

REVIEW ARTICLE

The multiple factors affecting the association between atopic dermatitis and contact sensitization

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Abstract

Atopic dermatitis and allergic contact dermatitis are both common skin diseases having an immune pathogenesis. There has been considerable interest about their inter-relationships with regard to altered susceptibility. Recent investigations have shed new light on this important question, and in this article, we explore whether there is evidence that atopic dermatitis affects the risk of contact sensitization and allergic contact dermatitis. The use of topical products to treat xerotic and inflamed skin in atopic dermatitis often results in a higher prevalence of sensitization to, for example, fragrances and other ingredients in emollients. Moreover, the prevalence of metal allergy seems to be increased, probably due to compromised chelation of the metals in the stratum corneum of patients with atopic dermatitis. However, conversely, the T-helper cell 2 bias that characterizes immune responses in atopic dermatitis appears to lower the risk of contact sensitization compared to healthy controls. Based on these observations, we conclude that multiple factors affect the association between atopic dermatitis and contact sensitization, and that these need to be appreciated in the clinical management of atopic dermatitis patients.

Atopic dermatitis (AD) is a heterogeneous disorder that primarily affects children, but which may persist into adulthood and even may have a late onset (1). Although the pathogenesis of AD is complex, and many different pathways may be involved, the phenotypic expression of the disease typically has common features of generalized xerotic and itchy skin, together with acute and chronic dermatitis located to distinct anatomical sites. As with other atopic diseases, AD is often associated with the presence of protein sensitization (so-called extrinsic AD), as characterized by positive tests (skin prick tests (SPT) and/or radioallergosorbent test (RAST)) indicating IgE antibody to allergens such as house dust mite, foods including egg and milk proteins, pollen and animal dander

(1). An atopy patch test (APT), presumably better adapting to the pathophysiology of AD, can be used to diagnose delayed allergic outbreaks of AD to aeroallergens and food allergens. Although the etiology of AD is incompletely understood, it is nevertheless clear that there exists both strong genetic predisposition and environmental triggers (2). AD is characterized by both skin barrier abnormalities and a T-helper (Th) cell 2 phenotype in mainly the acute phase and with additional roles for Th1, Th17, and Th22 cells in chronic disease (3).

Contact sensitization (CS) to chemicals is characterized by the induction of specific T lymphocyte responses (4). These are primarily T cytotoxic (Tc)1/Th1 responses, although concomitant Th2 cells may be induced also. Similar to AD, CS is common in both children and adults, and may affect up to 20% of the general population (5). Allergic contact dermatitis (ACD) typically develops following repeated or prolonged topical exposure to chemical allergens of which there are many hundreds. Included among contact allergens are metals, fragrance materials, and preservatives found in commonly used products such as cosmetics and jewellery.

Abbreviations

ACD, allergic contact dermatitis; AD, atopic dermatitis; APT, atopy patch test; CS, contact sensitization; DNCB, dinitrochlorobenzene; FLG, filaggrin gene; LPS, lipopolysaccharide; RAST, radioallergosorbent test; SLS, sodium lauryl sulfate; SPT, skin prick tests; TCR, T-cell receptors; Tc, T cytotoxic; Th, T helper; TLR, Toll-like receptors; Treg, T-regulatory.

Pertinently, topical therapy is inevitably prescribed in patients with AD, often for longer periods, to treat xerotic and inflamed skin resulting in continuous exposure to chemicals. A diagnosis of CS is established by patch testing, wherein the elicitation of ACD reactions provoked by challenge with standardized concentrations of test allergens is assessed. As AD is associated with protein allergy, there has been considerable interest in exploring whether patients with AD also display an altered risk of developing allergy to chemicals (6). While experimental models provide some insights into a possible interplay between CS and AD, they do not incorporate exposure paradigms that reflect human experience. Moreover, epidemiological studies have been unable to unpick the possible relationship between AD and CS. In this review article, we discuss factors that may influence this relationship.

Skin barrier abnormality in atopic dermatitis increases hapten penetration and possibly the acquisition of contact sensitization

The normal stratum corneum is characterized by an intercellular matrix that consists of multiple lipid layers surrounding flattened anucleate corneocytes (7, 8). The lamellar sheets are enriched in cholesterol, free fatty acids, and ceramides. These highly hydrophobic lipids inhibit water loss and constitute the primary pathway of penetration for lipid-soluble chemical allergens (haptens). While the lipid-rich stratum corneum normally resists the penetration of water-soluble haptens, these may instead penetrate transcellularly or via the eccrine glands and pilosebaceous follicles ('shunt pathway') (9). Naturally, haptens have varying chemical properties and can be either water- or lipid-soluble. They also differ in size and polarity; factors that influence their ability to penetrate the stratum corneum. Some chemicals may even have properties that prevent their penetration through the normal stratum corneum (9). Besides the barrier provided by the stratum corneum, the risk of CS depends on a variety of other factors including the sensitizing potency of the chemical, the extent, duration and frequency of exposure, the presence of occlusion and local irritation/trauma, and the inherent susceptibility of the subject.

Skin in AD is characterized by xerosis due to either a genetic predisposition or as the result of inflammation following exposure to exogenous stressor (7). For example, mutations in the filaggrin gene (*FLG*) are associated with reduced skin hydration and increased transepidermal water loss and skin pH (10, 11). Mutations affect 10% of Northern Europeans and 5% of Asians and are strongly associated with AD (12). Importantly, Th2 inflammation in AD reduces the expression of filaggrin molecules in lesional and nonlesional skin leading to acquired filaggrin deficiency (13, 14). A positive association between *FLG* mutations and CS to nickel was found among German adults (15), but could only be confirmed in Danish adults without ear-piercings (16). Moreover, *FLG* mutation carriers reported ACD to nickel at a significantly younger age than controls with normal filaggrin, and they also displayed stronger patch test reactivity (17).

Nickel ions, like many other metal ions, are electrophilic in nature, which causes reactivity toward certain protein elements. The hypothesis is that subjects who have *FLG* mutations are more susceptible to the acquisition of CS to nickel following topical exposure. This was supported by a study showing strong nickel chelation by the histidine-rich filaggrin proteins (18). Furthermore, trivalent chromium ions penetrated filaggrin-depleted murine skin more easily than normal skin (19). Accordingly, CS to metals has been found to have a significant association with AD in both children and adults (20–23), probably due to the compromised chelating functions of AD skin. Finally, an *in vivo* study, using polyethylene glycols, showed that the diffusion coefficient across the stratum corneum was about twice as high in patients with AD compared to healthy controls (24). Similarly, the diffusion of sodium lauryl sulfate (SLS) through uninvolved AD skin was shown to be higher compared to normal skin (25). It can be concluded that in AD, there may be opportunity for the more effective access of chemical allergens to the viable epidermis, and that this could in theory enhance the acquisition of CS.

Altered colonization with bacteria in atopic dermatitis could affect the induction of contact sensitization

Besides the altered structure of the stratum corneum in AD, antimicrobial defenses in this condition are compromised. Thus, gram-negative bacteria are uncommon as a part of the normal skin flora, but up to 10% of the children with AD appear to be colonized with such bacteria (26). Lipopolysaccharide (LPS), the outer cell wall component of gram-negative bacteria, stimulates innate immunity via Toll-like receptors (TLR) that in turn modify adaptive immune function. The bacterial milieu in the cutaneous microenvironment of patients with AD could in theory facilitate the acquisition of CS. It is known in the case of nickel CS, for instance, that TLR receptors play an important role. In addition, the skin of patients with AD is readily colonized by *Staphylococcus aureus* that is known to secrete superantigenic exotoxins including staphylococcal exotoxin B (27, 28). Together with others, this superantigen targets the T-cell receptors (TCR) Vbeta 17 region leading to oligoclonal proliferation and expansion (29). Interestingly, similar Vbeta17 TCR expansion has been observed in nickel CS. It has also been reported that metal CS to agents contained within orthopedic prostheses is twice as likely in the presence of bacterial infection (30). Little is currently known about the effects of bacterial growth on the development of CS, but it would appear that, in principle, bacterial colonization could support or enhance the acquisition of CS to at least some chemical allergens.

The increased topical allergen exposure in atopic dermatitis should affect the prevalence of contact sensitization

The skin of patients with AD is xerotic and intermittently or chronically affected by dermatitis. Consequently, patients and their carers frequently use moisturizers as well as

topical corticosteroids and calcineurin inhibitors to reduce inflammation. For instance, it has been reported that Swedish children with moderate to severe AD used both moisturizers and topical corticosteroids significantly more frequently than do children with mild AD (31). This increased exposure and the access of chemical allergens to the viable epidermis that can be expected in AD might, in theory at least, be expected to translate into an increased acquisition of CS, particularly to ingredients within personal care products and to topical medicaments. Notably, the application of weak haptens to skin that is already inflamed means that no 'danger signal' needs to be generated to promote ACD, as it is already present. In fact, there are reports that there does exist an association between AD and an increased prevalence of CS to chemicals we encounter on the skin (32). Although such an association does not necessarily imply that increased susceptibility to CS is necessarily driven by enhanced access to the viable skin of chemical allergens, that is the implication. We here provide examples of studies supporting this view. In 641 children with AD, seven compounds commonly found in topical therapeutics gave positive patch test reactions in 6.2% of the subjects (33). Allergens included those found in the emollients used by the patients as well as chlorhexidine, tixocortol pivalate, and bufexamac. Risk factors for positive patch test reactivity were AD severity, onset before the age of 6 months, and IgE-mediated sensitization emphasizing that those who are most strongly exposed tend to have a higher incidence of CS (33). Moreover, a Danish patient-based study found that CS to the corticosteroid tixocortol-21-pivalate, and to topical drugs in general, was significantly associated with AD (34), and several studies have shown that patients with AD have a higher prevalence of fragrance CS than controls (35–38). Furthermore, a general population study showed that patients with AD, and especially those with *FLG* mutations, had a higher prevalence of CS to contact allergens found in topical products (39). AD has also been associated with multiple contact allergies ($x \geq 3$). Hence, 45% of 563 polysensitized patients had AD compared to 31% of 1124 single/double sensitized controls (40). A similar association was found among 126,878 German patients with dermatitis (41). Finally, a large US study revealed a higher prevalence of CS to lanolin, an ingredient frequently used in cosmetics, in patients with AD when compared to non-AD patients (42). Likewise, CS to preservatives can be higher in patients with AD when compared to non-AD controls (32). However, it is possible that the apparent higher prevalence of CS in subjects with AD is, at least to some extent, a result of false-positive reactions in diagnostic patch tests as discussed below.

False-positive patch test reactivity could affect the apparent prevalence of contact sensitization in atopic dermatitis

While dermatologists are fully aware of the difficulties of performing patch test readings correctly, some reactions are

mistakenly read as positive, although they are not truly allergic in nature. In this respect, metals can provide a particular challenge due to changes in pH of the skin and non-specific inflammation resulting from penetration via sweat ducts and hair follicles (43). Based on patch testing of 853 hard metal workers, Fischer and Rystedt emphasized that the reading of metal reactions is generally difficult. In that study, pustular patch test reactions to nickel were observed in patients with AD but without CS to nickel, when the patches were placed over areas of skin with follicular papules, erythema, lichenification, or minimal trauma (44). Irritant reactions to other chemicals are also common in patients with AD. Thus, 24% of 851 atopic patients were reported to display irritant patch test reactions, the most important being to fragrance mix I, formaldehyde, carba mix, and propylene glycol (45). Similar findings were reported among German patients with AD who were found to have more doubtful and irritant reactions on early readings compared to controls, and tended to have stronger reactions on day 3 to fragrances and formaldehyde (46). Pertinently, the typical crescendo pattern with increasing reactivity on later readings in true allergic reactions was not observed in patients with AD. Taken together, the available data suggest that the observed association between AD and CS may be at least in part attributable to a higher prevalence of false-positive patch test reactions in AD, particularly in the case of metal allergens.

Both experimental and clinical studies have shown reduced contact sensitivity in individuals with atopic dermatitis

Despite the positive association between AD and CS described above, which is likely to be explained by increased exposure to allergens at skin surfaces, other studies, especially experimental ones, have paradoxically found a reduced risk of CS in AD. Thus, the proportion of patients with AD who reacted to dinitrochlorobenzene (DNCB) challenge depended on the severity of AD with 100% mildly, 95% moderately, and 33% severely affected patients with AD having positive test reactions (47). In another investigation, the DNCB dose-response sensitization relationships were characterized in 22 patients with minimal AD and in 27 non-atopic controls. It was found that patients with AD were significantly less responsive than control subjects (48). This is consistent with another study in which the development of CS to *Rhus* was determined in patients with AD and in healthy controls. It was found that only 3% of 40 patients with AD developed CS, whereas 37% of 131 healthy controls were sensitized (49). In addition to the clinical experimental studies summarized above, there have been other reports of a dose-dependent inverse association between AD and CS. Thus, a 15-year prospective study found an apparent lower prevalence of CS in the group with severe AD when compared to a group of patients with moderate AD (36). It is relevant also that there has been reported a dose-dependent inverse correlation between serum levels of IgE and CS (50). Finally, a recent register-based clinical study

found a significant inverse association between severe AD and CS (51).

A T-helper cell 2 profile in atopic dermatitis affects the acquisition of contact sensitization

It has been suggested that the opposing and mutually antagonistic influences of Th1 and Th2 cells may provide a mechanistic basis for the observed inverse correlation between AD and CS in the experimental studies. The acquisition of CS is commonly associated with the development of Th1 and Tc1 effector cells. Although Th2 cells can also be identified, type 1 responses are the usual and dominant influence in CS (52, 53). The argument is that in AD, where the atopic phenotype is driven by preferential Th2-type responses, the development of Th1/Tc1 responses will be disadvantaged and the acquisition of sensitization will be less effective and/or require higher concentrations of the inducing allergens to drive the response. One manifestation of this might be that in patients with AD, there is a shift in the dose metrics required for effective sensitization. A recent report supports this picture. Newell et al. compared the effectiveness of *de novo* sensitization to DNCB in patients with AD compared to normal controls (54). They reported that the acquisition of sensitization to DNCB through uninvolved skin sites in patients with AD was less effective than in control subjects. The less effective development of sensitization to DNCB was found to be associated in patients with AD with a skewing of immune responses to a Th2 phenotype, whereas in nonatopic controls, immune responses to DNCB were consistently of Th1 type. The implication is that the qualitative immunological bias in the skin can influence the selectivity of responses induced to novel antigens, including chemical allergens. However, the situation may be somewhat more complicated than a simple balance between the opposing influences of Th1 and Th2 cells. Animal and human reports suggest that repeated exposure to potent contact allergens (in animals for example oxazolone) can result in first CS and then a gradual shift toward an AD like phenotype (55–57). For example, Williams et al. described how occupational exposure to chemicals on the hands lead first to localized hand dermatitis, which then spread in a flexural pattern mimicking AD (58). Moreover, a series of patients, most of whom had AD in infancy that had since resolved, redeveloped AD at the site of chemical exposure after repeated topical exposure to chemicals, either through occupational use as an adult, or from the use of cosmetics as a teenager (59). Collectively, these data suggest that repeated topical exposure to allergenic chemicals can result in an eventual skewing of the skin immune system to a preferential Th2-type phenotype. The argument is that a selective Th2 phenotype will then promote the development of AD. In summary, the presence of AD, or a general atopic phenotype in the skin, may impact negatively on the acquisition of CS, but in addition, repeated exposure to low levels of chemical allergens may itself generate a selective Th2 environment in the skin that predisposes to the development or exacerbation of AD. Finally, it must be emphasized that the immune responses in

AD and CS are clearly far more complicated than described here. There are, for example, important roles played by various functional subpopulations of T cells, including Th9, Th17, Th22, and regulatory T cells (Treg) (60). There is, in addition, evidence to suggest that Tregs can convert to Th2 cells and that this pathway is bidirectional (61). To what extent T cells other than Th1 and Th2 contribute to the interplay between AD and CS is currently unknown.

The hapten-atopy hypothesis

There has been a 300–500% increase in the frequency of atopic diseases and associated allergies in the last half century (62–64). One popular explanation for this phenomenon is the ‘hygiene hypothesis’ suggesting that when our developing immune system encounters less microbial exposure, it matures differently and lead to atopy (65). Yet, another explanation is the increased exposure to ‘urban’ protein allergens. Patients with AD are generally more prone to develop IgE sensitization to proteins such as pollen, foods, and animal dander. One could therefore argue that urbanization has simply exchanged exposure from one set of (rural) protein allergens (such as farm animals, pollens, and crops) for another set of (urban) protein allergens (including house dust mites and pet animal hairs). Also, in westernized countries, there has in recent decades been an increasing exposure to chemical allergens/haptens from a variety of sources (such as personal care products, processed foods, and drugs) (62–64). It is feasible that such exposures could influence the maturation of the immune system during its development and specifically impact the balance between type 1 and type 2 immunological preferences. We have proposed previously that the significant increase in the prevalence of atopic disease and allergy seen in westernized countries during the last 50 years may, at least in part, be associated with, and driven by, increased exposure (and altered patterns of exposure) to chemical allergens and irritants that in turn favors the development of Th2-type responses (62–64). The argument has been advanced that such exposures may distract the immune system such that the establishment of tolerance toward potentially allergenic environmental and dietary proteins is compromised.

Other factors that may affect the association between atopic dermatitis and contact sensitization

As indicated above, it is commonly the case that clinical and epidemiological studies have yielded conflicting results when investigating the association between AD and CS. Obviously, the populations can be very different concerning referral patterns, severity, gender, race, age, and previous environmental and occupational exposures. Pertinently, environmental exposures and medical access have changed over the decades that researchers have evaluated the association between AD and CS. For example, over the last 60 years, there has been a substantial increase in chemical exposure in the personal environment, namely in the form of personal care products, drugs, and processed food. Therefore, cohorts may differ

markedly. Also, it is obvious that definitions need to be agreed and standardized. For example, a diagnosis of AD can be made on the basis of clinical examination, or assessed through questionnaires using different criteria. CS is evaluated using patch tests, but their interpretation can be affected by a number of variables (66). We here suggest some additional factors that may explain the discrepancies from the past reports. First, epidemiological studies have until recently not stratified the analyses for skin-piercing. This is important as the skin compartments are bypassed following piercing directly exposing the immune apparatus to the metal ions. Therefore, the genetic and acquired skin barrier alterations in AD have not been sufficiently studied. The bypass theory has previously been applied to explain the conflicting findings on nickel sensitization from past studies, because ear-piercing has become increasingly popular over the twentieth century (17). Thus, it has been suggested that if one neglects to stratify the data analyses, it may introduce bias as incident metal CS following ear-piercing is now very frequent. Second, because patients with AD have a 3-fold increased risk of developing hand eczema, especially the irritant contact dermatitis subtype, this may lead to an increased risk of becoming occupationally contact sensitized. However, such information has resulted in altered behavior in Danish patients with AD as they now tend to avoid high risk occupations that again reduce hapten exposure and therefore the risk of CS (67). Moreover, patient education may now result in reduced hapten leisure exposure in some populations, for example due to the use of low allergenic topical products. Third, systemic allergic dermatitis reactions due to systemic exposure to haptens may mimic AD eventually resulting in misclassification. This has been shown for several allergens including nickel, chromium, and preservatives (57, 68). While only four of 400 female patients with nickel allergic dermatitis seen by Calnan had AD, 75% had 'hematogenous' spread of dermatitis affecting the elbow flex-

ures, eyelids, sides of neck and face, and inner aspects of the thighs (69). Fourth, in clinical databases, it is possible that patients with dermatitis with negative patch test reactivity may falsely be categorized as having AD leading to misclassification. Finally, one should consider the very different scenarios that take place when evaluating the association between AD and CS in children and adults as the environmental exposure time obviously is much longer in adults and as the immune reactivity may change with age. Studies have indeed shown that infants have unexplained high rates of positive patch test reactions and that these tend to decrease with age (70).

Remaining conundrum

At least one major conundrum remains regarding the association between AD and CS. For example, a higher prevalence of sensitization to airborne allergens such as fragrances and compositae plant haptens has often been observed in patients with AD in epidemiological studies (35, 71–73). One obvious explanation could be increased exposure to fragrance products to treat xerotic and inflamed skin in AD, as suggested above, resulting in secondary fragrance sensitization. However, this does not explain the association between CS to plant haptens and AD. Under normal conditions, adaptive immune stimulation through the respiratory system occurs through the Th2 immune pathway, which is not readily accessed by experimental contact sensitizers such as DNCB (74). This therefore invites the question as to whether contact sensitizers such as fragrance chemicals and compositae may be able to primarily stimulate the adaptive immune system through the respiratory pathway in individuals with Th2-skewed immune systems and result in secondary increased systemic and cutaneous skin reactivity to the sensitizer. Hence, while we are abundantly exposed to plants and fragrances on the skin, which in turn may result in CS,

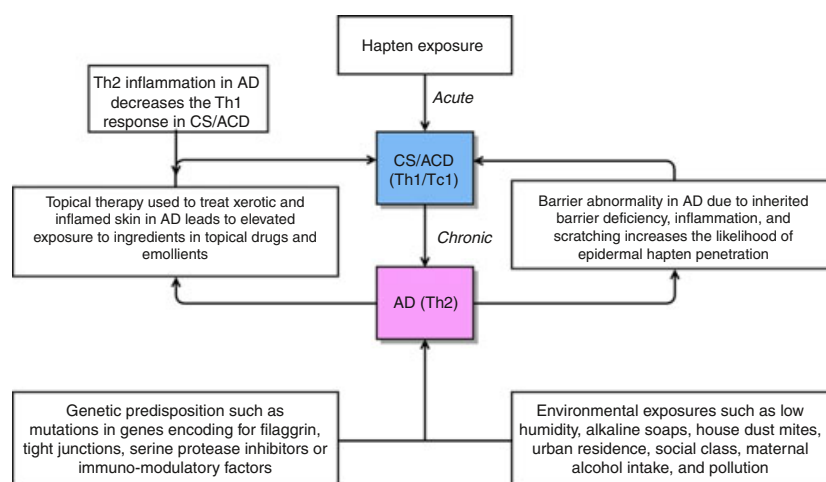


Figure 1 Simplified pathomechanistic interplay between contact sensitization and atopic dermatitis. ACD, allergic contact dermatitis;

AD, atopic dermatitis; CS, contact sensitization; Tc, cytotoxic T cell; Th, T-helper cell.

airway exposure may prove to be crucial. This suggested pathway unites the skin and the airways as recently suggested for *FLG* mutations and aeroallergen sensitization but in a different direction (75). Here, a primary skin barrier abnormality due to *FLG* mutations allows penetration of protein allergens through the skin causing sensitization and then subsequent airway exposure to the allergens cause secondary inflammation in the respiratory compartments. Perhaps, primary airway exposure to fragrances and compositae haptens may cause sensitization in Th2 skewed airways, which can be detected and confirmed in skin patch tests. An epidemiological study showed a significant association between airway

symptoms to fragranced products and fragrance CS suggesting a link between the skin and the airways (76).

Concluding remarks

This review article provides an overview of the multiple factors that affect the association between AD and CS (Fig. 1, Tables 1 and 2). It is obvious that neither experimental nor epidemiological studies can adjust for all of these. There appears to be an overall dose-dependent tendency toward a less effective CS response among subjects with AD, but that this effect may be reduced to some extent by the fact that the

Table 1 Factors that may affect the observed association between atopic dermatitis (AD) and contact sensitization (CS)

Skin barrier status

- Hydration (low hydration in AD impairs the skin barrier and can lead to irritant patch test reactions)
- pH (elevated pH will increase the risk of AD due to premature protease activity and possibly also the risk of CS due to barrier abnormality)
- Inflammation (the presence of Th2 inflammation in AD seems to reduce the CS response, which is primarily a Th1 response)
- Filaggrin gene (*FLG*) mutations (*FLG* mutations increase the risk of AD and likely also the risk of CS to nickel and other bivalent metal ions due to compromised chelation activity)
- Bacterial colonization (colonization with gram-negative bacteria and *Staphylococcus Aureus* is common in AD, likely increasing the risk of CS due to the presence of lipopolysaccharide (LPS) that activates innate immunity via Toll-like receptors (TLR) and *S. Aureus* exotoxins that targets the T-cell receptors (TCR) Vbeta 17 region)

Environmental exposures

- Topical therapies to treat xerotic and inflamed skin (increased skin exposure to contact sensitizers in AD increases the risk of CS and therefore affect the association between the two entities)
- Skin-piercing (skin-piercing leads to a bypass of the skin the barrier which affects the risk estimates on the association between AD and CS; this should be adjusted for in epidemiological studies)
- Occupation (individuals with AD are often guided away from occupations with skin exposure to chemicals potentially leading to a lower prevalence of CS in patients with AD. However, AD increases the risk of irritant contact dermatitis on the hands, which again increases the risk of CS)

Diagnostic factors

- Severity of dermatitis at the time of testing (patch testing at the time of strong AD inflammatory activity will decrease the CS response; this is important as testing is sometimes performed during episodes of aggravation to identify a culprit allergen then leading to a 'false-negative response' affecting the association estimate)
- Definition of atopic dermatitis (AD can be determined clinically and by questionnaires potentially leading to misclassification)
- Definition of contact sensitization (the definition of a positive patch test reaction some time differs between patch test readers despite international criteria have been agreed upon, also, the irritant metal reactions in patients with AD can mimic allergic ones)
- Patch test system, the number of haptens included, day of patch test reading (these factors can affect the association estimate, as, for example, the typical 'crescendo' pattern is not observed to the same degree in patients with AD)
- Misclassification (clinically, systemic contact dermatitis may look like AD and result in misclassification)

Other factors

- Age, gender, and genetic background of the population investigated (it is unknown whether the age effect of skin reactivity to haptens is altered in patients with AD when compared to controls. Also, comparing the children's and adult studies from different populations might affect the association estimate incorrectly due to different environmental skin exposures)
- Changes in cohorts and their exposures over time (environmental skin exposures has changed over time along with the information of patients with AD)
- Changes in referral to clinical evaluation in a hospital or clinic (referral to secondary or tertiary evaluation of patients with AD likely has changed over time affecting the likelihood of patch testing)
- Characteristics of participants (participation rates in general population studies have dropped in recent decades introducing a risk of participation bias as those with disease are more likely to participate)
- Concomitant systemic immunomodulating therapy (the effect of immunosuppressant's on association estimates is often not accounted for in the association studies)
- Meteorological and climate effects (a dry and arid climate resulting in xerotic skin tend to affect the rate of positive patch test reactions to a higher degree in patients with AD)

Table 2 Summary of the key knowledge points regarding the association between atopic dermatitis and contact sensitization

- There is a significant prevalence of contact sensitization among both children and adults with atopic dermatitis; therefore, patch testing is a useful investigation in these patients
- The prevalence of contact sensitization to some medicament agents, e.g., lanolin and corticosteroids, appears to be higher in patients with atopic dermatitis
- The prevalence of metal contact sensitization following topical exposures is increased in patients with atopic dermatitis due to compromised chelation in the stratum corneum.
- 'False-positive' patch test readings to certain contact allergens, in particular to metals, are higher in patients with atopic dermatitis
- Experimental contact sensitization is reduced in patients with atopic dermatitis
- Patients with atopic dermatitis are immune stimulated by haptens/contact allergens through the Th2 immune pathway as opposed to the Th1 pathway in normal controls.
- Increased exposure to immunomodulatory (hapten/irritant) chemicals at early stages of development may predispose to the development of atopic disease and related atopic allergies.
- Excessive and prolonged chemical exposure appears to cause a local re-flare and re-exacerbation of quiescent atopic dermatitis.
- Patients with atopic dermatitis are predisposed to irritant contact dermatitis.
- The observed increased prevalence in patients with atopic dermatitis of some airborne haptens (plants and fragrances) remains unexplained.

compromised barrier function in AD may facilitate increased exposure to chemicals encountered at skin surfaces and that overall allergen exposure from topical products is elevated. This may serve to explain the differences in various experimental and epidemiological studies, which have sought to investigate the relationships between AD and ACD.

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Author contributions

J. P. Thyssen took the initiative with the article and drafted the first manuscript. J. P. McFadden and I. Kimber provided critical comments on the manuscript. All the authors approved the final version.

Conflicts of interest

None declared.

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