topical steroid withdrawal syndrome (TSWS), or "red skin syndromes" specifically refers to manifestations occurring after TCS cessation (2, 11) and usually results from long-term application of moderate-to-high potency TCS on sensitive areas such as the face, genitals, and intertriginous regions. In severe cases, the skin lesion extends to the entire body. It is often depicted as severe cutaneous rebound inflammation and new distressing symptoms upon TCS discontinuation (3, 12, 13). Various terms have been used to describe TSA/TSW, including, but not limited to, "red skin syndromes" (2, 11), "red face" (4), and "red scrotum" (4). The face is the most affected area in TSA/TSW; however, other areas with high percutaneous penetration, such as the genitals and intertriginous regions, are more likely to be affected as well (3, 4, 10, 12).

Two primary morphological subtypes of TSW have been identified: erythematoedematous (47.9%) (Figure 1A) and papulopustular (52.1%) (Figure 1B) (4). The erythematoedematous subtype is prevalent among patients with chronic eczematous conditions such as AD and seborrheic dermatitis. It is characterized by erythema, scaling, edema, and burning sensations. Conversely, the papulopustular subtype is more common in patients using TCS for the treatment of cosmetic, pigmentary, or acneiform conditions and frequently occurs in those who develop steroid rosacea, although its presence is not required for diagnosis. As the name suggests, the papulopustular subtype typically presents with erythema, papules, and pustules and is associated with less frequent occurrences of swelling, edema, burning and stinging (4). While clinical overlaps between the two variants exist, the erythematoedematous subtype is distinguished by more pronounced burning, stinging sensations, and edema. Specifically, burning sensations and edema are present in 94.6% and 43.3% of erythematoedematous cases, respectively, compared to 35.4% and 2.9% of papulopustular cases (4). The terms "topical steroid induced facial rosaceiform dermatitis" (15) and "topical corticosteroid-induced rosacea-like dermatitis" (16) have been used to describe patients experiencing erythema and telangiectasias with prolonged TCS use. These conditions are believed to correspond with the erythematoedematous subtype of TSW (13).

Despite TSA/TSW being recognized in 1979, and patients reporting it on online platforms, research on these conditions has been limited. Furthermore, an absence of consensus in diagnostic criteria contributes to the incomplete understanding of these conditions within the dermatological community (2, 3). Therefore, a more comprehensive understanding of TSA/TSW among medical professionals is required to mitigate the burden of these conditions. Accordingly, this review summarizes key information regarding TSA/TSW.

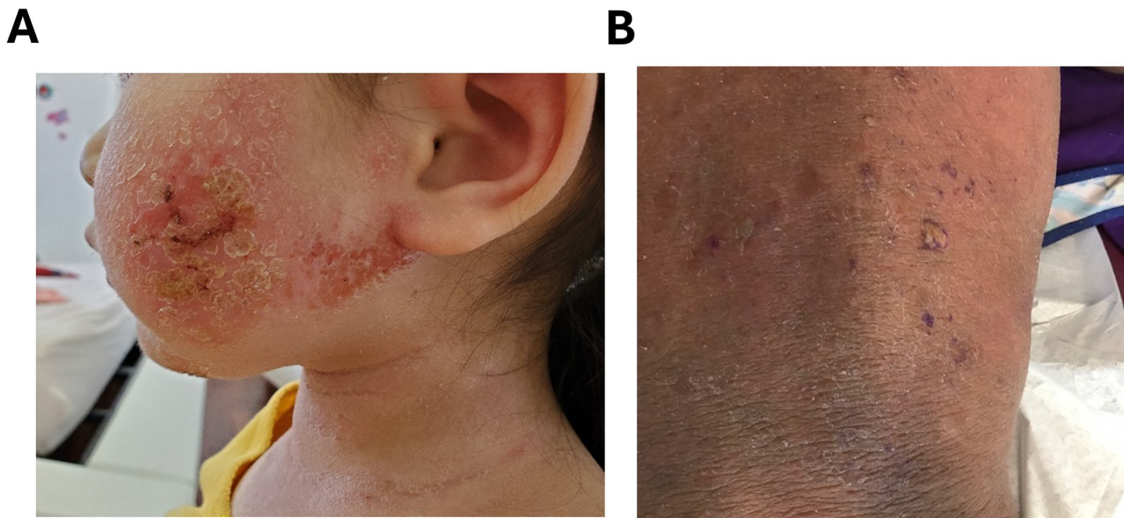

FIGURE 1
(A) Erythematoedematous subtype of steroid withdrawal characterized by severe oozing, crust, redness and excoriation. (B) Papulopustular subtype of steroid withdrawal with erythema, papules and pustules. *Permission obtained to reuse figure from* (14).

2 Epidemiology and risk factors

Determining the prevalence of TSA/TSW is challenging due to the lack of clear diagnostic criteria and significant variation in literature reports. For example, a Japanese study conducted in 2000 found that 12% of patients with AD using TCS were experiencing TSA (9). On the other hand, a multinational study involving 2,160 subjects with eczema (aged 18 years or older or caregivers of children with eczema) reported that 79% of adults and 43% of caregivers observed symptoms consistent with TSW in themselves and in their children, respectively (3).

While determining the prevalence of TSA/TSW is challenging, more is known about the associated risk factors. Increased TCS potency has been identified as a risk factor for TSA/TSW, with moderate- to high-potency TCS use being associated with an increased likelihood of disease (2–4, 13). Mid- or high-potency TCS use has been reported in 98.6% of patients with TSW (4), and in 73% of children with AD demonstrating symptoms of TSW (12). The vasoconstrictor assay categorizes TCS into seven potency groups, ranging from ultra-high potency (Group I) to low potency (Group VII) based on the extent of cutaneous vasoconstriction (17). For example, mometasone is a medium potency steroid (class IV–V) with strong topical efficacy but limited systemic absorption, making it more suitable for long term use. In contrast, clobetasol propionate is ultra-high potency (class I) with significantly higher penetration and ability to cause irritation, skin atrophy, striae and systemic side effects such as hypothalamic-pituitary-adrenal suppression, glaucoma, septic necrosis of the femoral head, hyperglycemia, hypertension (17). Given that a high proportion of patients with TSA/TSW have used mid- or high- potency TCS and more potent molecules are associated with greater dependence (18), caution must be practiced when prescribing these medications. Being mindful of TCS potency is particularly important in pediatric populations, who have a larger body surface area (BSA)-to-weight-ratio, promoting greater TCS absorption and increased systemic effects such as hypothalamic-pituitary-adrenal (HPA) axis suppression. Mid-potency TCS may be a safer alternative to high-potency TCS when treating TSW in these populations, as they do not affect the HPA axis when used "up to 3 times a day for 4 weeks or twice daily for 16 weeks" (19). Furthermore, the use of a topical steroid ladder, which classifies TCS based on potency, may be a useful tool in facilitating tapering strategies and minimizing adverse effects in both adult and pediatric patient population (20).

Similarly, dosage also influences the risk of TSW, with the use of multiple TCSs increasing the likelihood of its occurrence. A previous study reported that, among 1,702 participants with symptoms consistent with TSW, 82% experienced TSW symptoms when using two TCSs, compared to 64% with one TCS (3). Not only does TCS dosage matter, but total corticosteroid use also plays a role. History of oral corticosteroid use may indicate more severe clinical conditions and is associated with TCS overuse, contributing to a greater likelihood of TSW (21). Lastly, longer duration of TCS application is another critical factor; 86% of individuals using TCS for 6 or more years reported symptoms consistent with TSW, compared to 53% of individuals using TCS for less than 1 year (3). Generally, the duration of TCS usage is 6 months or more (13), with 85.2% of patients with TSW reporting use longer than 12 months (4).

Certain patient factors, such as gender, primary concern, and region of application, have also been identified to increase risk. Individuals with AD are particularly susceptible to TSW, with AD being the initial indication for TCS use in one-third of cases. Furthermore, adult women are the largest demographic, comprising 81% of cases, and nearly all patients with TSW (97%) having a history of applying TCS to the face (4). The reason for the predominance in women is not fully understood (13), but it is believed to result from TCS use related to cosmetic and pigmentary concerns of the face (22). In particular, the anti-melanogenic properties of TCS may be favorable in those seeking skin lightening, contributing to misuse and subsequent TSA/TSW (13, 22). Additionally, patient age, accessibility of TCS, and behavior can also be risk factors. Studies show that younger patients are associated with an increased sensitivity to TCS and are likely to develop TSA/TSW. Unlike adults, who typically develop TSW after 6 months of TCS use (13), children can develop TSW after just 2 months of use, with symptoms potentially persisting for over 12 months (12). Studies show that recovery rates and prognosis also differ between children and adults, with 44% of children recovering from TSW compared to 28% of adults, and 8% of adults experiencing symptoms for more than 5 years (3). Additionally, TCS misuse is more prevalent in developing countries due to unregulated and over-the-counter sales of TCS and self-treatment, often for cosmetic purposes or non-responsive dermatoses. Moreover, patient behaviors such as self-treatment, seeking prescriptions from practitioners other than dermatologists, reusing old prescriptions for recurrent or similar rashes, and sharing prescriptions with others are concerning and can increase one's susceptibility (22). Furthermore, clinical evidence suggests that young females, especially those with skin of color are predominantly affected by this condition owing their vulnerability to TCS misuse for cosmetic reasons, such as use of fairness creams (22).

Lastly, an often-overlooked risk factor for TSW is occupational exposure to steroids. Specifically, healthcare professionals treating eczema patients may be exposed to TCS when applying them to patients, which can lead to skin irritation or allergic reactions if proper handling procedures are not followed—particularly with repeated exposure to high-potency steroids. This exposure can be mitigated if appropriate safety measures are taken. Wearing protective gloves, maintaining proper hand hygiene, minimizing direct skin contact, and employing correct application techniques are essential strategies to reduce the likelihood of developing TSW due to occupational exposure. Furthermore, occupational contact allergy, often presented as chronic irritative hand dermatitis, is primarily caused by water exposure or humidity in gloves, and corticosteroid use in such cases may be problematic. In these cases, protection and allergen avoidance are of utmost importance and corticosteroids should be the last choice.

Alternative treatments such as tacrolimus and delgocitinib could be considered for its management.

3 Pathophysiology

The pathophysiology of TSA/TSW is not fully understood. However, previous research and literature suggest that the progression of TSA/TSW is multifactorial. Some of the key contributing factors are outlined in Figure 2.

3.1 Dysregulation of endogenous cortisol production by keratinocytes

Former studies have revealed that keratinocytes possess all the necessary mRNA and enzymes for the metabolic conversion of cholesterol to cortisol, suggesting the presence of a non-adrenal steroidal system in human skin (23, 24). During TSA, exogenous application of TCS may thus suppress the intrinsic production of cortisol by keratinocytes (Figure 2A) through negative feedback mechanisms. This could involve the downregulation of enzymes involved in cortisol synthesis in keratinocytes such as CYP11A1, CYP17A1, 3bHSD1, CYP21, and CYP11B1 (24). It is likely that TCS withdrawal results in elimination of exogenous cortisol, and the suppressed enzymatic activity of keratinocytes may take a while to return to baseline levels, resulting in a period of decreased cortisol production. Given that cortisol produced from keratinocytes helps to modulate inflammatory reactions, the temporary reduction in cortisol may be responsible for the worsening inflammation seen in TSW.

3.2 Skin atrophy

TCS suppress proliferation and the extracellular matrix (ECM) protein synthesis of keratinocytes (Figure 2A) and fibroblasts (Figure 2B), which can be viewed histopathologically. This

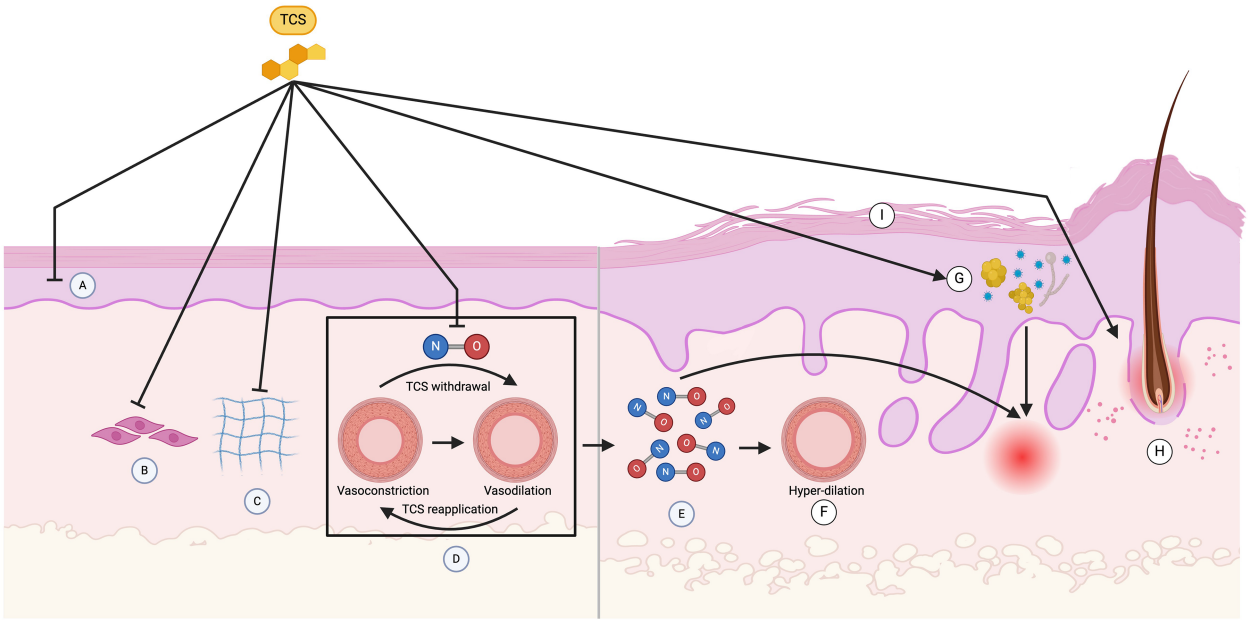

FIGURE 2
Pathophysiology of topical steroid addiction (TSA) and withdrawal (TSW). Exogenous application of topical corticosteroids (TCS) suppresses intrinsic cortisol production by keratinocytes **(A)** through negative feedback mechanisms involving the downregulation of enzymes like CYP11A1, CYP17A1, 3βHSD1, CYP21, and CYP11B1. Upon TCS withdrawal, the elimination of exogenous cortisol and reduced enzymatic activity leads to a temporary reduction in cortisol production, worsening inflammation in TSW. TCS also inhibits the proliferation and extracellular matrix protein synthesis of keratinocytes and fibroblasts **(B)**, reducing steroidogenesis of epidermal lipids such as ceramides, cholesterol, and fatty acids, resulting in a thinned stratum corneum and increased transepidermal water loss (I). Skin atrophy arises from TCS-induced reduction in collagen synthesis **(C)**, caused by decreased prolyl hydroxylase activity and collagen mRNA degradation. Chronic TCS use also inhibits endothelial nitric oxide (NO) production, leading to vasoconstriction, which reverses upon TCS withdrawal, causing excess NO release and subsequent vasodilation **(D)**. The vasodilation is associated with adverse effects such as erythema, itching and burning. Reapplication of TCS is often sought to reverse these adverse effects, resulting in a cycle of vasoconstriction and vasodilation **(D)**, termed the "trampoline effect" or "neon sign," and excess NO accumulation **(E)**, leading to hyperdilation of blood vessels beyond their pre-steroid state **(F)**. This excess NO and prolonged hyperdilation are thought to contribute significantly to the erythema characteristic of TSA/TSW. Prolonged TCS use induces immunosuppression as well, making the skin more susceptible to the overgrowth of microorganisms. When TCS are withdrawn, these microorganisms can act as superantigens, inducing cytokine release and subsequent inflammation **(G)**. Papulopustular and acneiform lesions, characteristic of the papulopustular subtype of TSW, are thought to result from TCS degradation of the follicular epithelium and subsequent extrusion of follicular contents **(H)**. These interconnected processes illustrate the impact of TCS on keratinocyte and fibroblast function, endothelial response, immune function, and follicular epithelium and skin barrier integrity, ultimately driving the pathological changes observed in TSA and TSW (Created with BioRender).

inhibition results in reduced steroidogenesis of epidermal lipids such as ceramides, cholesterol, and fatty acids. As a result, the stratum corneum is thinned (Figure 2I), and greater transepidermal water loss (TEWL) transpires. The resultant skin has reduced skin barrier function, tensile strength, and elasticity (25), which could correspond to the formation of "elephant wrinkles" seen in TSA/TSW.

Similarly, skin atrophy may also occur from reduced collagen synthesis (Figure 2C). TCS indirectly inhibits collagen synthesis by reducing prolyl hydroxylase activity or promoting collagen mRNA degradation (25). They also directly inhibit synthesis by reducing procollagen gene expression through glucocorticoid response elements that negatively regulate Smad proteins, which are necessary for type I collagen transcription (25). Additionally, they may promote epidermal atrophy by overexpression of tissue proteases and keratinocyte proteins (12). For instance, TCS increases thymic stromal lymphopoietin activity, which shifts the T-helper (Th) lymphocyte ratio from a balanced Th1/Th2 population to Th2 predominance, like that seen in AD (12).

3.3 Role of nitric oxide

Nitric oxide (NO), an endothelium-derived relaxing factor (EDRF), released by vascular endothelial cells, functions as a potent vasodilator (26). Chronic TCS use inhibits endothelial NO, causing persistent vasoconstriction. Following TCS removal, accumulated endothelial NO is released, resulting in vasodilation and TSW symptoms such as erythema, itching, and burning sensation. Reapplying TCS to alleviate these unwanted symptoms results in vasoconstriction. The dependency on TCS results in alternating cycles of vasoconstriction and vasodilation, known as the "trampoline effect" or "neon sign," (Figure 2D) and leads to excess NO accumulation (Figure 2E) (22) and hyperdilation of blood vessels beyond their pre- steroid diameter (Figure 2F) (22, 27). In summary, excess NO results in prolonged hyperdilation of vessels in TSA/TSW and is thought to contribute to the cardinal sign of erythema.

While NO is believed to contribute to the pathophysiology of TSA/TSW, its effects are difficult to discern and are inconclusive. Previous studies have demonstrated higher serum NO levels in inflammatory skin diseases like AD (10, 28), making it challenging to identify if elevated NO is due to TSA/TSW or the underlying condition. Furthermore, NO acts as a signaling molecule with both pro-inflammatory and anti-inflammatory effects depending on the context of its production. It is anti-inflammatory under normal physiological conditions (29) and participates in various biological functions including barrier homeostasis, wound healing, and antimicrobial defense (30). On the other hand, it is also pro- inflammatory and can participate in cutaneous inflammation in pathological conditions (29, 30). Topical NO-releasing products have also been shown to improve AD symptoms in humans and murine models (30). The dual nature of NO's effects in inflammation complicates the understanding of its role in TSA/TSW. However, despite its contradictory effects, NO levels have been found to be elevated in patients with TSA compared to cured patients and patients with eczema, indicating that serum NO may be useful in identifying addicted individuals (31). Enhancing our understanding of NO and its role in the pathology of TSA/TSW, as well as other inflammatory conditions like atopic dermatitis, could lead to the development of more effective treatments.

3.4 Topical corticosteroid-induced immunosuppression

Prolonged TCS use induces immunosuppression, making the skin more susceptible to the overgrowth of microorganisms. This may initially be helpful to patients with AD and other skin conditions, as a skin microbiome lacking biodiversity has been linked to many skin problems (32). However, when TCS are discontinued or withdrawn, these flourishing microorganisms can act as superantigens. As a result, the immune system which is no longer being suppressed induces cytokine release in response to the microbes and subsequent inflammation (Figure 2G) (18, 22, 32).

3.5 Direct effects on follicular epithelium

Papulopustular and acneiform lesions, characteristic of the papulopustular subtype, are thought to result from TCS degradation of the follicular epithelium and subsequent extrusion of follicular contents (Figure 2H) (22).

3.6 Glucocorticoid receptor expression

TCS acts by binding to intracellular glucocorticoid receptors (GR), of which two splicing variants have been identified, the GRa and GRb isoforms (10). Patients with a poor response following TCS treatment were shown to have upregulated GRb expression, while patients with a good response showed no changes in expression (10). Having higher GRb expression is thought to correlate to TCS insensitivity (10). Patients exhibiting TCS insensitivity may consequently use higher doses of TCS for extended periods, thereby elevating their risk of developing TSA/TSW.

3.7 Cytokines

TCS withdrawal has been associated with upregulation of IL1-α TNF-α, inhibitor of nuclear factor kappa-B kinase subunits alpha and beta (IKK1, IKK2) and nuclear factor kappa-B (NF-kB) in the epidermis. These cytokines gradually diminish after 1 week (33).

4 Clinical features of TSA/TSW

4.1 Signs and symptoms

When patients with TSA discontinue TCS, they may experience widespread erythema (Figure 3A), the most common sign of TSW.

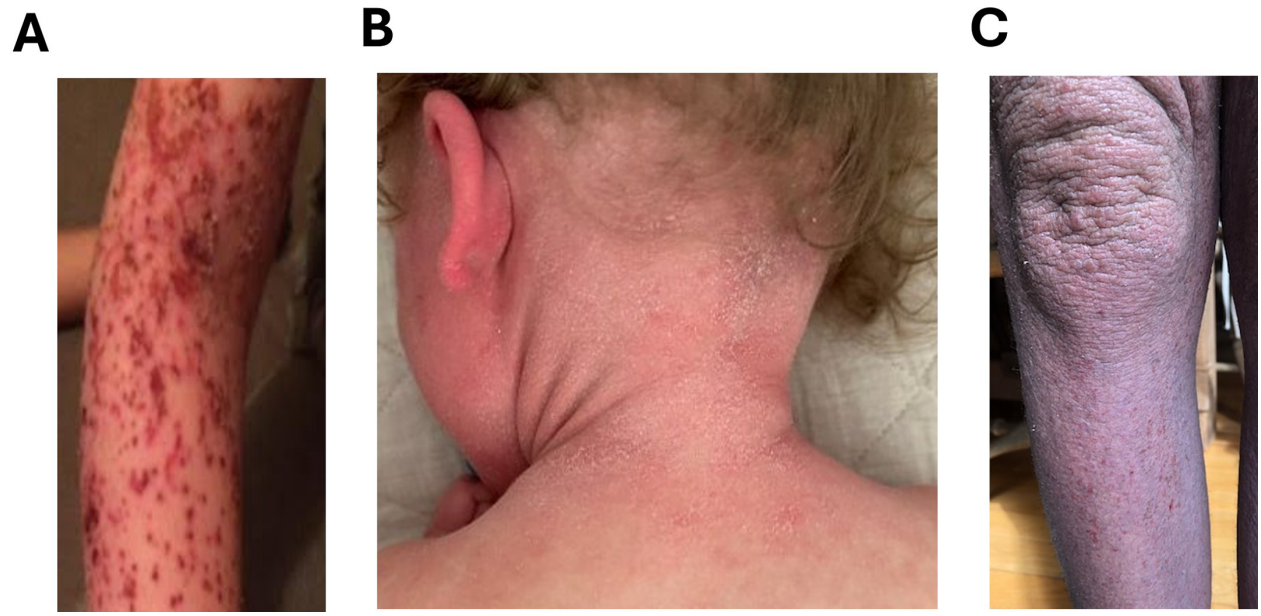

FIGURE 3
Signs and symptoms of TSW. **(A)** Widespread redness in the arm. **(B)** Serious redness in the ear. **(C)** Elephant wrinkles. *Permission obtained to reuse figure from* (14).

The erythema can extend beyond original eczematous areas to previously untreated sites (22) and be accompanied by other signs associated with TSW such as the headlight sign (Figure 3B), red sleeve sign, and "elephant wrinkles" (Figure 3C). Patients undergoing TSW commonly exhibit symptoms such as intense burning sensations, pruritus, and edema, amongst others (4). Clinical signs and symptoms of TSW described in literature are summarized in Table 1.

In patients with TSW, correlating clinical signs and symptoms with a detailed history of TCS use is essential. Key elements for identifying TSW include the specific TCS used, their potency, dosage, frequency, and duration of application. However, it is important to note that limited health literacy can hinder patients' ability to recall these details, complicating diagnosis. A 2012 review found that up to 48% of patients lack functional health literacy (34), which can make it challenging to attain accurate histories.

4.2 Histological features

The histological features of TSA/TSW are non-specific, rendering diagnosis by histology alone improbable. In a former study, biopsies from 4 patients with TSW demonstrated spongiosis and parakeratosis; however, these histological slides were excluded from the study (21). Nevertheless, research on TSA/TSW has identified some common histological findings between the two subtypes of TSW. Both subtypes have demonstrated dilated vessels in the dermis and collagen degeneration (4).

Additionally, histological analysis of the erythematoedematous subtype revealed a thinned epidermis, spongiosis, a thin or absent granular layer, sparse perivascular infiltrate, and prominent sebaceous glands surrounded by inflammatory cells. On the other hand, the papulopustular subtype, akin to rosacea, displayed a perifollicular or granulomatous infiltrate containing neutrophils and lymphocytes (4).

5 Differentiating TSW/TSA from other related conditions

5.1 Topical steroid damaged/dependent face

In recent years, instances of improper TCS use on the face have risen in India, prompting dermatologist Koushik Lahiri to introduce the term "topical steroid damaged/dependent face (TSDF)" in March 2008. Lahiri defined TSDF as "the semi-permanent or permanent damage to the skin of the face precipitated by the irrational, indiscriminate, unsupervised, or prolonged use of TCS resulting in a plethora of cutaneous signs and symptoms and psychological dependence on the drug" (35). Although TSDF shares characteristics with TSA, such as dependency on TCS and exacerbation of cutaneous symptoms upon withdrawal (22), TSDF is specifically localized to the face, whereas TSA encompasses a broader dependency affecting various body regions.

5.2 Tachyphylaxis

Additionally, the terms tachyphylaxis and steroid phobia are often incorrectly associated with TSA/TSW.

TABLE 1 Clinical signs and symptoms.

Major dermatological signs	Features
Erythema (cardinal sign) (3, 4, 9, 11, 13)	• May appear less pronounced (22) or occur as hyperpigmentation depending on skin tone (3) • May extend beyond the initial application site or spread to distal sites (22) • Reported in 92.3% of patients with TSW (4)
Headlight sign (2, 4, 13)	• Distinct demarcation between erythematous and normal skin, in which redness normally ends at mid-cheek • The nasal, perinasal, and perioral areas are spared
Red sleeve (3)	• Rebound eruption of the extremities with a sharp cutoff at the margin of the dorsal and palmer (or solar) sides (21) • May appear dark depending on skin tone (3)
"Elephant wrinkles" (2, 3, 13)	• Thickened skin with diminished elasticity, commonly affecting extensor surfaces such as the anterior knees, elbows and neck (2, 13)
Other dermatological signs and symptoms	**Features**
Burning or stinging skin (3, 4, 9, 11)	• Affects 94.6% of the erythematoedematous type (4)
Skin peeling, flaking, or exfoliation (3, 4, 9, 11)	• Reported in 33.3% of patients with TSW (4)
Pruritis (3, 4, 9, 11)	• Reported in 45.4% of patients with TSW (4)
New skin hypersensitivity or dysesthesias (to various materials or environmental conditions) (3, 4, 13)	• Sensitivity to water, movement, moisturizers, fabric, temperature, sunlight (3) • Facial hot flashes are a common symptom of TSW (4) • Dysesthesia reported in 13.4% of patients with TSW (13)
Papulopustules (4)	• Papules ± nodules reported in 61.6% of patients with TSW (4) • More prevalent in the papulopustular type (4) • Often accompany vascular changes due to TCS use, attributed to focal degeneration and inflammatory reactions in the intrafollicular and perifollicular areas (22)
Hyperhidrosis or itchy wheals	• Signify recovery (9)
Alopecia (3)	• Can involve the head and/or body
Skin oozing or weeping (3, 4, 9, 11)	• Less common, reported in 1% of patients with TSW (4)
Changes to skin of the genitalia (11)	• Burning erythema ± pain of the scrotum, inguinal and penile area that may be accompanied by atrophy of the glans with disease progression • May be described in males as "red scrotum syndrome" • Pruritis vulvae and vulvodynia in females
Skin atrophy (2, 22)	• Increased skin transparency and sheen (22)
Telangiectasia (2, 3, 8, 13, 22)	• Dermal atrophy allows easier visualization of dermal capillaries
Non-dermatological signs and symptoms	**Features**
	• Reported in 69% of adults and 43% of children with TSW (3)
Swelling/Edema (3, 4, 9, 11)	• Reported in 43.3% of patients with TSW (4)
Nerve pain (3)	• May be described as "sparklers" or "zingers" (3)
Lymphadenopathy (3)	• Reported in 57% of adults and 54% of children with TSW (3)
Appetite changes (3)	• Not described in detail • May be caused by psychological changes
Psychological changes	**Features**
Intense emotional fluctuations (3), depression (3, 9) anxiety (3, 11)	• Reported in 81% of adults and 56% of children with TSW (3)
Suicidality (3)	• Reported in 47% of adults presenting with TSW (3)
Insomnia, sleep disturbances, or altered circadian rhythm (3, 11)	• Reported in 80% of adults and 62% of children with TSW (3)
Fatigue (3)	• Reported in 79% of adults and 53% of children with TSW (3)
Pediatric signs and symptoms	**Features**
Subjective growth delays (failure to meet milestones, decreased weight gain) (12)	• A systematic review of 27 pediatric patients with TSW reported 7 patients (26%) with subjective growth delays • May occur because of HPA suppression or avascular necrosis

Tachyphylaxis is an acute condition characterized by reduced medication efficacy after successive dosing. It can be distinguished from TSA/TSW, as tachyphylaxis occurs before TCS withdrawal, while TSA/TSW exhibit cutaneous eruptions after withdrawal (9). Moreover, steroid phobia, defined as the fear or reluctance to use TCS, is associated with TSA/TSW. Awareness of TSA/TSW may exacerbate steroid phobia. Conversely, steroid phobia may lead to improper TCS usage that could perpetuate TSA/TSW. It is important to note that TSA is often attributed to TCS misuse or overuse, while steroid phobia results in TCS underuse (2).

5.3 Psoriasis

Psoriasis flares can be triggered by the abrupt cessation of systemic or topical corticosteroids (36). Withdrawal of these medications may lead to rebound psoriasis, often presenting with symptoms that are more severe than the initial presentation (37). These drug-associated flares of psoriasis should not be misinterpreted as TSW. Drug- induced psoriasis is similar to conventional psoriasis, but is associated with an eosinophilic infiltrate in the dermis and a lichenoid pattern on histology (36, 38).

TABLE 2 Phases of TSW.

Phases	Features
Phase I: Acute Red Exudative Phase (4, 11)	• Begins a few days after TCS cessation, lasts days to weeks (4, 11) • Rebound eruption extending to previously untreated areas, sparing palms and soles (4, 11) • Erythema develops from areas of intractable eczema and spreads gradually (4, 11) • Thickened eczematous areas may flatten, obscuring the borders of erythema (4, 11)
Phase II: Dry, Itchy, Desquamative Phase (Acute Phase) (11)	• Skin is dry, itchy, and thickened or desquamative (11) • Patients may experience depression and pessimism due to symptoms or lack of effective treatments offered by physicians (4)
Phase III: Recovery Phase (11)	• Gradual skin improvement (11) • Sensitivity to minor stimuli that gradually decreases (11) • Intermittent periods of aggravation and flares (11)
Phase IV: Recovered Phase (11)	• May take weeks to years- over time, the skin normalizes, and the increased hypersensitivity following withdrawal decreases (4, 11) • Complete withdrawal of the offending TCS leads to the skin regaining its original appearance or returning to the pre-TSA/TSW condition (e.g., AD) (4, 11) • Some patients achieve completely healthy skin if the eruption was caused by TSA rather than the underlying condition (4)

6 Phases of TCS withdrawal

Before discontinuing TCS, patients' skin may appear normal or well-controlled by TCS, although some begin to experience symptoms such as increased pruritis or diminished TCS efficacy. In certain cases, prurigo-like eruptions or intractable nodules with severe itching emerge, often signaling addiction (9). As symptoms worsen, patients may choose to discontinue TCS for various personal reasons, such as steroid phobia, or diminished benefits despite prolonged or increased usage (2, 12, 39). TCS discontinuation is particularly relevant for patients with recalcitrant eczema, where withdrawal is a critical aspect of management. Four phases of TCS withdrawal have been proposed from previous studies (10). The sequence of events in each phase is described and illustrated in Table 2 and Figure 4 respectively.

7 Diagnosing TSA/TSW

The non-specific features of TSA/TSW can propagate misdiagnosis and mistreatment. Several conditions can be considered in the case of TSA/TSW, such as rosacea, cutaneous T-cell lymphoma, and psoriasis (13). However, the 3 main differential diagnoses include eczematous/AD flares, allergic contact dermatitis (ACD), and infection (2).

Differentiating TSW from a flare-up of the underlying disease may be challenging but is of utmost importance. Misdiagnosing a withdrawal episode as an AD flare can lead to inappropriate treatment, often escalating TCS use. Conversely, AD flares can be misinterpreted as TSW. Both scenarios result in insufficient treatment, worsened patient outcomes, and unnecessary morbidity (6). No consensus criteria for distinguishing TSW from eczematous flares have been established. Nonetheless, previous studies suggest 3 essential diagnostic criteria for favoring a diagnosis of TSW over worsening AD:

1. Burning (4, 13) or itch (13, 21) as the prominent symptom
2. Erythema- confluent redness within days to weeks of TCS withdrawal (4, 13, 21)
3. History of prolonged, frequent TCS use on the affected region (typically the face or genitals) (4, 13, 21)

Additionally, to rule out ACD to an active steroid molecule or its vehicular excipients, patch testing may be indicated (4, 12). Localization of a rash can help identify the offending allergen or point clinicians toward suspecting ACD, such as supraumbilical dermatitis from ACD to nickel in a belt buckle (1). Despite challenges, like lack of clear skin for testing in atopic individuals (13), and potential false positives due to vasodilation (10), patch testing can determine reactions to the active steroid, its vehicle, or other environmental allergens. Given a high clinical suspicion of TSW, patch testing should be performed with the awareness of potential delayed positive reactions (13), as ACD is a type IV delayed hypersensitivity reaction. When indicated, patch testing should be administered, as mistaking ACD for TSW could prevent patients from receiving necessary anti-inflammatory therapy (4).

8 Treatment

Despite the lack of general guidelines for treating TSA/TSW, several treatment approaches have shown potential value for both physicians and patients. The most widely recommended intervention is TCS discontinuation, which is advised in nearly all cases of TSA/TSW. In addition, some physicians may prescribe immune-modulating agents such as oral steroids, monoclonal antibodies, non-steroidal anti-inflammatory drugs (NSAIDs), among others. In addition, use of multi-component TCM therapy, complementary integrative medicine, black tea, coal tar and tannins are widely recognized in the literature. A summary of all these immune-modulating therapies, along with other recommended treatments, is provided in Table 3 and Figure 5.

9 Prevention

To prevent TSA/TSW, it is recommended that continuous TCS use be limited to 2–4 weeks to prevent long-term histological

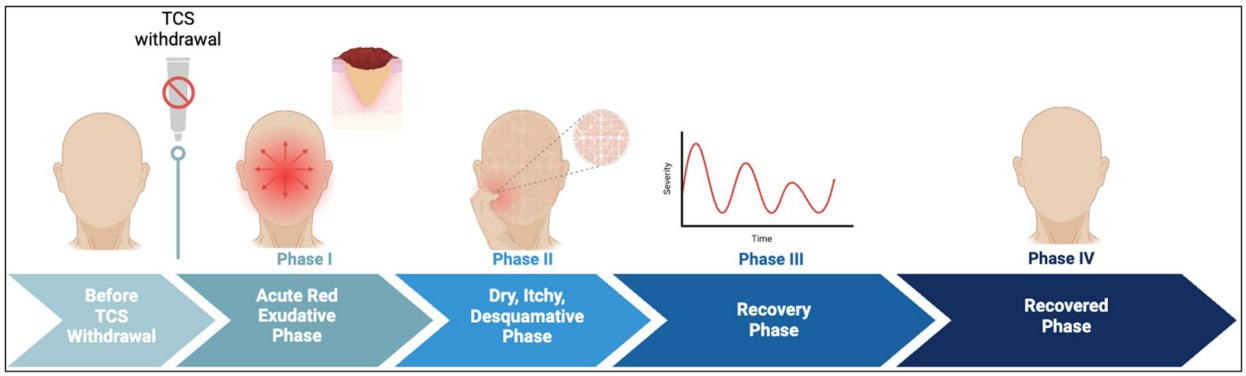

FIGURE 4
Phases of TCS withdrawal. Before TCS withdrawal patients' skin appears normal. Phase I is characterized by acute red skin which spreads gradually. It lasts for a few days to weeks. Phase II is marked by dry, itchy, thickened skin. Some patients show signs of depression due to lack of treatment and continuous worsening of skin lesion. Phase III is the recovery phase where patients show gradual improvement of skin lesion with occasional aggravated skin flares. Phase IV is the recovered phase where patients skin normalizes and regains its original appearance. This phase may take weeks to years.

effects. Periods of interruption where TCS use is discontinued may allow the skin to recover from the previous TCS cycle to permit continuation of treatment (9). Additionally, another method of preventing TSW is by dampening moderate or severe AD before disease escalation. In such cases, administering a short-term systemic corticosteroid as a rescue therapy, followed by site-specific TCS, and tapering of all steroids may be appropriate (Figure 6). In doing so, the severity of AD should dampen with time, reducing the need for corticosteroids and limiting adverse effects like TSA/TSW (6).

10 Prognosis and psychological impact

Active TSA/TSW symptoms can persist even for 20 months after discontinuing the offending agent (12). One survey found that 26% of patients with TSA/TSW who had stopped TCS for over 5 years still experienced symptoms. Not only can TSA/TSW be long-lasting, but it also has a sizeable psychological impact. Concern over TSW was high among adults with AD and caregivers of children with AD, with 74% of adults and 49% of caregivers reporting concern about TSW. Alarmingly, 47% of adults with symptoms consistent with TSW reported having suicidal thoughts (3). Given that TSW can persist for months to years, and is associated with high levels of concern, suicidal ideation, and significant psychological toll, frequent check-ins are crucial for evaluating and maintaining patients' emotional well-being (2). Despite increasing patient concern over TCS use and TSA/TSW, many patients find that they are met with a dismissive, ignorant or unempathetic response from their doctors. The response has resulted in patient mistrust of the medical profession, with one study reporting that 9 of 26 participants withdrew from typical dermatologic care. The resultant lack of validation for patient concerns has led some to discontinue TCS without guidance from providers and has led many to seek alternative care such as TCM (39).

11 Discussion and conclusion

Estimates of the prevalence of TSA/TSW vary widely, with studies suggesting that 12%–79% of patients with atopic dermatitis (AD) may experience TSW (3, 9). Therefore, it is necessary to calm down the underlying Th2 mediated immune response in early stages of AD development. Additionally, 47% of patients with symptoms consistent with TSW experience suicidal ideations. Despite the large potential burden, studying TSA/TSW presents several limitations, such as the unclear temporal relationship between TCS use and symptom onset (4), a predominance of female survey respondents (3), reliance on self-reported symptoms, and the absence of standardized diagnostic criteria. Given the substantial physical and psychological impact of TSA/TSW, continued research is necessary to establish consensus diagnostic criteria and effective treatment protocols. TSA/TSW share similarities with other dermatologic conditions; however, cardinal signs have been identified. Determination of consensus diagnostic criteria may thus be achieved by combination of these clinical signs with histological findings and detailed history of TCS use. Additionally, inflammatory markers involved in pathophysiology, such as NO, may enable quantitative differentiation from other conditions.

While diagnostic criteria are needed, proposals of such criteria cannot occur unless physicians, particularly dermatologists, recognize the legitimacy of TSA/TSW. Despite numerous patients sharing their experiences with chronic TCS use and withdrawal on online platforms, TSA/

TABLE 3 Treatment of TSA/TSW.

Treatment	Details	Adverse effects
TCS discontinuation	• In almost all cases of TSW, discontinuation of TCS is recommended • It has been suggested that a negligible difference exists between gradual tapering and immediate cessation, but patients with severe TCS addiction are more likely to benefit from immediate TCS cessation (9)	• Discontinuation may initially worsen withdrawal effects
TCS discontinuation with oral steroid supplementation	• Discontinuation of TCS followed by supplementation with systemic steroids during withdrawal rebound appears to be an effective treatment • The mechanism for this effect is currently unknown, but it is thought that systemic steroids reduce inflammatory responses with fewer dermatologic effects (9)	• Weight gain, mood changes, and increased susceptibility to infections
NSAIDs	• Along with discontinuation of TCS, the most common treatments for TSW involve agents which either dampen the immune response or have anti-inflammatory effects on the skin	• In the United States, TCIs such as tacrolimus carry a Boxed warning due to a potential for increased risk of cancer (40)
Antibiotic treatment: doxycycline, tetracycline, and erythromycin	• Frequently used in patients with the papulopustular subgroup, with oral antibiotics being more common (4) • Doxycycline, tetracycline, and erythromycin are often used for this purpose—used in 45.5% of cases (4)	• Overuse carries an increased risk of iatrogenic infection—particularly with *C. difficile* • Caution in antibiotic selection is warranted during pregnancy, as some antibiotics can be teratogenic or have unwanted side-effects
Supportive therapy (antihistamines, ice/cool compresses, etc.)	• Patients with the erythematoedematous subgroup benefited from supportive therapy with antihistamines and ice/cool compresses (4)	
Dupilumab (Dupixent®)	• A monoclonal antibody which blocks interleukins 4 and 13 • One case series showed marked improvement with dupilumab compared to other standard therapies (41)	• Some patients may experience an increased risk of headaches and conjunctivitis (42) • Some studies have shown an increased risk of certain types of cancers such as cutaneous T-cell lymphoma in patients taking dupilumab for AD (43)
Complementary integrative medicine	• Triple therapy containing traditional chines medicine (TCM) formula in the form of digestion tea, bath additives and cream has shown to markedly improved skin lesion, itching, and sleep loss in patients with TSW (44, 45) (Figure 5). • Berberine, a natural alkaloid, showed to inhibit pro-inflammatory response associated with S. aureus isolated from TSW patients (46, 47). • Multi-component TCM therapy improved SCORAD, TEWL and significantly reduced abundance of S. aureus burden and increased alpha-diversity in the skin (48). • Treatments include apple cider vinegar baths, gauze wrapping, cool compresses, hot packs, and narrowband UVB light (12) • Recent preliminary studies have shown possible benefits to increasing skin and gut microbiome biodiversity by using specialized body washes or personalized probiotics (32) • Acupuncture therapy improves clinical efficacy of itch (49).	
Black tea formulation	• Some studies have shown black tea dressings to be an effective treatment option for facial dermatitis within only a few days (50).	
Coal tar	• The topical application of coal tar is one of the oldest known treatments for AD, but its mechanism of action remains elusive (51).	
Tannins	• The benefits of tannins have been well-characterized in recent years for their anti-microbial, anti-pruritic, and anti-inflammatory effects, especially when applied topically to soothe inflammatory skin conditions (52).	
Basic skin care	• Basic routine skin care is essential for the management of eczema-related conditions. One study suggests applying 250–500 g of emollients topically each week as first-line therapy to manage inflammatory skin conditions (53).	

TSW remains a contentious topic within the dermatologic community. Therefore, emphasis should be given on educational training, patient-clinician symposiums and appropriate presentations on management of TSA/TSW are essential to ensure effective care. Well-informed providers will not only enhance patient trust and treatment adherence but also help mitigate steroid phobia and prevent therapeutic failures associated with improper TCS use. Enhanced provider education will lead to greater recognition of these conditions, drive the establishment of standardized diagnostic criteria, and ultimately improve clinical outcomes for patients.

Several corticosteroid-sparing strategies have been explored, however, there is an urgent need for continued research to develop new therapeutic regimens that effectively manage TSA/TSW with minimal side effects. Besides, use of natural active

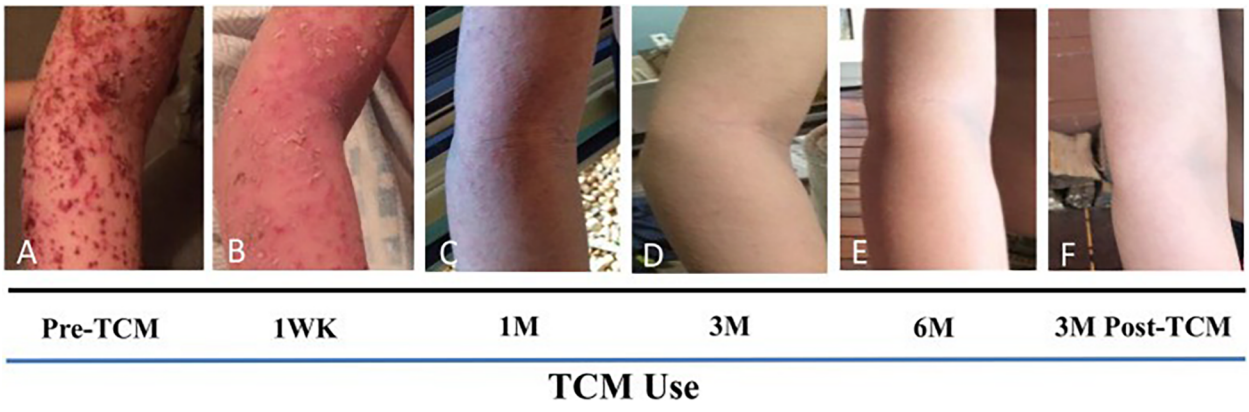

FIGURE 5
TCM therapy showed marked improved skin lesion. **(A)** 12 days after the last course of prednisone, with MSSA *Staphylococcus aureus* infection and poor response to steroid injection. **(B)** Improvement of skin lesions by 1 Week of TCM use including internal tea, external herbal bath and creams. **(C)** 1 month of TCM use, **(D)** 3 months of TCM use, **(E)** By 6 months, skin remained to be well controlled. No steroids or antibiotics were used during the course of TCM therapy. **(F)** Skin reveals no apparent recurrence 3 months after TCM discontinuation. *Figure permitted to use from* (45).

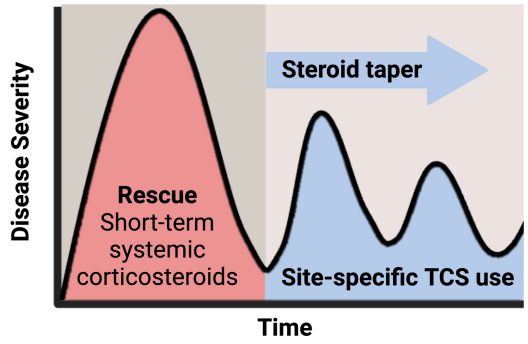

FIGURE 6
Damping moderate to severe AD with corticosteroid. Topical corticosteroid use should be limited to 2–4 weeks for appropriate response. Tapering steroid dose, followed by site-specific corticosteroids may help dampen AD severity by reducing the need for corticosteroids and limiting adverse effects like TSW.

compounds based therapeutic strategies for steroid-dependent or steroid withdrawal associated with severe eczema along with early introduction of TCM in young adults with eczema is well discussed previously (14). A case series summary shows remarkable improvement of skin lesion, reduced itch sensation, and sleep improvement following initiation of TCM therapy protocol. Furthermore, patients undergoing substantial topical steroids, light therapy, and biological treatment showed no improvement in quality of life, however introduction of TCM therapy led to significantly improved skin integrity within 3 months. This evidence suggests TCM therapy has great potential in managing TSA/TSW. This should be further studies in controlled clinical studies of patients with severe refractory eczema and TSW to better achieve expected milestones. Additionally, advancing our understanding and treatment of TSA/TSW is crucial to restoring patient trust and ensuring compassionate care for those afflicted by these conditions.

Author contributions

AM: Conceptualization, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. AS: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing. MK: Formal analysis, Supervision, Writing – original draft, Writing – review & editing. RT: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. JG: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. BS: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. X-ML: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Cure for the itch: current clinical standards and therapies in allergic eczema

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Allergic Eczema (AE) is a chronic, relapsing skin condition that significantly affects the quality of life of the AE patients and their caretakers. Decades of scientific and clinical research has helped understand the highly complex underpinnings of AE presentation wherein a multitude of variables, including the conspicuous variables such as environmental allergens, immunological triggers, genetic predisposition of individuals, to more nuanced socio-economic status, play an important part. Given the complexity of the disease, it is imperative to develop biomarkers enabling early and reliable clinical identifications and help in the active management of the disease, thereby minimizing the impact and burden of the disease on the patients. In this mini review, we provide a brief overview of AE, affected demographics, variables that trigger its onset, and summarize the discovery of various clinical biomarkers such as total and specific serum IgE levels, Th2 cytokine levels, filaggrin (FLG) mutations, periostin levels in skin, etc. that have been developed over the years to further improve the state of clinical monitoring of AE presentation and progression. Lastly, we also provide an overview of the clinical interventions and therapies, such as topical agents, phototherapy, and biologics, that are available to the patients to manage AE-related complications. While we have vastly improved the standard of care and diagnosis for the AE patients, there are still many unmet needs such as developing non-invasive, effective, and reliable clinical predictors and biomarkers which can usher better personalized treatments and provide a better quality of life to affected demographics.

KEYWORDS

allergic eczema, biomarkers, clinical research, skin disorders, allergy, IgE-mediated disease, atopic dermatatis, phototherapy

Introduction

Eczema is a cluster of skin conditions often characterized by inflammation, dry skin, rashes, scaly patches, and itchiness (1). Eczema affects people of all skin tones and types. In Individuals with a lighter skin tone, manifestation typically occurs in the form of erythema and skin inflammation. Eczema patients who are people of color experience brown, purple, ashen, or a gray skin tone. Though eczema affects people of all races and ethnicities, some groups are more likely to be affected (2, 3).

Around 31.6 million people, or 10% of the total population of the United States of America, suffer from some type or form of eczema. Within this population, the Asian and Pacific Islanders and Native Americans are the most affected demographics and

tend to have the highest likelihood to develop eczema at 13% incidence rate, closely followed by the white population at 11%, and the black population with 10% (4).

Allergic eczema (AE) refers to a specific form of eczema which is often associated with pruritis and other IgE associated disorders such as food allergies, asthma, etc. The highest prevalence of eczema is during early childhood, with a typical onset prior to 5 years old which resolves by adulthood; however, it can re-appear later in life or continue throughout adulthood (5). Besides biological age, the gender of the person also has a bearing on the eczema incidence rates. Women have a higher incidence of eczema compared to men (8.9% and 5.7, respectively) (6). The gender discrepancy in eczema manifestation that leads to a higher incidence of allergic eczema (AE) in women is often attributed to menopause related changes. During menopause, the estrogen levels decline leading to changes in the skin which make it more prone to eczema manifestation (7).

Causes of allergic eczema

AE pathophysiology is highly complex but is thought to primarily develop from a combination of genetic (8), immunological (9), and environmental (10) variables. Food hypersensitivity may also cause or exacerbate atopic dermatitis in 10% to 30% of patients; the majority being caused by sensitivities to egg, milk, peanuts, soy, and wheat (11, 12).

AE is one of the most common chronic, inflammatory diseases afflicting 11.3%–12.7% of children and 6.9%–7.6% adults in the USA (13)—with *pruritus* or skin barrier defects observed as the most common symptom in the patients (14). In AE, it is common to observe an immunological response imbalance, which usually results in an epidermal barrier defect, IgE mediated hypersensitivity, and other related conditions (15, 16).

Over the years, numerous scientific studies have explored the interplay of genetics and immune responses in driving AE development and flare-ups. Some of these studies looked at (i) atopic march—the early life presentation of the atopic disease and its progression with time (17), (ii) studies linking increased levels of total serum IgE and IgEs specific for environmental and food allergens (18), (iii) studies linking the incidence of AE with the loss of function mutations in the gene coding filaggrin (FLG) (19)—a filament-aggregating protein in skin that is responsible for binding the keratin fibers and maintaining the integrity of the skin and its barrier function. A common highlight shared by these studies was the role of skin as a peripheral lymphoid organ (20), and the importance of skin integrity in determining the severity of AE onset and progression (21, 22).

Abbreviations

AE, allergic eczema; FLG, filaggrin; IgE, immunoglobulin E; TCS, topical corticosteroids; WWT, wet wrap therapy; JAK, Janus Kinase; STAT, signal transducer and activator of transcription; TARC, thymus and activation regulated chemokine; MEL, monochromatic excimer light; BBUVB, broadband ultraviolet B; NBUVB, narrowband ultraviolet B; ECP, eosinophil cationic protein; TEWL, trans-epidermal water loss; Th2, T-helper 2; mAb-TX, monoclonal antibody based therapeutics.

These immunologic and genetic studies have led to better patient stratification via the identification of other related traits or sub-phenotypes of AE (23, 24) allowing for better standard of care and clinical identifications. While the complete understanding of the pathophysiology of AE still eludes us, the high degree of coincidence of skin barrier dysfunction and immune dysregulation observed in clinical studies suggest their potential role in the etiology of disease progression in AE patients.

Reviews by Umehara et al. (25) and Sroka-Tomaszewska et al. (9) provide a comprehensive background on the complexities of AE, its possible causes and immunological underpinnings behind some of the commonly observed symptoms.

Factors affecting the severity of allergic eczema

AE significantly affects the quality of life of both the patient and their caretakers making disease management difficult without proper planning and support. An overview of the impact and multi-faceted effects of AE disease, on patients and their caretakers alike, is provided in Figure 1.

Insomnia is frequently associated with AE (26, 27), which often leads to increased itching urges at night further disrupting sleep. Melatonin production is reduced by the lack of sleep which inhibits the body's ability to decrease temperature, resulting in the increased skin temperature during sleep, causing itching episodes (28). Irregular sleep habits can cause systemic imbalances, exhaustion, and impact the overall quality of life of the patients and their caretakers (27).

Clinical presentation and diagnosis of allergic eczema

AE clinical characteristics change depending on age and disease duration. The characteristics in childhood centers on eczematous changes that are accompanied by serous papules which often cause a strong urge to itch, and upon scratching, may lead to excoriation and development of new papules (29).

When AE progresses from childhood to adulthood, the clinical presentation changes and the Skin lesions transition to a more varied phenotype compared to those in childhood, a condition referred to as Besnier's prurigo or disseminated neurodermatitis (30). Mental nervousness, continuous itch prior to abnormal skin, distribution of skin lesions, dryness of the skin, visible papillae of hypertrophy of skin pigment, and an apparent circumscribed plaque that appears in the same site as the original itch are all characteristics of a chronic condition of disseminated neurodermatitis (1, 29–33).

The predominant criteria used for AE diagnosis in clinical setting remains the Hanifin-Rajka criteria (23)—first introduced in 1980, and included almost 30 signs, symptoms, and laboratory abnormalities (34), of which 3 out of 4 major criteria and 3 out of 23 minor criteria need to be met for a conclusive diagnosis. Given challenges around the difficult interpretation of the Hanifin-Rajka criteria outside a clinical setting, the United Kingdom (UK) Working Party Criteria was introduced in 1994 (35, 36). This simplified and condensed the Hanifin-Rajka criteria for a

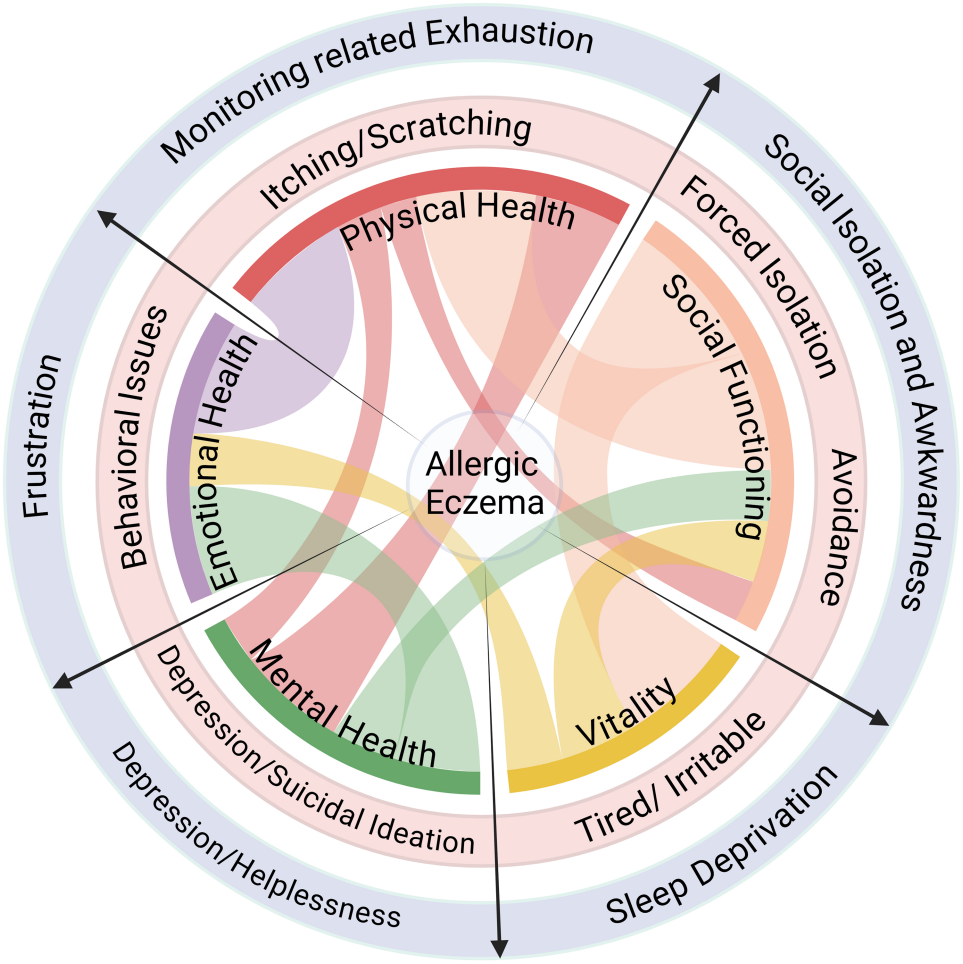

FIGURE 1
Impact of AE on quality of life. AE affects multiple facets of life and compromises the holistic well-being of the patient (light red circle) as well as their caretakers (light purple circle). Created with Biorender.com.

broader application to a range of ethnic groups, with pruritus being elevated to be the sole mandatory criteria in addition to coincidence of 3 or more of other 5 major criteria. A further distillation of diagnosis criteria was observed in the millennium criteria, introduced in 1998 by Bos et al. (37), and was the first to include the presence of allergen-specific IgE as a diagnostic biomarker.

Later, in 2011 Schram et al. elaborated on the millennium criteria and proposed meeting ≥5 of the criteria outlined in the original millennium criteria (35). A head-to-head assessment of the modified millennium criteria with the established UK working party criteria and Hanifin-Rajka criteria, over a cohort of 201 patients and observed that the modified minimum criteria showed a sensitivity of 81.8% with a specificity of 98.8%, compared to 100% and 48.8% for the Hanifin-Rajka criteria and 97.7% and 72.9% for the UK working party criteria (35, 38). In 2014, the American Academy of Dermatology laid out the guidelines for AE diagnosis and assessments which emphasized the role of hallmark features of AE opposed to features that are non-specific while excluding the conditions that mimic AE, such as scabies, seborrheic dermatitis, psoriasis, etc. (23).

To determine the severity of the disease in the clinic, the following two tests are commonly used and have been validated: Scoring Atopic Dermatitis (SCORAD) index, and the Eczema Area severity index (EASI) (39, 40). These tests are typically used to measure the extent of erythema, edema, papulation, excoriation, and the degree of lichenification. Additionally, other factors, such as pruritus and loss of sleep, are incorporated into the diagnosis and severity assessment (22, 26, 27).

Many of the current clinical practices for diagnosing cases of AE rely on previous clinical learnings and established biomarker tracking in order properly identify and stratify the patient and recommend therapeutic interventions accordingly.

Biomarkers of allergic eczema

Identification and characterization of appropriate biomarkers allows for a precise understanding of multi-factorial disease such as AE and its complex underpinnings. This understanding is crucial for enabling tailored therapeutic approaches for individual

patient profiles. The utility of such biomarkers ranges from the assessment of disease severity to predicting flares and guiding treatment decisions, which in turn aids in improvement of patient outcomes overall.

Monitoring critical biomarkers can also help in tracking the therapeutic responses of the treatment and allows for a more involved and dynamic approach in clinics, where timely modifications in treatment plan can ensure rapid alleviation of the disease condition.

The last few decades of intense research around AE and its underpinnings have allowed clinicians to come up with several biomarkers that are used in clinics to track the disease state. Some of these commonly used biomarkers have been summarized in Table 1.

Limitations of historical research

In the past, significant progress was made in identifying and understanding various biomarkers associated with allergic eczema. Key studies highlighted the roles of immunological factors, genetic predispositions, cutaneous protein levels, and cytokine profiles in the disease's pathogenesis and management (21, 24, 32, 41). However, further validation and exploration of these biomarkers are needed to enhance their clinical applicability and improve patient outcomes.

Despite the identification of several potential biomarkers, significant limitations persist including issues with specificity, sensitivity, and inconsistency of findings across diverse populations. Many biomarkers were not widely validated for routine clinical use, emphasizing the need for further research into more reliable and clinically applicable biomarker candidates.

Research in the past decade has significantly advanced the understanding of biomarkers in AE. Key findings include the identification of genetic (e.g., FLG mutations), immune (e.g., Th2 cytokines), and skin barrier-related biomarkers (e.g., filaggrin, periostin) that are pivotal for diagnosing, monitoring, and personalizing treatment for AE. Additionally, the role of the microbiome, serum biomarkers, and exosomes is gaining attention as potential tools for precision medicine in AE. This ongoing research is improving both the management of the disease and the development of targeted therapies, ultimately aiming for more effective and individualized treatment strategies.

TABLE 1 Various biomarkers currently used in AE diagnosis and tracking.

Immunological biomarkers	
Total and specific serum IgE levels	Numerous studies have established that patients with allergic eczema frequently exhibit elevated total serum IgE levels (32, 33). Leung et al. demonstrated that high IgE levels correlate with increased disease severity and are indicative of atopic sensitization to environmental allergens (33). Specific IgE responses to common allergens [e.g., dust mites (76), pollen (77)] have also been linked to the exacerbation of AE symptoms.
Eosinophil cationic protein (ECP)	ECP is a marker of eosinophilic inflammation associated with allergic diseases (78). Early studies, such as those by Hozumi et al. (79), reported elevated ECP levels in AE patients, suggesting its utility as an inflammatory marker reflective of disease activity.
Genetic Markers	
Filaggrin Mutations	Filaggrin (FLG) is crucial for maintaining skin barrier integrity. Research by Brown et al. Identified mutations in the FLG gene as a significant risk factor for developing allergic eczema, particularly in patients of European descent (80). This study linked genetic predisposition to the clinical presentation of atopic dermatitis and highlighted the importance of barrier dysfunction in AE pathogenesis.
Cutaneous biomarkers	
Skin barrier function	Studies assessing skin hydration and trans-epidermal water loss (TEWL) have consistently shown that impaired skin barrier function is a hallmark of atopic eczema like conditions (21, 81). Research conducted by Flohr et al. Explored the relationship between TEWL and disease severity, demonstrating that increased TEWL correlates with worse clinical outcomes (15, 82).
Periostin	Periostin has been implicated in the regulation of inflammation in AE (15, 32, 41, 83). A study by Kou et al. found that periostin levels in the skin are positively associated with clinical severity, suggesting it may serve as a potential biomarker for chronic inflammation in AE (84).
Cytokine profiles	
Th2 cytokine dominance	A pivotal characteristic of allergic eczema is the Th2-skewed immune response (14, 29, 85–87). Research has documented elevated levels of cytokines such as IL-4, IL-13, IL-17 and IL-5 in AE patients (15, 22, 32, 70, 73, 88–90).

Treatment modalities

Traditional

Traditional therapy for AE could be split into two types of treatments: topical or systemic. Topical agents include moisturizers, corticosteroids, antimicrobials, wet wrap therapy, and calcineurin inhibitors (1, 23, 33, 42, 43). Systemic treatments are used for more severe forms of AE. These treatments consist of systemic corticosteroids, cyclosporine, azathioprine, phototherapy, and more (21, 42, 44–46).

Topical therapies for AE

Topical agents

Use of topical emollients (lotions, creams, hydrating gels, sprays, and ointments) and anti-inflammatory agents (antihistamines, phosphodiesterase inhibitors, calcineurin inhibitors) can achieve short term control of acute symptoms and clinical improvement in mild allergic eczema and dermatitis skin diseases. Topical agents are more effective in controlling mild disease conditions as opposed to moderate-to-severe stage of AE (42). Topical corticosteroids (TCS) suppress the release of proinflammatory cytokines and inhibit antigen processing (47, 48). TCS is efficient as a maintenance therapy to help reduce the number of relapses. TCS is often clinically used along with moisturizers as the topical agent in wet wrap therapy (WWT) which is an efficient method to reduce and manage severe dermal flares.

Both traditional and prescription moisturizers have shown to decrease the symptoms of AE. They soften the skin and reduce the evaporation of water which prevents skin from drying out. These therapeutic interventions are the primary treatment for

mild forms of AE but are generally included in the regimen for moderate-to-severe forms, due to the reduction of inflammation and alleviation of physical discomfort.

Systemic therapies for AE

Systemic corticosteroids

Systemic corticosteroids are generally reserved as a short-term bridging therapy for acute and severe flare-ups, as they can have both short- and long-term adverse effects. A systematic corticosteroid treatment consists of an oral corticosteroid with or without an additional immune suppressant such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil (44). Three distinct clinical trials performed over varied ages and gender concluded that short-courses of systemic corticosteroid interventions could provide relief to patients with severe flare-ups or while awaiting response to other therapeutic interventions (49–51).

Phototherapy

Phototherapy as a therapeutic intervention was first introduced in 1925 in the Mayo Clinic by William Goeckerman for treatment of psoriasis (52, 53) and falls under the umbrella of systemic therapeutic options available for patients. Phototherapy treatment decreases cutaneous inflammation and is beneficial for moderate to severe AE, with limited systemic side effects (54, 55) compared to the alternatives and is suitable for patients of all age demographics.

Phototherapy, while very effective for some patients, has its limitations such as inconvenience and potential adverse effects. An inconvenience includes the access to in-office treatments, a 3-times per week regimen for patients, which can be difficult to maintain. Rare potential adverse effects include increased risk of skin cancer and flare-ups from the excessive heat (45, 56, 57). Some studies have shown that narrowband UVB can be considered an efficient treatment with patients suffering from chronic AE exhibiting at least a 50% reduction in SCORAD index scores with the phototherapy. The disease activity reversal was associated with the elimination of the inflammatory leukocytes (58).

Novel therapeutics modalities

Learnings from the clinical studies and research have driven the introduction of novel drug delivery systems and therapeutics that address the AE-related symptoms, which were previously without a cure or as effective. While these therapies do provide a promising outlook for the patients of AE, the data on their efficacy and applicability for various demographics is limited for some. A detailed review by Waligóra-Dziwak et al. provides an excellent primer on various novel biologics currently in Phase III and Phase IV clinical trials (59).

Vehicles for drug delivery

Currently, topical application of creams or ointments are the predominant vehicle for delivery of drugs for AE. Novel delivery approaches such as electrospun patches (60, 61), sprays (62), liposomes (63), nanoparticles (64), and lasers have recently been developed to enhance transdermal delivery with a focus on increasing treatment adherence while minimizing the side effects.

Biological modalities

Small-molecule inhibitors

New biologics and small-molecule inhibitors are being developed against key molecules for addressing the full spectrum of AE disease manifestations. Novel topical drugs that are currently approved or in late-stage clinical trials include, but are not limited to, Janus family protein kinases (JAK) inhibitor (ruxolitinib) (65), phosphodiesterase-4 inhibitors (crisaborole) (66, 67), and roflumilast (68).

Monoclonal antibody based therapeutics (mAb Tx)

Monoclonal antibodies that target specifically offer a focused and highly efficacious therapeutic option. mAb Tx against cytokine receptor IL-4Rα (e.g dupilumab, CM310, and CBP201) have also been developed to address unmet AE-related conditions. Th2 cytokines, IL-4 and IL-13, have a significant impact on the role in pathogenesis of allergic eczema (69–71). The IL-4Rα binds the IL-4 and IL-13 cytokines via the formation of type I and type II receptors, respectively. This binding event leads to the activation of the JAK inhibitors and its downstream counterpart—signal transducer and activator of transcription (STAT)—that acts as an activator of transcription leading to downstream signaling pathways associated with IL-14 and IL-13 (72).

JAK inhibitors can block multiple cytokine-signaling pathways and is thus the preferred target when aiming for broad immunomodulation (73). Historically, topical JAK inhibitors have exhibited fewer adverse events compared to oral JAK inhibitors (69); however, the US Food and Drug Administration (FDA) recently placed a black box warning on this class of medications due to safety concerns based on data from studies investigating tofacitinib in patients with rheumatoid arthritis (74). This news along with the inadequate guidance on communicating the merits and drawbacks of JAK inhibitors has been a source of hesitation for the dermatologists in recommending this treatment modality (75).

Conclusion

Eczema cases have seen a steady rise in the past decades with about 10% of the total population of the United States exhibiting some form of eczema. Incidences of AE have been closely linked to genetic and environmental factors leading to a loss of proper regulation of the housekeeping immunological functions, which results in eventual compromise in the dermal integrity and presentation of AE symptoms. Most of the AE patients experience a chronic, relapsing disease course with hallmark remissions and flare-ups. Clinical presentation of AE can be varied and nuanced, and early and accurate clinical diagnosis is imperative in ensuring an appropriate standard of care is provided to the patient. To this end, several biomarkers have historically been identified which have had a wide range of successes and clinical applications. While we have come a long

way in terms of the biomarker reliability and effectiveness, there is still a huge scope of improvement in their performance and applicability across the multiple facets of AE. Recent advancements in therapeutic and palliative interventions have allowed patients to manage flare-ups and minimize the impact of AE on their quality of life. These interventions range from (i) topical emollients to moisturize and soothe the affected skin areas, (ii) phototherapy to decrease cutaneous inflammation with very limited side effects, and (iii) biologic modalities, such as JAK inhibitors and antibody-based therapeutics, which directly address the cytokine signaling pathways thereby putting the brakes on the progressive inflammatory immune responses.

Developing a better understanding of the underpinnings of AE pathogenesis will allow for the development of novel treatment options with breakthrough potential, personalized treatment plans, and recovery strategies, all of which will help address the unmet needs of a huge patient demographic and allow them and their caretakers to live a more enjoyable and holistic life.

Author contributions

JL: Writing – original draft. BB: Writing – review & editing. PB: Conceptualization, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

JL, BB and PB are employees of Boehringer Ingelheim Pharmaceuticals Inc.

Generative AI statement

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Association between systemic inflammatory response index and eczema among children and adolescents: a cross-sectional study based on NHANES database

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Background: In previous studies, the systemic inflammatory response index (SIRI) might be a predictor for chronic inflammation, but the relationship between SIRI and eczema continues to be ambiguous. The objective of the study was to clarify the connection between the level of SIRI and eczema prevalence among children and adolescents.

Methods: The National Health and Nutrition Examination Survey (NHANES) was the database from which we accessed information, comprising participants aged 3–19 years. Furthermore, the investigation of the association between SIRI and eczema was carried out by using logistic regression, and restricted cubic spline models were used to explore nonlinear relationships.

Results: A total of 3,397 subjects, featuring a median age of 11.97 ± 4.87 years, were selected, and 368 (10.83%) were diagnosed with eczema among these participants. Statistically significant differences were observed in the baseline SIRI characteristics for age, race, and BMI quartiles ($p < 0.001$). In adjusted logistic regression models, the negative association between SIRI and eczema was indicated (OR: 0.83; 95% CI: 0.69–1.00, $p < 0.05$), suggesting that a one-unit increase in SIRI corresponds to a 17.17% decline in the odds of eczema prevalence. Meanwhile, a nonlinear relationship was revealed by the restricted cubic spline (RCS) between SIRI and eczema prevalence among children and adolescents. The findings of subgroup analysis suggested that there were no significant effects of any covariates on this relationship (all p for interaction > 0.05).

Conclusion: The association between SIRI and eczema prevalence in children and adolescents is negative, indicating that elevated SIRI exhibits a protective effect against eczema in children and adolescents, whereas those with low SIRI may require closer monitoring for eczema development.

KEYWORDS

systemic inflammatory response index, eczema, NHANES, association, a cross-sectional study

1 Introduction

Eczema is an inflammation of the skin condition that impacts the superficial dermis and epidermis, which is influenced by various factors (1). It is marked by dysfunction in the skin barrier and abnormally hyperactive immune responses, resulting in symptoms such as itchy rashes and dry skin (2), which can progress with age (3, 4). A study shows that the proportion of children affected by eczema can vary from 10.6% to 35.7% (5). Scratching can trigger a harmful cycle of skin damage, leading to abrasions and increased inflammation (6). Furthermore, eczema is involved with a breadth of comorbid conditions, including depression, anxiety, and sleep issues (7–10), all of which can severely impair a child's quality of life (11, 12) and create considerable financial strain for families (13). A significant aspect of eczema is the compromised function of the skin barrier (14). Reduction of critical proteins and lipids comprising the stratum corneum compromises the skin barrier function, enabling the penetration of irritants, including allergens and microbes, which may subsequently exacerbate tissue damage (15). Immune dysfunction is essential to the disease's development, noted for T helper type 2 (Th2) cells' activation and the cytokines' release like interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-9 (IL-9), and interleukin-13 (IL-13), contributing to itching, inflammation, and tissue damage (16, 17). Disruptions in the skin's microbial balance can worsen inflammation and further damage the skin barrier, often leading to an overgrowth of Staphylococcus aureus (18, 19). Environmental factors, such as changes in climate and exposure to allergens like dust mites, pollen, and pollutants, can exacerbate eczema symptoms and perpetuate inflammation (20). Genetic influences are significant in determining an individual's risk of eczema, as certain variants impact protective epidermal shield integrity, immune system modulation, and the differentiation of epidermal cells, thereby heightening the likelihood of progression to atopic dermatitis (AD) (21). While no curative treatment currently exists for eczema, ongoing investigations into novel risk factors and biomarkers hold promise for advancing assessment protocols and preventive approaches, underscoring the need to elucidate the multifactorial etiology of this condition.

Researches have indicated that eczema is a chronic inflammatory skin disorder, and evaluating circulating pro-inflammatory markers is fundamental to diagnosing and determining the prognosis of different chronic diseases (22, 23). The systemic inflammatory response index (SIRI) is an innovative inflammatory marker that incorporates immune cell subsets (24). It captures the balance between systemic inflammation and the immune response through neutrophils, lymphocytes, and monocytes, reflecting the overall systemic inflammatory state (25). The evaluation of SIRI is straightforward, relying on the counts of these three blood cell types. It is increasingly utilized to explore the connections between chronic inflammation and a range of diseases, such as metabolic disorders, cancer, and other inflammatory conditions (23, 26, 27). In a retrospective study, the findings indicated that SIRI surpassed platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), and demonstrated potential benefits for diagnostic and prognostic indicators for Bell's palsy (28). The association between the elevation of SIRI levels and the reduction of patients' overall survival (OS) with breast cancer was demonstrated in a meta-analysis (29). In another retrospective clinical study focusing on patients suffering from distal cholangiocarcinoma (dCCA) who were treated with pancreatoduodenectomy (PD), the survival analysis indicated that the lower SIRI levels, the better prognoses with statistical significance ($p < 0.001$), supporting the conclusion that SIRI serves as a reliable and independent indicator for recurrence-free survival (RFS) and 5-year OS for prognosis (30). The prospect of SII and SIRI as capable diagnostic devices for gestational diabetes mellitus (GDM) was highlighted in a recent study. The findings indicated that elevated levels of SII and SIRI in early pregnancy were associated with an amplified probability of GDM's initial stages (31).

However, the exact dynamics of the relationship between SIRI and eczema remain incompletely understood, and its prognostic potential in this disease context has yet to be firmly established. In order to investigate this latent relationship, the authors turned to the National Health and Nutrition Examination Survey (NHANES) database, seeking to provide new perspectives on eczema prevention and treatment. The authors hypothesized that SIRI could predict the prevalence of eczema in pediatric populations.

2 Methods

2.1 Data sources

NHANES is a multi-stage, ongoing cross-sectional survey, the purpose of which is to evaluate the American's health and nutrition status. NHANES is a significant undertaking of the National Center for Health Statistics (NCHS), which functions under the Centers for Disease Control and Prevention (CDC) and is assigned to compile critical health data for the country. The NHANES survey has been granted permission by the NCHS Research Ethics Review Board, and all survey participants, as well as the parents or legal guardians of those under 16 years, have given written informed consent.

2.2 Study population

In this cross-sectional investigation, we used NHANES survey data from the 2005–2006 cycle, as it is the only cycle providing comprehensive questionnaire data related to allergies, relevant to eczema as an outcome variable. Initially, 10,348 participants were considered. The exclusion criteria were: (1) lack of data on eczema diagnosis, (2) age < 3 years or >19 years, (3) missing data on SIRI, and (4) absence of data on other covariates. The screening process is illustrated in Figure 1.

2.3 Exposure variable and outcome variable

SIRI is an emerging biomarker and predictor of inflammation. The Mobile Examination Center (MEC) is the place where the medical staff collect peripheral blood samples from NHANES participants with the tool of a Beckman Coulter HMX blood

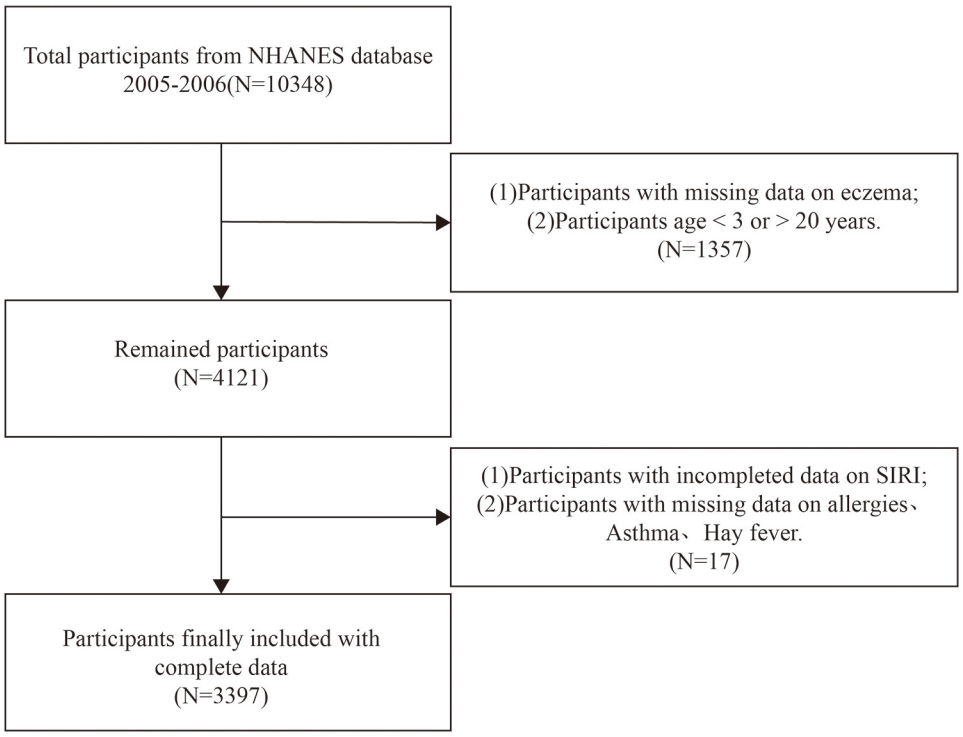

FIGURE 1
Flow chart of participants selection.

analyzer. A complete blood count was conducted to measure lymphocytes, neutrophils, and monocytes. SIRI levels were calculated as follows: (monocyte count × neutrophil count)/ lymphocyte count, with counts and results reported in units of 10^3 cells/ml (32). SIRI served as the exposure variable in this study.

The definition of eczema in this study depends on the question, "Has a doctor or other health professional ever told you that you have eczema (ek-zi-ma)?" (https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2005/DataFiles/AGQ_D.htmAGQ_D) Participants who either declined to answer or responded with "don't know" were excluded from the analysis. The question was asked before the physical examination, in the home, using the Computer-Assisted Personal Interviewing (interviewer-administered) (CAPI) system. This study used the presence or absence of eczema as the outcome variable.

2.4 Covariates

This study investigated potential confounding factors that could impact eczema. The covariates selected for inclusion were based on their relevance to eczema and the inclusion of similar studies in the past. The covariates included demographic variables [sex, age, race, family poverty income ratio (PIR)], body mass index (BMI, kg/m^2), serum total immunoglobulin E (IgE) antibodies (kU/L), hay fever, allergies, and asthma.

Racial categories were classified into four groups: Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races. The household poverty income ratio (PIR) was segmented into three groups based on the United States Department of Agriculture (USDA) food assistance program's eligibility criteria: low-income level (0.00–1.85), medium-income level (1.85–3.50), and high-income level (3.50+) (33). According to the guidelines proposed by the World Health Organization (WHO) in 2008 (34), BMI is grouped into three categories: normal weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Serum total IgE antibodies are classified into low-level groups (<100 kU/L) and high-level groups (≥100 kU/L).

The medical comorbidities assessed as potential risk factors for eczema in this study included hay fever, allergies, and asthma. Participants who responded "yes" to these questions were classified as "ever had", while those who indicated "no" or "don't know" were categorized as "never had".

2.5 Statistical analysis

In this research, the NHANES database was applied. Continuous variables were calculated and displayed as means and standard deviations (SD), and categorical variables were expressed as numbers and percentages [(*n*)%]. *T*-tests and Chi-Square tests were respectively utilized to analyze continuous and categorical variables, and to examine the association between SIRI and eczema, multivariate linear regression was conducted with SIRI scores treated as a continuous variable, and three distinct models were subjected to logistic regression to analyze the association between SIRI scores and eczema, with the results presented as odds ratios (ORs) and 95% confidence intervals (CIs). In Model 1, no adjustments were applied to the variables. Adjustments for sex, age,

race, and PIR were applied in Model 2. Every covariate, encompassing sex, age, race, PIR, BMI, serum total IgE, hay fever, allergies, and asthma, is accounted for in Model 3. We also used restricted cubic splines(RCS) to detect the nonlinear effect of SIRI on eczema. For the subgroup analysis, stratified factors including sex, age, race, PIR, BMI, serum total IgE, hay fever, allergies, and asthma were utilized as potential effect modifiers. To control for Type I errors, we implemented false discovery rate (FDR) correction for multiple hypothesis testing in subgroup analysis. We set the significance threshold at $\alpha = 0.05$ and calculated FDR-adjusted *q-values* using the Benjamini-Hochberg (BH) method. In the process of handling missing data, we used multiple imputation to improve data integrity and the reliability of the analysis results, with skewed distributions filled in using the median and normally distributed data using the mean. All data analyses were performed using R software version 4.2.1 and Empower Stats (version 2.0), and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of participants

A total of 3,397 participants ranging from 3 to 19 years of age were analyzed from the 2005–2006 NHANES database, the selected subjects featuring a median age of 11.97 ± 4.87 years. This sample comprised 1,686 boys (49.63%) and 1,711 girls (50.37%). Among these participants, 368 (10.83%) were diagnosed with eczema. Significant statistical differences ($p < 0.001$) were noted in baseline SIRI characteristics based on age, race, and BMI quartiles. A statistical difference ($p < 0.05$) was ascertained concerning the baseline SIRI characteristics on the subject of "whether or not you have ever had allergies". The group with the highest SIRI showed both increased BMI and a higher prevalence of allergies, relative to the lowest SIRI group. The baseline characteristics are illustrated in Table 1.

3.2 Analysis of the relationship between SIRI and eczema

Table 2 describes the relationship between SIRI and eczema. Current statistical results showed a correlation between higher levels of SIRI and a reduced risk of eczema ($p < 0.05$). This relationship was significant in the unadjusted model 1 (OR: 0.66; 95% CI: 0.55–0.80, $p < 0.001$). In model 2, which was adjusted for age, sex, race, and PIR, the association remained statistically significant ($p < 0.05$) with OR: 0.83, 95% CI: 0.69–0.99. In the fully adjusted model 3, SIRI still exhibited a negative correlation with eczema (OR: 0.83; 95% CI: 0.69–1.00, $p < 0.05$), suggesting that a one-unit increase in SIRI corresponds to a 17.17% decrease in the odds of eczema prevalence. This significant association persisted after performing a quartile analysis of SIRI, with model 3 results demonstrating that

TABLE 1 Basic characteristics of participants by systemic inflammation response index among children and adolescents.

Characteristics	Systemic inflammation response index				*p*-value
	Q1 (*N* = 827)	Q2 (*N* = 869)	Q3 (*N* = 841)	Q4 (*N* = 860)	
Age (years)	9.88 ± 4.83	11.43 ± 4.77	12.59 ± 4.61	13.90 ± 4.37	<0.001
Sex, (%)					0.195
Male	402 (48.61)	457 (52.59)	417 (49.58)	410 (47.67)	
Female	425 (51.39)	412 (47.41)	424 (50.42)	450 (52.33)	
Race/ethnicity, (%)					<0.001
Mexican American	199 (24.06)	273 (31.42)	296 (35.20)	369 (42.91)	
Other Hispanic	25 (3.02)	21 (2.42)	31 (3.69)	35 (4.07)	
Non-Hispanic White	152 (18.38)	236 (27.16)	268 (31.87)	226 (26.28)	
Non-Hispanic Black	399 (48.25)	284 (32.68)	207 (24.61)	188 (21.86)	
Other races	52 (6.29)	55 (6.33)	39 (4.64)	42 (4.88)	
Family PIR	2.05 ± 1.49	2.16 ± 1.56	2.12 ± 1.44	1.98 ± 1.44	0.057
BMI	18.99 ± 4.63	20.76 ± 5.77	22.57 ± 6.38	24.26 ± 6.96	<0.001
IgE (kU/L)	201.73 ± 446.84	204.57 ± 543.89	178.43 ± 371.38	182.99 ± 382.31	0.522
Allergies, (%)					0.039
Yes	176 (21.28)	215 (24.74)	195 (23.19)	233 (27.09)	
No	651 (78.72)	654 (75.26)	646 (76.81)	627 (72.91)	
Asthma, (%)					0.796
Yes	124 (14.99)	144 (16.57)	133 (15.81)	142 (16.51)	
No	703 (85.01)	725 (83.43)	708 (84.19)	718 (83.49)	
Hay fever, (%)					0.527
Yes	30 (3.63)	34 (3.91)	30 (3.57)	23 (2.67)	
No	797 (96.37)	835 (96.09)	811 (96.43)	837 (97.33)	
Eczema, (%)					<0.001
Yes	120 (14.51)	110 (12.66)	77 (9.16)	61 (7.09)	
No	707 (85.49)	759 (87.34)	764 (90.84)	799 (92.91)	

Mean ± SD for continuous variables: the *P* value was calculated by the weighted linear regression model; (%) for categorical variables: the *P* value was calculated by the weighted chi-square test. PIR, the ratio of income to poverty, BMI, body mass index; Q, quartile.

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TABLE 2 Associations between systemic inflammation response index and eczema among children and adolescents.

Exposure	Model 1 [β (95% CI)], *p* value	Model 2 [β (95% CI)], *p* value	Model 3 [β (95% CI)], *p* value
SIRI (continuous)	0.66 (0.55,0.80), <0.001	0.83 (0.69,0.99), 0.04	0.83 (0.69,1.00), 0.04
SIRI (quartile)			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	0.85 (0.65, 1.13), 0.27	0.91 (0.69, 1.22), 0.54	0.97 (0.72, 1.31), 0.84
Quartile 3	0.59 (0.44, 0.80), <0.001	0.67 (0.49, 0.92), 0.01	0.79 (0.57, 1.10), 0.16
Quartile 4	0.45 (0.33, 0.62), <0.001	0.58 (0.41, 0.81), 0.00	0.68 (0.47, 0.97), 0.03
P for tend	<0.001	<0.001	<0.001

Model 1: no covariates were adjusted. Model 2: age, sex, race, and PIR were adjusted. Model 3: age, sex, race, PIR, BMI, serum total IgE antibody, allergies, asthma, and hay fever were adjusted. PIR, the ratio of income to poverty, BMI, body mass index; Q, quartile; SIRI, systemic inflammatory response index.

those in the top SIRI quartile (Q4) had a 32.49% reduction in eczema prevalence compared to individuals in the lowest quartile (Q1) (OR: 0.68; 95% CI: 0.47–0.97, $p < 0.05$).

In addition, the negative association was reinforced by the restricted cubic splines between SIRI and eczema prevalence among children and adolescents. Figure 2 shows the results of the restricted cubic splines after outlier values were removed. The nonlinear association was observed in both unadjusted (Figure 2A) (p -value < 0.001, p -nonlinear < 0.05) and adjusted models (Figure 2B) (p –value > 0.05, p –nonlinear > 0.05).

3.3 Subgroup analysis

A subgroup analysis was conducted to determine whether the connection between SIRI and eczema remained consistent across various population groups. The findings suggested that there were no significant effects of any variables on this relationship (p for interaction all > 0.05). To control for Type I errors, we implemented FDR correction for multiple hypothesis testing. All *q-values* exceeded the threshold of $\alpha = 0.05$, indicating no statistically significant findings. This multiple testing correction further reduced the risk of false positive results. As shown in Figure 3, all the stratification factors, such as sex, age, race, BMI, serum IgE antibodies, asthma, hay fever, and allergies, do not significantly affect the negative correlation between SIRI and eczema.

4 Discussion

This investigation employed a cross-sectional approach, involving 3,397 youth aged 3–19 from the 2005–2006 NHANES database. A negative correlation was found between SIRI and eczema prevalence, illustrating that an upsurge in SIRI levels is tied to a lower eczema prevalence in children and adolescents. No significant associations were identified between this correlation and covariates such as sex, age, race, serum IgE antibodies, BMI, asthma, hay fever, or allergies. Subgroup analysis and interaction testing confirmed that this association remained consistent across different subgroups.

To our knowledge, this study is the first investigation to analyze the connection between SIRI and eczema among children and adolescents. Systemic inflammation is a key characteristic of eczema, and routine blood tests, along with derived inflammatory indicators, are frequently employed to evaluate inflammatory conditions (17). Previous researches have explored the association between inflammatory markers from blood counts and a series of skin diseases. A clinical observation revealed a positive correlation between NLR and PLR concerning the activity of Bullous pemphigoid (BP) (35). SIRI and other blood count-derived inflammatory markers were recognized as effective indicators for

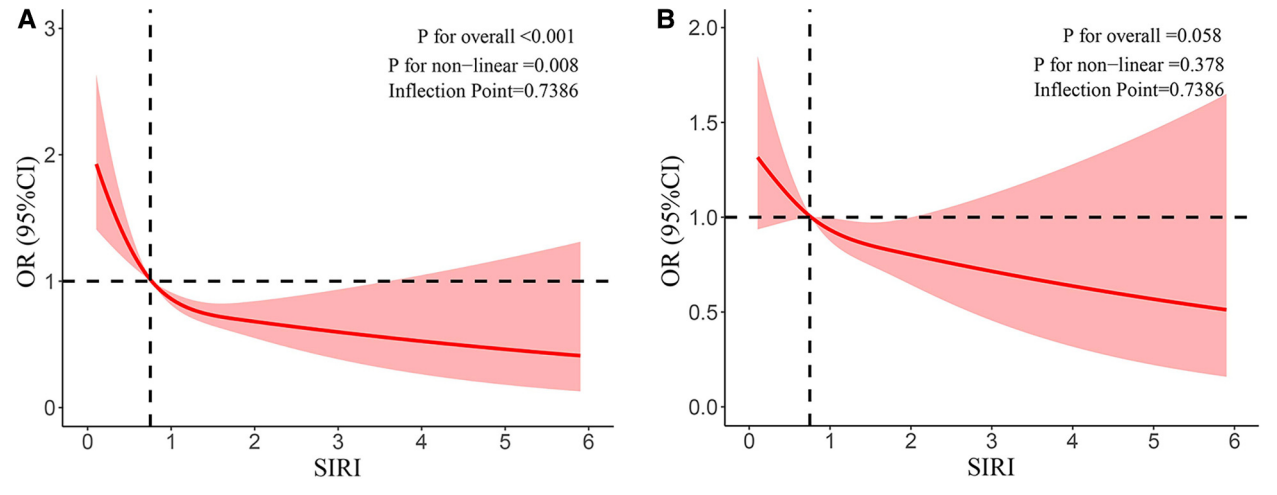

FIGURE 2
(A) Results of RCS after outlier values were removed (unadjusted model). (B) Results of RCS after outlier values were removed (adjusted model).

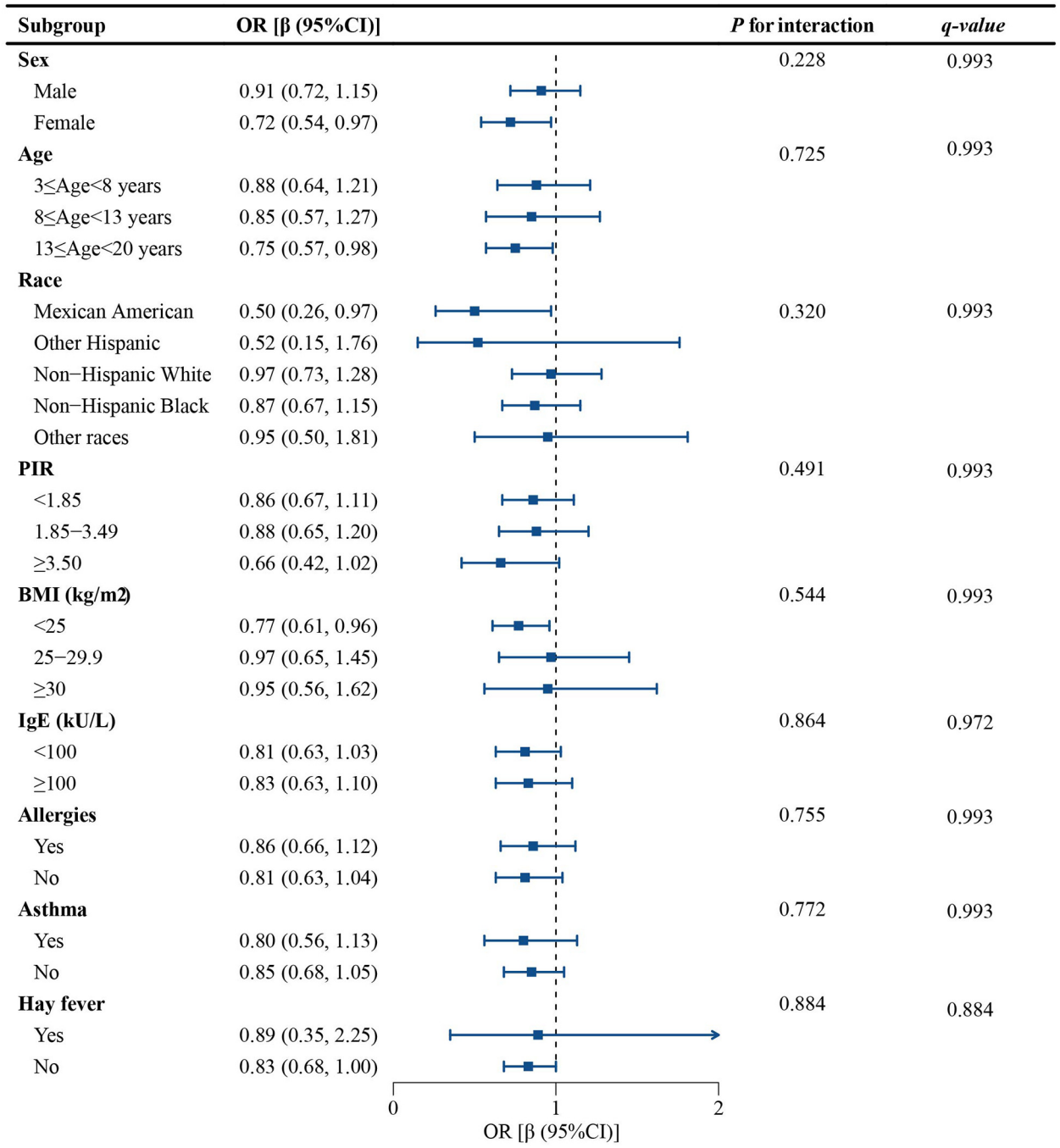

FIGURE 3.
Results of subgroup analysis.

assessing systemic inflammation and the severity of psoriasis (36). A cross-sectional study from NHANES also contributed to the findings that SIRI and psoriasis prevalence are positively associated (37). Additionally, a strong positive connection was observed between the psoriasis area severity index (PASI) and SIRI in a multicenter retrospective study, concluding that SIRI could be identified as an independent predictor for hyperresponse (38).

Potential underlying mechanisms for the negative association between SIRI and eczema in children and adolescents are summarized as follows. Firstly, the inverse correlation between SIRI and eczema prevalence may represent a protective effect conferred by relatively enhanced T helper type 1 (Th1) activity against the Th2-dominant pathophysiology of eczema. Th1 cells and Th2 cells represent two distinct subsets of T helper cells. During disease development, significantly overexpressed Th2 cells dominate the immune response (39). Earlier studies indicated that enhanced Th1 reactivity exerts protective effects against eczema development (40). The cytokine interferon-

gamma (IFN-γ) produced by Th1 cells can inhibit Th2 cell differentiation, suppressing inflammatory responses (41). Therefore, individuals with elevated SIRI levels may exhibit relatively stronger Th1 activity. Secondly, individuals with low SIRI may exhibit impaired regulatory T (Treg) cells function. The fundamental immunoregulatory mechanism of Treg cells involves the secretion of inhibitory cytokines, like transforming growth factor-beta (TGF-β), attenuating inflammatory responses in eczema (42). Consequently, individuals with low SIRI may have insufficient Treg cell numbers or functional deficiency, which can lead to compromised immune tolerance, potentially resulting in compromised immune tolerance and subsequent exacerbation of eczema pathogenesis. Thirdly, SIRI levels may serve as an indicator of the host's immune reactivity to the cutaneous microbiome. In healthy skin, microbial diversity promotes balanced innate immune activation, resulting in moderate SIRI elevation that appears to confer protection against eczema development. Fourthly, the inverse correlation between SIRI and eczema prevalence observed in pediatric populations demonstrates marked age specificity. This phenomenon may stem from the ongoing dynamic development of the immune system during childhood and adolescence. The establishment of cutaneous microbiota during early life remains incomplete, elevated SIRI levels may indicate enhanced microbial recognition capacity. Finally, distinct dietary patterns may influence the SIRI, with pro-inflammatory diets potentially elevating eczema risk through the induction of systemic low-grade inflammation. Our findings may suggest that increasing intake of whole grains and vegetables while reducing consumption of high-sugar and trans-fatty acid foods could potentially prevent eczema development.

The findings of this research indicated that significant alterations in SIRI show an independent association with eczema prevalence in children and adolescents based on the NHANES database. Moreover, a non-linear relationship was shown between SIRI and eczema prevalence. This study represents the first investigation with a large sample examining the association between SIRI levels and eczema prevalence in pediatric and adolescent populations. Utilizing data from the nationally representative NHANES database strengthened the generalizability of our findings. The comprehensive adjustment for potential confounding variables enhanced the validity of the observed associations.

Several constraints also appear in this study. First, the diagnostic criteria for eczema in this study were limited to questionnaire-based assessments available in the NHANES database, which may lack diagnostic precision compared to comprehensive clinical evaluation. And potential confounding factors have not been ruled out, relevant studies have shown that local use of steroids (43), or serum vitamin D levels (44) can have an impact on SIRI-related parameters. Second, although this study accounted for various confounding variables, the conceivable implications of unintegrated covariates remain. Third, we did not conduct a multicollinearity test to rule out the mutual influence between covariates. Fourth, our analysis did not incorporate sampling weights, which could enhance the accuracy of the findings. Future studies that incorporate weights are likely to provide a better representation of the national situation. Moreover, the cross-sectional study is unable to demonstrate a cause-and-effect correlation between SIRI and eczema, highlighting the necessity for further investigation.

Our findings suggest several critical next steps. First, multi-omics analyses (e.g., transcriptomics, metabolomics) could be performed in patients with eczema exhibiting low SIRI to identify key signaling pathways. Second, a prospective cohort study may be adopted to verify whether low SIRI can predict the onset or recurrence of eczema. Third, randomized controlled trials (RCTs) could be conducted to monitor the dynamic changes in SIRI and their association with eczema severity. Finally, whether dietary interventions can improve eczema by elevating the SIRI index and modulating immune balance requires further clinical investigation.

5 Conclusion

The association between SIRI and eczema prevalence in children and adolescents is negative. The results indicate that elevated SIRI exhibits a protective effect against eczema in children and adolescents, whereas those with low SIRI may require closer monitoring for eczema development. Nonetheless, the current results are unable to demonstrate a cause-and-effect relationship between the factors, highlighting the necessity for further longitudinal investigations to corroborate the authors' results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

TS: Writing – original draft, Writing – review & editing, Data curation, Formal analysis. YD: Methodology, Resources, Software, Writing – review & editing. KX: Conceptualization, Supervision, Writing – review & editing. SY: Writing – review & editing, Project administration, Resources, Supervision. RY: Project

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between vitamin B_6 status and eczema in children and adolescents: results from the NHANES database

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Aim: There are few studies investigating the relationship between vitamin B6 status and the odds of eczema in children and adolescents. Hereby, this study aims to explore the association between vitamin B6 status and eczema in children and adolescents.

Methods: A cross-sectional study was conducted based on National Health and Nutrition Examination Surveys (NHANES) 2005–2006. The vitamin B6 status was assessed based on levels of 4-PA, PLP and vitamin B6 metabolic rate (4-PA/PLP) by high-performance liquid chromatography. The weighted univariate and multivariate logistics regression models were adopted to explore the association between vitamin B6 status with and the odds of eczema in children and adolescents, with odds ratio (ORs) and 95% confidence intervals (CIs). The subgroup analysis based on age, gender, atopy and body mass index (BMI) were further performed to explore whether the association between vitamin B6 status and eczema in children and adolescents remains robust.

Results: A total of 2,256 eligible children and adolescents were included for further analysis, with the mean aged of 11.81 ($\pm$0.09) years old. Among them, 247 (10.95%) had eczema. After adjusted all covariates, we observed high 4-PA was associated with high odds of eczema (OR = 1.57, 95%CI: 1.01–2.44, $P = 0.044$). High 4-PA/PLP was associated with high odds of eczema (OR = 1.46, 95%CI: 1.05–2.03, $P = 0.028$); however, no significant associations were found between dietary vitamin B6 intake and serum PLP level (all $P > 0.05$). The results of subgroup analysis shown that the association between 4-PA and 4-PA/PLP remain robust, especially among children and adolescents aged 6–11 years old, boys, with atopy, and with overweight/obese.

Conclusion: Our study observed that high 4-PA and high vitamin B6 metabolic rate were associated with increased odds of eczema in children and adolescents. Maintaining high vitamin level may have potential benefits in reducing odds for eczema in children and adolescents.

KEYWORDS

vitamin B6, 5′-pyridoxal phosphate, 4-pyridoxic acid, childhood eczema, NHANES database, vitamin B6

Introduction

Eczema, featured by defective skin barrier function, is a chronic relapsing skin inflammatory disease worldwide. Approximately, the prevalence of eczema in children has reached 20%, imposing a burden on affected children, families, as well as health care system (1–3). Previous studies reported that the consequences of eczema reach beyond the skin and past childhood and are related to an increased risk of a range of diseases in adulthood, including obese, cardiovascular disease (CVD), and autoimmune disease (4, 5). Hence, positive identification and intervention of the risk factor of childhood eczema is of great significance to reduce the disease burden of childhood eczema to the public health-care systems.

Eczema as an immune disease is closely related to the nutritional changes (6). Vitamin B_6, including pyridoxine, pyridoxal, and pyridoxamine, is an essential water-soluble vitamin of the B vitamins acting a vital effect in normal brain development and immune system health (7). Previous epidemiological studies suggested that vitamin B6 deficiency is associated with polyneuropathy and dermatitis (8, 9). However, the association between vitamin B6 and skin diseases remains controversial. Miyake et al. (10) reported that after adjustment for confounding factors, there were no evident relationships between vitamin B6 intake and childhood eczema. Therefore, the association between vitamin B6 and childhood eczema needs to be further studied. In the naturally occurring form of vitamin B6, 5'-pyridoxal phosphate (PLP) is the biologically active form of vitamin B6. Meanwhile, 4-pyridoxic acid (4-PA) is the major catabolite of vitamin B6 metabolism. PLP and 4-PA are widely used clinical biomarkers to characterize vitamin B6 levels, which can more accurately reflect the body's vitamin B6 levels than dietary vitamin B6 intake (11). Recently, the ratio of 4-PA to PLP (4-PA/PLP) was considered as a valuable biomarker for assessing vitamin B6 status *in vivo*, and several epidemiologic studies have reported the association between the 4-PA/PLP and some diseases (12–14). Less is known, however, the association between 4-PA, PLP and the ratio of 4-PA to PLP with eczema in children and adolescents.

Herein, based on above background, we explored the association between vitamin B6-related biomarkers with the occurrence of eczema in children and adolescents, aiming to provide data support for the targeted prevention of childhood eczema in the future.

Methods

Study design and participants

The study children and adolescents were from the National Health and Nutrition Examination Surveys (NHANES) and data of one survey circle (2005–2006) were extracted. NHANES, a nationally representative survey, aims to assess the nutrient and health status for U.S. civilian population. This database contains personal interviews, laboratory test, and standardized medical examinations (15). The National Health and Nutrition Examination Survey (NHANES) employs a complex, multistage probability sampling design to obtain a nationally representative sample of the U.S. civilian noninstitutionalized population. The survey first selects primary sampling units (counties or groups of contiguous counties), then segments (typically city blocks) within these units, followed by randomly selected households within segments, and finally individuals within households based on demographic characteristics. This design ensures proper representation across age, gender, and racial/ethnic groups. Written informed consent was obtained from all participants, and the survey protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board.

In present study, 2,849 children and adolescents aged 6–17 years old were initially included. Among them, 262 children missing dietary vitamin B6 intake information, 323 children and adolescents missing data of PLP and 4-PA and 8 children and adolescents missing diagnostic information of eczema were further excluded. Finally, 2,256 eligible children and adolescents were included for final analysis.

Diagnosis of eczema in children and adolescents

The diagnosis of eczema in children and adolescents was based on the self-reported NHANES questionnaire. Children and adolescents answered "yes" to "Has a doctor or other health professional ever told you that you have eczema?" were diagnosed with eczema (16). For children aged 6–8 years old, the questionnaires were responded by their guardian; children aged 9–11 years old were accompanied by their guardian to assist in responding, while adolescents aged 12–17 years old were responded by themselves.

Assessment of dietary vitamin B_6 intake

The data of dietary vitamin B6 were obtained by the 24-h dietary recall interview in the NHANES. This recall interview requires subjects to report all food and beverages consumed prior 24-h to the interview. Dietary consumption data were converted to the United States Department of Agriculture (USDA) standard reference codes, and dietary intake were linked to the USDA's Food and Nutrient Database for Dietary Studies (FNDDS) (17). In present study, the vitamin B6 intake were categorized to three levels according to its tertiles: <1.18, 1.18–1.97 and ≥1.97 mg.

Measurement serum PLP and 4-Pa concentrations

The serum PLP (nmol/L) and 4-PA (nmol/L), as well as their ratio 4-PA/PLP were used to evaluate vitamin B_6 status. The 4-PA and PLP were determined using high-performance liquid

chromatography (HPLC). Further detailed laboratory measurement procedures and quality control can be accessed at the Mobile Examination Center on the NHANES website (17). The higher the vitamin B6 metabolic rate expressed as the 4-PA/PLP value, the lower the vitamin B6 level in the body (18).

Potential covariates

In present study, we extracted social demographic information [age, gender, race, poverty-to-income ratio (PIR) and household education level], lifestyle (physical activity, screen time and tobacco exposure) complications (atopy, asthma, and hay fever), physical examination [body mass index (BMI) and birth weight], and laboratory parameters [4-PA, PLP, CRP (c-reactive protein)].

The physical activity (yes/no) of children aged 6–11 years old was assessed by the question "How many times per week does your play or exercise enough to make him/her sweat and breathe hard?" and more than one time was defined as "yes"; for adolescents aged 12–17 years old, the "yes" to "Over the past 30 day you walked or bicycled as part of getting to and from work, or school, or to do errands?" was defined as doing physical activity. Screen time was calculated based on the question "Over the past 30 days, on average about how many hours per day did you sit and watch TV, videos, use a computer or play computer games?" (< 3 h/≥3 h). The overall NHANES 2005–2006 Allergy Component is designed to assess the allergen exposure, allergic sensitization, allergic symptoms and diseases, and their complex relationship in the general U.S. population. Accordingly, in present study, atopy was defined as a binary variable indicating serum levels ≥0.35 kU/L for any of the 19 specific IgE antibodies measured (LBXID2, LBXID1, LBXIE1, LBXIE5, LBXII6, LBXIM6, LBXF13, LBXIF1, LBXIF2, LBXIW1, LBXIG5, LBXIG2, LBXIT7, LBXIT3, LBXF24, LBXIM3, LBXW11, LBXE72, LBXE74). The complete documentation of these IgE codes, including their corresponding allergens and detection methodologies, is available in the official NHANES laboratory manual: https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2005/DataFiles/AL_IGE_D.htm#LBXID1. Children and adolescents who answered "yes" to the question "Has a doctor or other health professional ever told you that you had asthma?" were defined as having asthma history. Birth weight was categorized into four groups: <5.5, 5.5–8.9, ≥ 9 and unknown (19). Tobacco exposure was assessed by the question "Does anyone smoke in the home?" (yes/no). BMI was converted to a BMI Z-score accounting for age and gender using recommended CDC percentiles. A BMI Z-score of ≥85th percentile and <95th percentile indicates overweight status, and a BMI Z-score of ≥95th percentile indicates obesity (20).

Statistical analysis

Continuous data were expressed as mean and standard error (S.E.), and the weighted t-test was used for comparison between groups. Categorical variables were described as the number and percentage [*N* (%)], and comparisons between groups used the weighted chi-square test or Fisher's test. The univariate logistics regression analysis was conducted to screen the covariates related to eczema in children and adolescents (Supplementary Table S1). The weighted multivariate logistics regression analysis was utilized to evaluate the association between vitamin B_6 status and eczema, with odds ratio (ORs) and 95% confidence intervals (CIs). Multivariate imputation by chained equations (MICE) was used to missing data imputation. Sensitivity analysis was performed before and after missing data imputation (Supplementary Table S2). Model 1 adjusted age, gender and race; model 2 adjusted age, race, asthma history, hay fever and birth weight. Subgroups analysis based on different age, gender, atopy and BMI were further performed to evaluate whether the association between vitamin B_6 status and eczema remain robust. All statistical analyzes were performed using R v 4.20 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v 9.4 (SAS Institute, Cary, North Carolina) software. Two-sided *P*-value <0.05 was considered statistically significant.

Results

Characteristics of study population

The flow chart of population screening was shown in Figure 1. Finally, 2,256 eligible children and adolescents were included, with the mean age of 11.81 (±0.09) years old. Among them, 247 (10.95%) had eczema. The level of 4-PA in children and adolescents with eczema was significant higher than in children and adolescents without eczema [32.55 (±1.61) nmol/L *vs.* 27.88 (±1.32) nmol/L)]. Difference was found between age, race, the history of asthma and hay fever, the level of birth weight and 4-PA between eczema and non-eczema groups (all $P < 0.05$). Characteristics of included children and adolescents were shown in Table 1.

Association between vitamin B6 status and eczema

We employed two weighted multivariate logistics regression models to evaluate the association between dietary vitamin B6, 4-PA, PLP, and 4-PA/PLP with eczema, as depicted in Table 2. In fully adjusted model 2, no significant associations were observed between dietary vitamin B_6 intake and PLP levels and the odds of eczema ($P > 0.05$). Compare to children and adolescents with low and medium 4-PA levels, those with high 4-PA levels had a high odds of eczema (OR = 1.57, 95%CI: 1.01–2.44, $P = 0.044$). Moreover, the results also shown that a high ratio of 4-PA to PLP was associated with a high odd of eczema (OR = 1.46, 95%CI: 1.05–2.03, $P = 0.028$).

Subgroup analysis based on different age, gender, atopy and BMI

Subgroup analysis were performed to further evaluate whether the association between vitamin B6 status and eczema remain

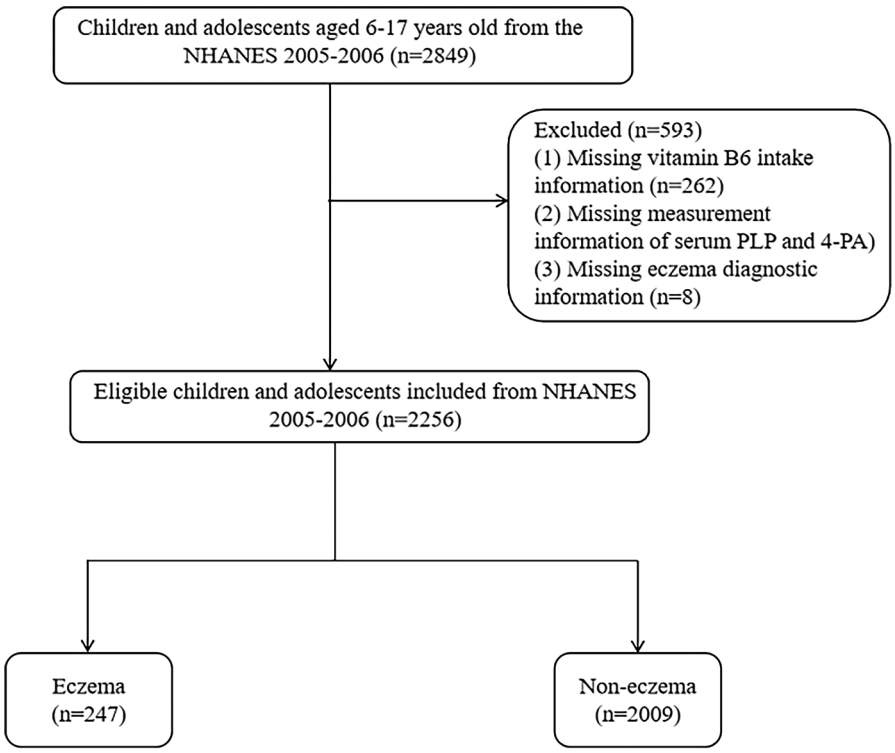

FIGURE 1
Participant selection flowchart for the analysis of vitamin B6 status and eczema association in US children (NHANES 2005–2006). Note: NHANES, National Health and Nutrition Examination Surveys; PLP, pyridoxal 5′-phosphate; 4-PA, 4-pyridoxic acid.

robust. When stratified by gender and BMI, we found the association between the ratio of 4-PA to PLP and eczema remain robust, especially in boys (OR = 2.61, 95%CI: 1.52–4.50, $P = 0.002$) and children and adolescents with overweight/obese (OR = 2.07, 95%CI: 1.07–4.02, $P = 0.033$). When stratified by age and atopy, we found the association between 4-PA and eczema also remain robust, especially in children and adolescents aged 6–11 years (OR = 1.70, 95%CI: 1.08–2.68, $P = 0.112$) and with atopy (OR = 2.06, 95%CI: 1.18–3.61, $P = 0.015$) (Figures 2–5).

Discussion

Based on the findings of NHANES database, we found positive correlation between serum 4-PA levels and 4-PA/PLP with the odds of eczema in children and adolescents. No significant associations were found between dietary B6 intake and serum PLP with the odds of eczema in this population. These associations remain robust after stratified analysis based on age, gender, atopy and BMI. To our best knowledge, this was the first cross-sectional to explore the association between biomarkers of vitamin B6 and eczema in children and adolescents in the United States.

Primary atopic diseases (PAD) are monogenic inherited diseases characterized by allergic or atopic-related symptoms. Atopic dermatitis, usually eczema, is one of the skin lesions characteristic of PAD. More and more researchers have found that disorders of vitamin levels are related to skin conditions, and systemic and topic treatments have shown significant improvements. Vitamin B6 is a water-soluble vitamin that can be obtained from a variety of foods and has been shown to be closely linked to inflammation and immunity levels in the body (21). A cross-sectional from the Korean Child Health and Environment enrolled 2,333 children aged 6–8 years to investigate the association between dietary methyl donor intake with asthma and atopy (22). Dietary methyl donors participate in homocysteine metabolism, providing methyl groups to the body and thus maintaining the balance of methyl reaction. Vitamin B6 has been shown to be an important dietary methyl donor (23). That study found high vitamin B6 intake were associated with the reduced risk of atopy as well as asthma symptoms. A small cohort study from rural southwestern Sweden investigated the association between prenatal diet and allergic disorders, including childhood eczema. The authors reported that vitamin B6 metabolism was significantly associated with the risk of future allergic disease (24). However, the association between vitamin B6 and atopy diseases remain clinically controversial. The Osaka Maternal and Child Health Study prospectively explored the association between maternal vitamin B intake during pregnancy and infant wheeze and eczema and reported that after adjusted several confounding, there was no significant evidence to support the association between vitamin B6 intake and the risk of wheeze

TABLE 1 Characteristics of children and adolescents.

Variable	Total (*n* = 2,256)	Eczema (*n* = 247)	Non-eczema (*n* = 2,009)	*P*
Age, years, mean (S.E)	11.81 (0.09)	10.96 (0.27)	11.94 (0.10)	0.004
Gender, *n* (%)				0.651
Female	1,138 (48.83)	130 (50.89)	1,008 (48.52)	
Male	1,118 (51.17)	117 (49.11)	1,001 (51.48)	
Race/ethnicity, *n* (%)				<0.001
Non-Hispanic White	614 (62.60)	82 (67.11)	532 (61.93)	
Non-Hispanic Black	700 (13.62)	115 (18.14)	585 (12.95)	
Mexican American	759 (12.66)	27 (3.54)	732 (14.00)	
Other race	183 (11.13)	23 (11.21)	160 (11.11)	
PIR, *n* (%)				0.081
≤3.5	1,724 (64.32)	167 (57.37)	1,557 (65.34)	
>3.5	532 (35.68)	80 (42.63)	452 (34.66)	
Household education level, *n* (%)				0.076
Less than 9th Grade	278 (5.90)	9 (3.57)	269 (6.24)	
9–11th Grade	428 (12.52)	40 (12.05)	388 (12.59)	
High school grad/GED or equivalent	532 (25.29)	58 (22.04)	474 (25.77)	
Some college or AA degree	620 (31.67)	74 (29.18)	546 (32.04)	
College graduate or above	398 (24.63)	66 (33.16)	332 (23.37)	
Physical activity, *n* (%)				0.629
No	82 (2.49)	6 (2.01)	76 (2.56)	
Yes	2,174 (97.51)	241 (97.99)	1,933 (97.44)	
Screen time, *n* (%)				0.590
<3 h	757 (41.04)	83 (42.47)	674 (40.83)	
≥3 h	1,499 (58.96)	164 (57.53)	1,335 (59.17)	
Atopy, *n* (%)				0.060
No	1,077 (53.78)	95 (47.19)	982 (54.76)	
Yes	1,179 (46.22)	152 (52.81)	1,027 (45.24)	
Asthma, *n* (%)				<0.001
No	1,880 (82.42)	171 (71.14)	1,709 (84.08)	
Yes	376 (17.58)	76 (28.86)	300 (15.92)	
Hay fever, *n* (%)				<0.001
No	2,168 (95.76)	222 (89.83)	1,946 (96.63)	
Yes	88 (4.24)	25 (10.17)	63 (3.37)	
Birth weight, pounds, *n* (%)				0.002
<5.5	205 (8.46)	31 (10.77)	174 (8.11)	
5.5–8.9	1,338 (62.78)	163 (72.32)	1,175 (61.37)	
≥9	152 (7.14)	10 (3.54)	142 (7.67)	
Unknown	561 (21.62)	43 (13.37)	518 (22.84)	
BMI, *n* (%)				0.513
Normal	1,368 (65.54)	154 (65.67)	1,214 (65.51)	
Overweight	364 (15.54)	50 (17.56)	314 (15.25)	
Obesity	524 (18.92)	43 (16.76)	481 (19.24)	
Vitamin B_6 intake, mg, Mean (S.E)	1.80 (0.05)	1.66 (0.13)	1.82 (0.05)	0.187
Vitamin B_6 intake, mg, *n* (%)			0.125	
<1.18	751 (32.93)	96 (39.59)	655 (31.95)	
1.18–1.94	742 (33.96)	86 (32.82)	656 (34.13)	
≥1.94	763 (33.11)	65 (27.59)	698 (33.92)	
Energy intake, kcal, mean (S.E)	2,182.21 (34.85)	2,117.27 (78.25)	2,191.80 (35.85)	0.359
4-PA, nmol/L, mean (S.E)	28.48 (1.19)	32.55 (1.61)	27.88 (1.32)	0.041
4-PA, nmol/L, *n* (%)				0.059
<16.26	1,018 (32.84)	93 (25.34)	925 (33.95)	
16.26–28.49	679 (34.05)	83 (36.98)	596 (33.61)	
≥28.49	559 (33.11)	71 (37.68)	488 (32.44)	
PLP, nmol/L, mean (S.E)	64.60 (1.72)	69.20 (4.12)	63.92 (1.58)	0.168

(*Continued*)

TABLE 1 Continued

Variable	Total (*n* = 2,256)	Eczema (*n* = 247)	Non-eczema (*n* = 2,009)	*P*
PLP, nmol/L, *n* (%)				0.882
<41.69	865 (33.00)	95 (32.34)	770 (33.10)	
41.69–68.80	765 (33.69)	83 (32.75)	682 (33.83)	
≥68.80	626 (33.31)	69 (34.91)	557 (33.08)	
Ratio of 4-PA to PLP, mean (S.E)	0.46 (0.01)	0.50 (0.02)	0.46 (0.01)	0.099
Ratio of 4-PA to PLP *n* (%)				0.272
<0.33	887 (32.97)	84 (28.51)	803 (33.63)	
0.33–0.48	770 (33.99)	88 (34.08)	682 (33.97)	
≥0.48	599 (33.04)	75 (37.40)	524 (32.40)	
CRP, mg/dl, mean (S.E)	169.52 (11.72)	199.51 (21.19)	165.08 (14.23)	0.255
Tobacco exposure, *n* (%)				0.194
No	1,866 (83.17)	201 (85.71)	1,665 (82.79)	
Yes	390 (16.83)	46 (14.29)	344 (17.21)	

S.E, standard error; PIR, poverty-to-income ratio; PIR ≤3.5, medium and low income; PIR >3.5, high income; GED, general equivalent diploma; BMI, body mass index; 4-PA, 4-pyridoxic acid; PLP, pyridoxal 5'-phosphate; CRP, C-reactive protein.

TABLE 2 Correlations between biomarkers of vitamin B_6 status and eczema in children and adolescents.

Variables	Model 1		Model 2	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Vitamin B_6 intake, mg				
<1.18	Ref		Ref	
1.18–1.97	0.77 (0.51–1.15)	0.185	0.76 (0.51–1.15)	0.182
≥1.97	0.71 (0.42–1.19)	0.177	0.70 (0.45–1.09)	0.110
4-PA, nmol/L				
<16.22	Ref		Ref	
16.22–26.65	1.61 (1.04–2.51)	0.036	1.55 (0.98–2.45)	0.057
≥26.66	1.67 (1.07–2.60)	0.027	1.57 (1.01–2.44)	0.044
PLP, nmol/L				
<41.69	Ref		Ref	
41.69–68.86	0.96 (0.59–1.55)	0.847	0.93 (0.58–1.50)	0.761
≥68.87	1.00 (0.58–1.75)	0.991	0.97 (0.59–1.59)	0.899
Ratio of 4-PA to PLP				
<0.33	Ref		Ref	
0.33–0.48	1.28 (0.77–2.15)	0.318	1.22 (0.72–2.09)	0.431
≥0.48	1.56 (1.12–2.19)	0.013	1.46 (1.05–2.03)	0.028

OR, odd ratio; CI, confidence interval; Ref, reference; 4-PA, 4-pyridoxic acid; PLP, pyridoxal-5′-Phosphate; Model 1 was adjusted for age, gender, race/ethnicity; Model 2 was additionally adjusted for asthma, hay fever and birth weight.

or eczema in the offspring (10). These studies have reported inconsistent associations between vitamin B6 and childhood eczema, which can partly attribute to differences of ethnic groups, outcomes and exposures definitions.

Currently, there is controversy about the association between vitamin B6 and childhood eczema due to the research population, definition of disease and exposure factors. Therefore, more evidence is needed to further explore the association between the vitamin B6 intake and childhood eczema. Our study recruited 2,256 children and adolescents aged 6–17 years from the NHANES database in 2005–2006, and used vitamin B6 metabolites as exposure to explore the association between vitamin B6 and childhood eczema. After considering a series of confounding factors that affect childhood eczema, we observed a positive association between 4-PA and childhood eczema. No significant association was observed between PLP and childhood eczema, and there was a positive correlation between the vitamin B6 metabolic rate represented by 4-PA/PLP and childhood eczema. Considering children's age, gender, BMI, and the history of atopy diseases may affect the outcomes, we performed subgroup analysis subsequently to verify whether the association between vitamin B6 levels and childhood eczema remained robust in different subgroups. The association between vitamin B6 levels and childhood eczema remain robust, especially in children aged 6–11years, boys, with the history of atopy diseases and with the overweight/obesity. Our study provides strong evidence for a beneficial association between high vitamin B6 levels and eczema in children. Several physiological mechanisms could support and explain these findings. From the perspective of inflammation, vitamin B6 has antioxidant and anti-inflammatory biological functions due to its γ-hydroxyl group on the pyridine structure, which can effectively quench singlet oxygen (25). Previous studies have shown that a lack of vitamin B6 can lead to a decrease in the body's antioxidant defense ability (26, 27). Inflammation is thought to result from disruption of the epidermal barrier and activation of epidermal inflammatory dendrites and innate lymphoid cells, which attract and interact with Th2 cells. The direct mechanism of eczematous lesions is inflammation associated with Th2 cell dysregulation. Activated T cells release cytokines into the skin, primarily interleukin-4, interleukin-13, and interleukin-31, which activate the downstream Janus kinase (JAK) pathway (28). Moreover, vitamin B6 is also associated with an imbalance in the microbial levels of the intestinal flora, which mediates autism-like behaviors by regulating the metabolism of vitamin B6 (29). The pathogenesis of eczema involves a complex interaction between defective epidermal barriers and microbial imbalance, leading to allergen penetration and stimulation of type 2 helper T cell responses (30). Alterations in the microbiome have been shown to contribute to susceptibility and exacerbation of eczema.

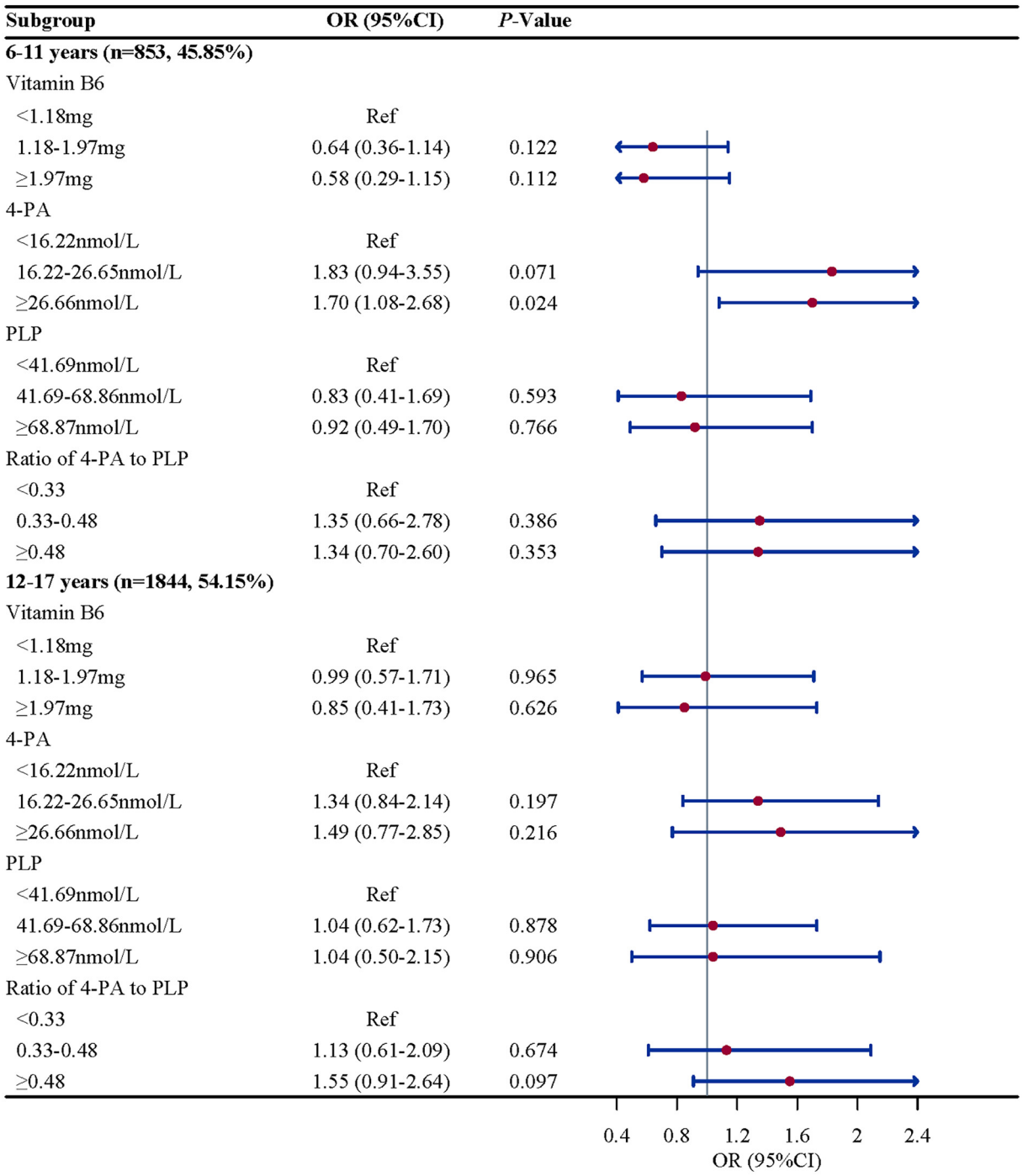

FIGURE 2
Age-stratified associations of vitamin B6 status with eczema in US children and adolescents (NHANES 2005–2006). Note: OR, odds ratio; CI, confidence intervals; PLP, pyridoxal 5′-phosphate; 4-PA, 4-pyridoxic acid.

Previous studies have demonstrated that children with eczema have reduced gut microbial diversity compared with healthy children (31).

Previous researches have focused on the relationship between vitamin B6 and chronic diseases in disease-specific populations, while evidence from studies in child and adolescent populations is limited. We utilized a large, high-quality NHANES dataset and performed comprehensive correction for confounding factors including age, race, asthma, hay fever and birth weight that affect childhood eczema to produce robust results. Moreover, our study used serum PLP and 4-PA measurements that better reflect bioavailability compared with dietary questionnaires. Our findings carry important clinical implications for pediatric eczema management. The association between PLP levels and

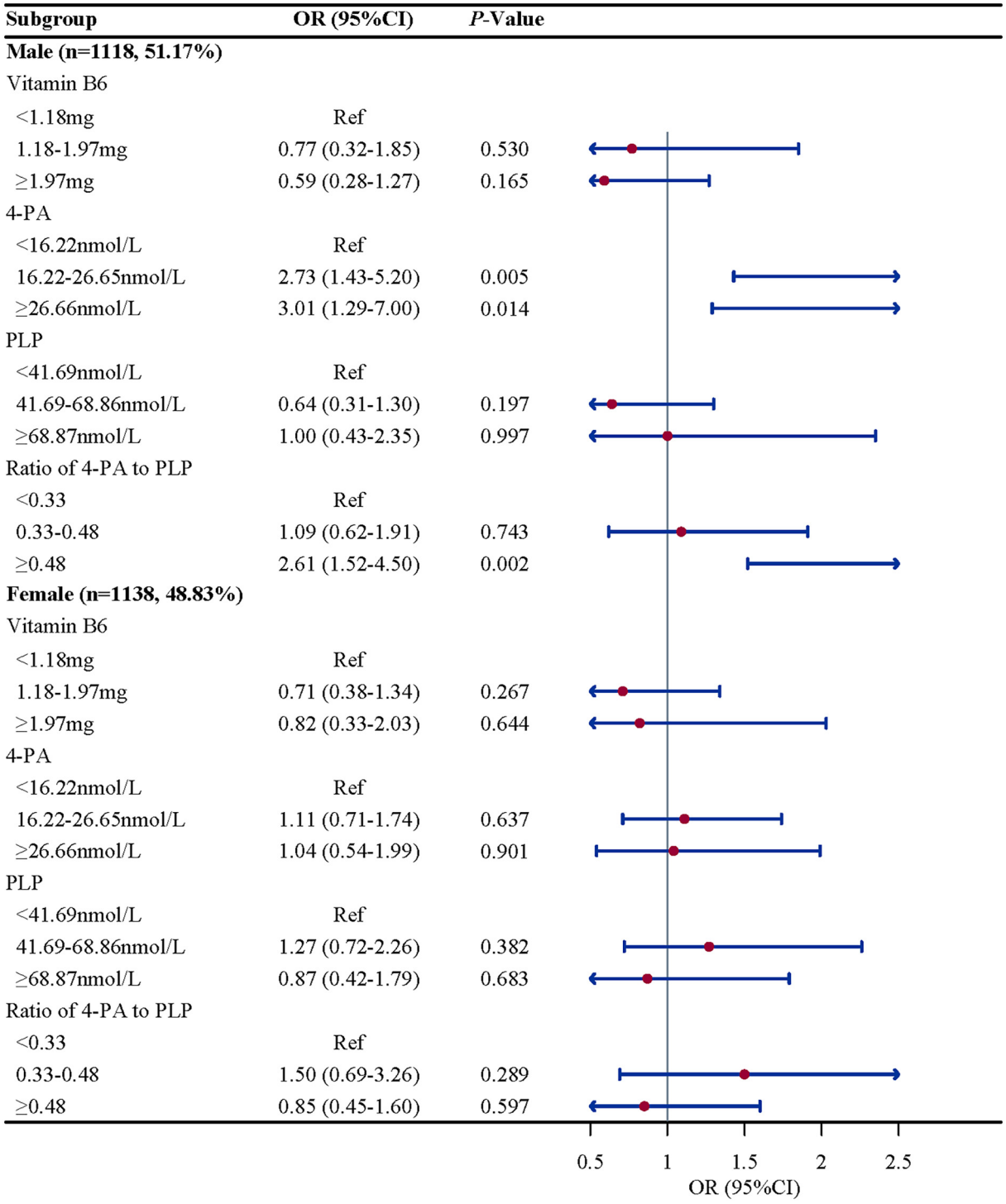

FIGURE 3
Gender-stratified associations between vitamin B6 status and eczema in US children and adolescents (NHANES 2005–2006). Note: OR, odds ratio; CI, confidence intervals; PLP, pyridoxal 5′-phosphate; 4-PA, 4-pyridoxic acid.

eczema suggests that vitamin B6 status assessment could be incorporated into routine nutritional screening for children with eczema, particularly in those with atopic predisposition. Clinicians may consider evaluating plasma PLP levels when standard therapies show limited efficacy, as suboptimal B6 status might exacerbate inflammatory pathways. For patients, these results highlight the potential dual benefit of maintaining adequate vitamin B6 status—not only supporting basic metabolic functions but possibly modulating eczema severity. This could be achieved through dietary counseling focusing on B6-rich foods

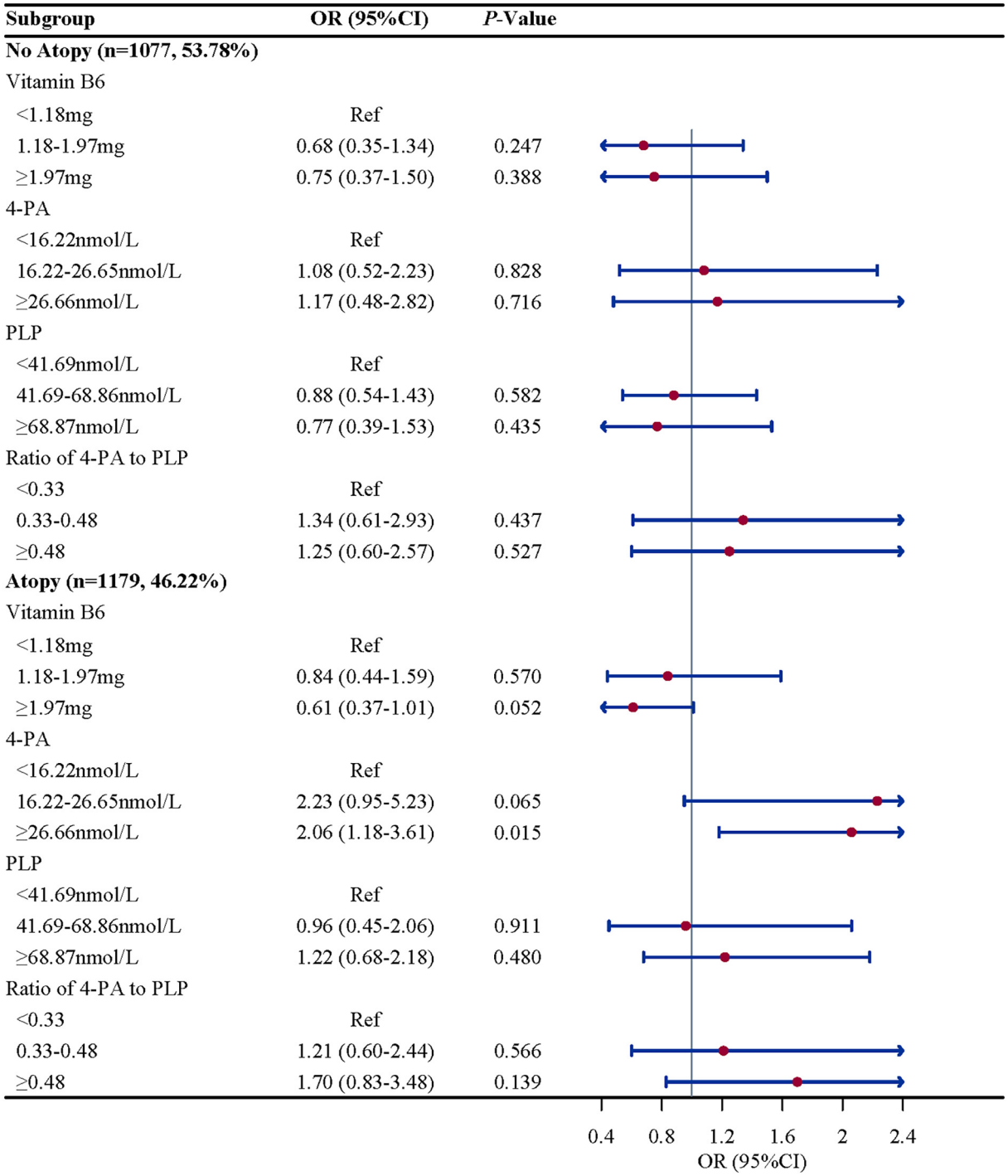

FIGURE 4
Atopy history-stratified associations between vitamin B6 status and eczema in US children and adolescents (NHANES 2005–2006). Note: OR, odds ratio; CI, confidence intervals; PLP, pyridoxal 5′-phosphate; 4-PA, 4-pyridoxic acid.

(e.g., poultry, fish, bananas) or targeted supplementation in deficient cases, though clinical trials are needed to confirm therapeutic efficacy. Our study still has several limitations that warrant attention. First, due to the cross-sectional nature of the study, only preliminary estimates of the association between vitamin B6-related biomarkers and childhood eczema can be made, and we cannot conclude the cause effect of this association. Second, although we adjusted for as many confounders as possible for childhood eczema, we were unable to exclude the influence of potential confounders on the outcomes. Thirdly, several covariates information was obtained through the NHANES questionnaire, which may be subject to recall bias.

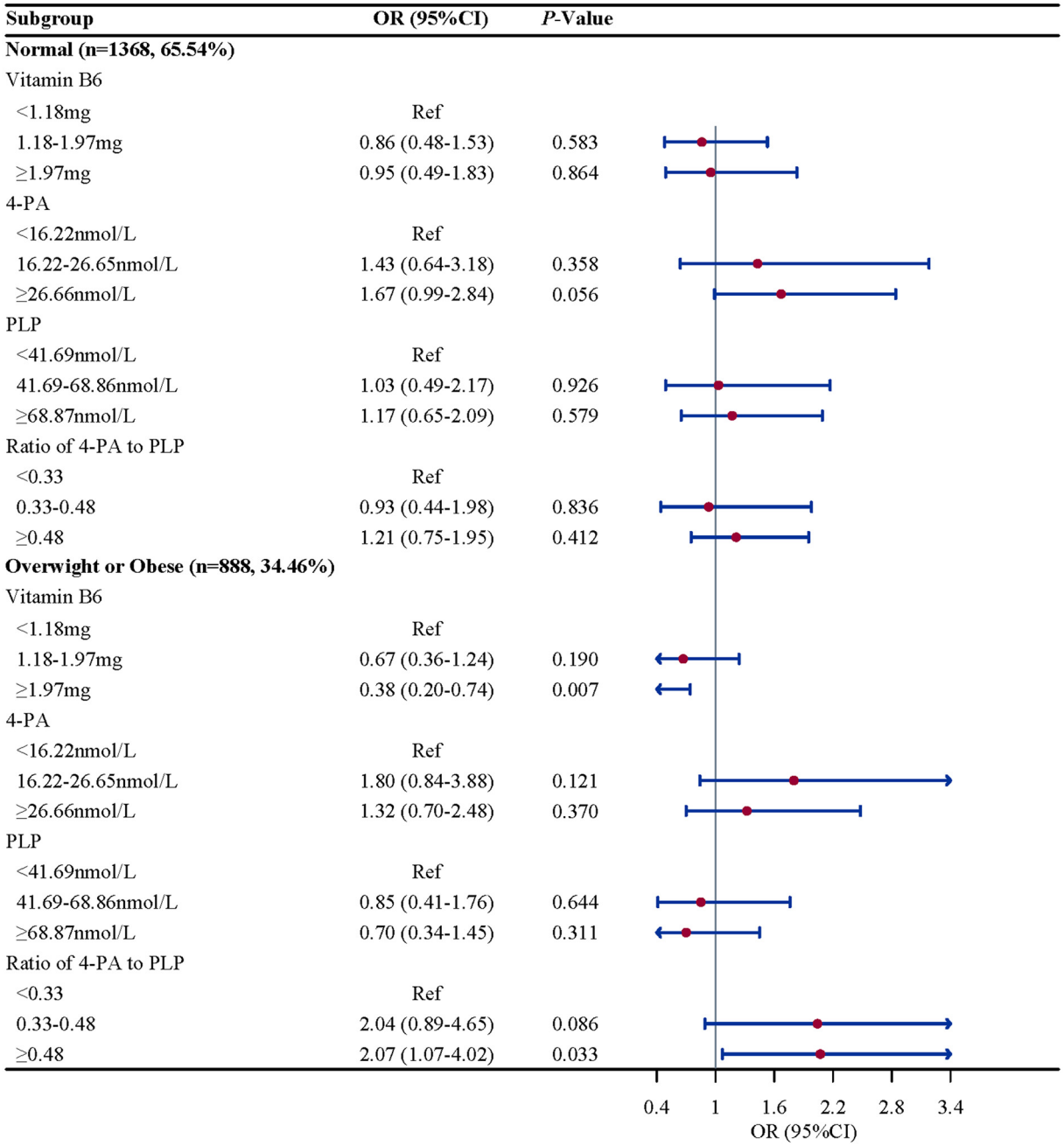

FIGURE 5
BMI-stratified associations between vitamin B6 status and eczema in US children and adolescents (NHANES 2005–2006). Note: BMI, body mass index.

Finally, as the NHANES database covers a representative U.S. population, extrapolating these findings to other populations requires caution. Future studies should prioritize longitudinal assessments to establish temporal relationships between B6 status and eczema. Additionally, randomized controlled trials of B6 supplementation in pediatric eczema patients stratified by baseline nutritional status are warranted. Finally, fundamental experimental research remains necessary to elucidate the mechanistic role of vitamin B6in skin microbiome modulation.

Conclusion

Among the study children and adolescents in present study, we observed a positive association between serum 4-PA and the odds of eczema, and a positive association between the metabolic rate of vitamin B6 and the odds of eczema. These findings suggest that maintaining a higher vitamin B6 level may have a potential benefit in preventing eczema in this population.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: NHANES database, https://wwwn.cdc.gov/nchs/nhanes/.

Ethics statement

The requirement of ethical approval was waived by the First People's Hospital of Yancheng for the studies involving humans because the survey protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

GD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2025.1557186/full#supplementary-material

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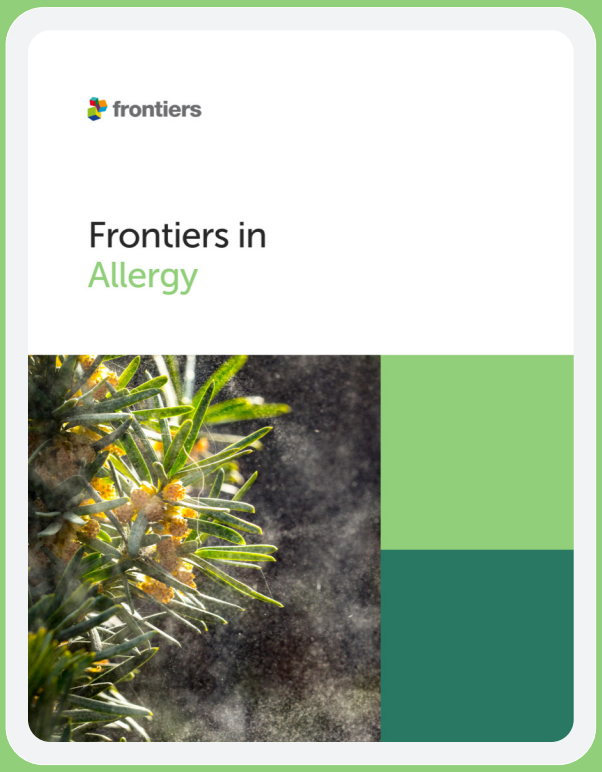

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