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Review

Moisturizer therapy in prevention of atopic dermatitis and food allergy: To use or disuse?

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Key Messages

- Allergic sensitization through a defective skin barrier predisposes to development of atopic dermatitis (AD) and food allergy.
- Moisturizers are an important baseline therapy for AD, owing to their ability to soften and soothe the skin, increase stratum corneum hydration, and spare the amount of topical anti-inflammatory treatments needed.
- Although some moisturizers exhibit skin barrier-strengthening properties that reduce the sensitivity of the skin to irritants, others exhibit contradictory effects by increasing skin permeability to irritants and drugs alike.
- There is limited evidence suggesting that moisturizers may modify the risk of allergen sensitization through their effects on the skin barrier.
- Primary prevention studies on AD and food allergy with moisturizer interventions have yielded mixed results which may be related to the often-undefined effects of moisturizer interventions on the skin barrier.

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ABSTRACT

Objective: To critically appraise the evidence for the role of regular moisturizer application in early life to prevent atopic dermatitis (AD) and food allergy (FA).
Data Sources: Primary peer-reviewed literature.
Study Selections: Original research articles based on systematic reviews, interventional studies, retrospective studies, case-control studies, and cohort studies related to the subject matter.
Results: There is good evidence to show that epicutaneous sensitization through a defective skin barrier is important in the development of AD and FA. This supports moisturizer use in prevention because some of them have been proven to restore skin barrier with clear benefits in AD, whereas there is some limited evidence that these products may reduce allergic sensitization. However, moisturizers have varied effects depending on ingredients and formulation, some of which are paradoxical, such as increasing

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transepidermal water loss and enhancing penetration of substances in the skin. These effects may be responsible for some of the conflicting outcomes of prevention studies, some of which suggest that moisturizers are not useful in prevention of AD and FA, whereas others show a positive trend. Interestingly, there is some suggestion that moisturizers may increase the risk for allergy development perhaps through these paradoxical effects.

Conclusion: Although moisturizer use is beneficial in the management of AD, current evidence suggests that it may be ineffective in prevention of AD and FA. Further studies are needed to determine the effects of moisturization on allergic sensitization and inflammation and to investigate whether moisturizer type, frequency, duration, and age of application substantially affect the prevention and development of these allergies.

Introduction

Worldwide, there has been an increasing prevalence of allergic diseases, which are a common heterogeneous group of diseases associated with considerable morbidity.[1] Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder seen in children with a prevalence of approximately 20% in children and 3% to 10% in adults.[1,2] It is characterized by physical discomfort and psychological distress which substantially affects the individual and the family.[3] Food allergy (FA) is an adverse, immunologic reaction to food which is reproducible on re-exposure with an estimated childhood incidence of 3% to 10% in developed countries.[4] It is closely linked to AD with reported food sensitization and challenge-proven FA prevalence of up to 66% and 81%, respectively, in established AD.[5] Early onset, severe and more persistent AD have been associated with development of FA.[5] Atopy which is the propensity to produce immunoglobulin E (IgE) to common environmental allergens has been a basis to link allergic disorders which may be seen as multimorbidity in the same individuals or close relatives. AD is usually the earliest atopic disease to manifest, followed by FA in infancy, asthma, and allergic rhinitis in later childhood. This chronological progression of 1 disorder to the other has led to the concept of the atopic march. This concept is however being contested as a clustering of complex diseases with similar genetic and environmental predisposing factors with tissue-specific peak time of occurrence.[6] This study aimed to review the scientific evidence for the use or disuse of moisturizer therapy to prevent AD and FA and highlight possible areas for further research.

The Effect of Regular Moisturizer Use on the Development of Atopic Dermatitis and Allergy

Recently, a significant dose-response relationship between moisturizer use at 3 months and subsequent development of FA at 12 and 36 months was reported from a large birth cohort study conducted in the United Kingdom.[7] Each additional moisturization per week was associated with a 20% increase in the odds for developing FA (odds ratio [OR] adj, 1.20; 95% confidence interval [CI], 1.13-1.27; $P < .001$). A similar relationship was found for food and aeroallergen sensitization. The authors postulated that moisturizers might be facilitating the passage of food allergens across the skin barrier (SB) or disrupting the SB allowing the passage of the allergens transferred from the parent's hands when applying moisturizer to their infant's skin. Particularly, as a dose-response relationship was found with increased moisturizer frequency and high transepidermal water loss (TEWL) values at 3 months of age. Although this sounds alarms bells, it is worth noting that the most used moisturizers in the study included natural and synthetic oils such as olive oil, sunflower oil, mineral oil, and moisturizing creams previously shown to have either detrimental or no relevant effect on the SB.[8,9] The findings from this retrospective review of data, however, will need to be confirmed further by randomized controlled studies.

In the primary prevention of AD and other allergies in infants, regular moisturization has yielded conflicting findings. A summary of AD prevention studies involving a moisturizer intervention is provided on Table 1. Horimukai et al[10] found a daily moisturizer to be effective in preventing AD when used in babies in the first 32 weeks of life. Incidence of AD was 32% fewer in the group using moisturizers, whereas those with AD had higher allergic sensitization to egg white. Simpson et al[11] also reported a protective effect of daily moisturizer on AD with a relative risk reduction of 50%. This was followed by a large randomized control trial (the Barrier Enhancement for Eczema Prevention or BEEP study) conducted among 1394 high-risk infants which did not find a significant effect of moisturizers used for the first 1 year of life in preventing eczema at 2 years of age ($P = 0{\cdot}61$).[12] They however reported a nonsignificant increase in food allergies in the moisturizer group compared with the control (7.5% vs 5.1% adjusted relative risk (RR), 1.47; 95% CI, 0.93-2.33).[12] The choice of moisturizers offered to participants in the studies differed and could have accounted for the contradictory outcomes. The moisturizers used in the BEEP trial have since been reported to have no substantial effect on the SB.[9]

In a pilot study (PEBBLES) that used a ceramide-dominant moisturizer, a trend toward reduced incidence of AD for the first 6 months of life and lower food sensitization at 12 months in the moisturizer group was found.[13] The authors postulated that the moisturizer may have superior effects in prevention compared with standard moisturizers used in previous studies, and this will be confirmed by the outcome of the larger trial which is being awaited. Skjerven et al,[14] in a large study of 2397 babies, found a nonsignificant increase in AD incidence in the moisturizer group compared with the no treatment group (11% vs 8% risk difference of 3.1%; 95% CI, −0.3 to 6.5). Similarly, a nonsignificant increase in the incidence of AD in the skin care group compared with the no intervention group was found in Japan ($P = 0.74$).[15] These findings were not anticipated and may be caused by increased skin permeability of some moisturizers with resultant allergic sensitization.

Although more studies are ongoing, 3 systematic reviews have published contradictory outcomes on the effect of moisturizers on prevention of AD. Kelleher et al[16] concluded that skin care interventions such as moisturizers did not change the risk of development of AD between 1 and 2 years, on the basis of a meta-analysis of individual patient data from 7 studies (RR, 1.03; 95% CI, 0.81-1.31; moderate-certainty evidence; 3075 participants). It also did not change the time to development of AD (hazard ratio, 0.86; 95% CI, 0.65-1.14; moderate-certainty evidence; 3349 participants, 9 trials). They also concluded that there was uncertainty as to the effects of skin care interventions on FA at 1 to 2 years of age. Some studies on moisturizer prevention were excluded in the meta-analysis owing to the lack of individual data.[16] Zhong et al,[17] however, who did a systematic review of aggregate data from 10 studies concluded that moisturizers prevented AD only in high-risk infants (RR, 0.75; 95% CI, 0.62, 8 trials) and was only beneficial if the moisturizers were used up to the point of AD assessment (RR 0.59; 95% CI, 0.43-0.81). They postulated that moisturizers probably delay development of AD and may not completely prevent development of AD. They also did not find any protective effects of moisturizers on FA. Both reviews noted the heterogeneity of the interventions used across all the studies, including the types, frequency, age at commencement, duration, and body region of application of moisturizers. There was also contamination from control groups,

Table 1
RCTs on Prophylactic Moisturization of Infants to Prevent AD and Other Allergies[a]

Autho/publication yearCountry(ies) of study	Study design	Population characteristics	Frequency, type, and instructions for moisturizer use	Outcome of skin parameters	Outcome of clinical allergyAllergic sensitization	Other outcome
Kataoka et al,[76] 2010 Japan	RCT	71 Neonates High risk for AD (family hx of AD, within second degree) Duration of treatment At birth-6 mo Outcome At 6 mo Diagnostic criteria Unspecified	Intervention Apply emollient (unspecified) more than once a day and do not wash infant's face with any other detergent Controls Parent preference in skin care ("do what they like") Adherence criteria NA	TEWL of subjects showed elevation between 1 and 4 mo, which was considerably suppressed by moisturizer intervention	No effect[b] 5/35 moisturizer gp vs 6/32 control	Eczema-onset ratio among infants with +ve prick test -5/1 vs 6/8 (considerably lower in the moisturizer gp)
Horimukai et al,[10] 2014 Japan	RCT Investigator-blinded, parallel group study 2010-2013	118 Neonates High risk for AD (family hx of AD, first degree) Duration of treatment From 1 wk of life to 32 wk Outcome At 32 wk Diagnostic criteria Modified Hanifin and Rajka	**Intervention** 2e Douhet emulsion + petroleum jelly. At least 1 × daily Whole-body surface. Bathe daily mild soap Controls Petroleum jelly. Bathe daily mild soap Adherence criteria NA	Higher SC hydration in lower legs in moisturizer gp than control gp (at weeks 12 and 24) (S)	Positive effect[b] Cumulative incidence of AD at 32 wk of life: 19/59 in moisturizer gp vs 28/59 in control gp (HR, 0.48; 95% CI 0.27-0.86) RRR- 32% (P = .01) (S) No effect of moisturizer on allergic sensitization (S) Higher rates of sIgE to egg in infants with AD and skin rash (OR, 2.86; 95% CI, 1.22-6.73) **(S)**	Skin rash -13 infants (6/59 - moisturizer gp and 7/59 - control gp). No difference No difference in *S aureus* colonization (S)
Simpson et al,[11] 2014 BEEP Pilot United Kingdom, United States	Pilot RCT (1:1)- 2-arm parallel-group, assessor-blind 2010-2011	124 Neonates High risk for AD (family hx of AR/AS/AR, first degree) Duration of treatment Within 3 wk of birth-6 mo Outcome 6 mo Diagnostic criteria As determined by investigator	Intervention At 1 × daily, full body except scalp Moisturizers of 3 different viscosities (United Kingdom- SSO, Double-base gel, liquid paraffin 50% in white soft paraffin. United States-SSO, Cetaphil, Aquaphor ointment) Adherence criteria At least 5 d a week Adherence rate- 85% Controls No moisturizers Both Avoid soap, bubble bath, bath oils, wipes Use fragrance-free cleanser and shampoo	NA	Positive effect[b] Cumulative incidence of AD at 6 mo: (43% control group vs 22% moisturizer group) RRR of 50% (RR, 0.50; 95% CI, 0.28-0.9; P = .01) (S)	Mild superficial cutaneous infections – similar in each gp Cream/gel most preferred by participants (67.2%), oil (23.4%)
Lowe et al,[13] 2018 PEBBLES Australia	Pilot RCT parallel, single blind (outcome assessor) 2013-2014	80 Neonates High risk for AD (family hx of AD/AR/FA, first degree) Duration of treatment Within 3 wk of life-6 mo of age Outcome-allergy 6 and 12 mo of age Diagnostic criteria UKWP	Intervention 2 × daily, full body, 6 g/d Ceramide-dominant moisturizer (EpiCeram) Adherence criteria At least 5 d/wk Adherence rate 76% Controls No skin care instructions	Similar TEWL, skin pH, hydration and "oiliness" (sebum) in the 2 gps	Positive trend[b] Reduced cumulative incidence of AD in the moisturizer gp At 6 mo, 13% (5/38) vs 22% (8/37), P = .38 (NS) At 12 mo, 18% (7/38) vs 31 (11/36), P = .28 (NS) Reduction in FS at 12 mo in the tx group (0% (0/21) vs 19.4% (7/36), P = .04	NA

(*continued*)

Table 1 (*Continued*)

Autho/publication yearCountry(ies) of study	Study design	Population characteristics	Frequency, type, and instructions for moisturizer use	Outcome of skin parameters	Outcome of clinical allergyAllergic sensitization	Other outcome
Bellemere et al[77] 2018, Bellemere et al [78] 2019 Country Not mentioned Specifically Europe	RCT	120 Neonates High risk (2 atopic first degree relatives) Parallel gp: 60 neonates, no risk (no family hx of atopy) Duration of treatment 2-3 wk to 6 mo Outcome -allergy 6 mo **Diagnostic criteria** Unspecified	Intervention Balm-French cosmetic brand dedicated to children' skin Apply balm 2 × a day, cleansing cream and bath oil twice a week from the same brand Adherence criteria - Control No intervention	NMF and ceramide levels increased significantly in the intervention group.	Positive effect[b] 9.8% in moisturizer gp, 18.3% in the control group, and 6.7% in the no-risk group: RR reduction of 54% owing to emollient applications ($P = .12$) After a follow-up of 24 mo, 7 new cases of AD were observed in the "prevention group" and 6 new cases in the "control group."	Predictive clinical signs of AD at D0 were desquamation of the face and erythema in neck skin folds.
Yonezawa et al,[79] 2018 and Yonezawa and Haruna,[80] 2019 Japan	RCT 2014-2015 Follow-up study of RCT 2015-2017	227 Neonates General population Duration of treatment 1 wk to 12 wk of age Outcome 3 mo 155 of 227 infants Outcome 2 y Diagnostic criteria Self-reported questionnaire	Intervention Pigeon baby milk lotion (Pigeon, Japan) or Atopita milky lotion (Tampei Pharmaceutical, Japan) Pigeon baby soap (Pigeon, Japan) or Kewpie baby body soap, cow brand soap (Kyoshinsha, Japan) Moisturizer – at least once a day Reduced bathing – every 2 d Adherence criteria None Control Daily bathing No moisturizer. Could be applied if preferred	Lower face TEWL, higher face and body SCH- intervention gp at 3 mo ($P < .05$) (S) High face TEWL at 3 mo associated with FA and AD by 2 y (S)	No effect[b] No diff btw AD and FA by 2 y in both moisturizer and control gp Assoc btw short-term skin problem at ≤3 mo and AD and FA until 2 y (S)	Reduced rates of diaper dermatitis – intervention gp at 3 mo (S) Reduced rates of skin problems at 3 mo in intervention gp
Dissanayake et al,[15] 2019 Japan	RCT 2 × 2 factorial, nontreatment No date specified 2012-2014	459 Neonates General population Duration of treatment Birth to 6 mo of life Outcome-allergy 1 y of age Diagnostic criteria Japanese Dermatologic Association	Intervention Locobase Repair Cream (Daiichi Sankyo, Japan): Ingredients - ceramide, cholesterol, and free fatty acids. 2-3 times per day. Areas - cheeks and perioral area. Other body parts at discretion Adherence criteria Moisturizer used at least twice a day Adherence rate 80% Controls Synbiotics twice daily; Synbiotics + moisturizers; no treatment	NA	No effect[b] No effect of moisturizer on AD and FA at 1 y Cumulative incidence of AD at 1 y 30.9% in skin + synbiotic gp 32.1% in synbiotic gp 38.3% in skin only gp 25.6% in no Tx gp (NS) No significant diff in sensitization to food and aeroallergen between the gps	TARC & EASI not significant across gps

(*continued*)

Table 1 (*Continued*)

Autho/publication yearCountry(ies) of study	Study design	Population characteristics	Frequency, type, and instructions for moisturizer use	Outcome of skin parameters	Outcome of clinical allergyAllergic sensitization	Other outcome
McClanahan et al,[81] 2019 United States	RCT Investigator blinded 2011-2014	100 Neonates High risk (family hx of AD/AR/FA, first degree) Duration of treatment Within 3 wk of birth to 2 y Outcome -allergy 1 y and 2 y Diagnostic criteria UKWP	Intervention Cetaphil Restoraderm moisturizer and cleanser (Galderma) Contains shea butter, pseudoceramide, arginine, and sodium pyrrolidone carboxylic acid. Daily, all body areas except scalp and diaper region Cleanser used when needed for bathing Adherence criteria Moisturizer applied 5 or more days per week Adherence rate At 1 y, 66.7% vs 45.5% (moist vs control) At 2 y, 40.0% vs 33.3% (moist vs control) Control Baby wash, shampoo, lotion (Johnson's and Johnson's head-to-toe, United States). Used when needed, not compulsory	TEWL, Capacitance - no significant differences btw intervention vs control at 2, 6, and 12 mo pH - significant increase at 2 mo in intervention gp vs control -pH-no significant difference at 6 and 12 mo	Positive trend[b] AD at 1 y-13.2% vs 25.0% in favor of intervention gp (P = .20) (NS) AD at 2 y -19.4% vs 31.0% in favor of intervention gp (P = .29) (NS)	No difference in NMF No difference in skin microbiome btw 2 gps at 6 mo Bacterial skin infection: 7.4% vs 6.5% (intervention vs control gp) Hypersensitivity reactions - 14.8% vs 8.7% (Intervention vs control gp)
Skjerven et al,[14] 2020 PreventADALL (Preventing Atopic Dermatitis and ALLergies in Childhood) Sweden and Norway	RCT 2 × 2 factorial, multicentre 2015-2017	2397 Neonates General population Duration of treatment From 2 wk of life -8 mo of life Outcome 12 mo Diagnostic criteria UKWP or Hanifin and Rajka	Intervention Bath oil containing liquid paraffin, at least 4 d/wk. Bath with oil for 5-10 min, facial cream (Ceridal, GSK) applied to face after bath. Soap discouraged Food intervention: peanut butter, cow's milk, wheat porridge, scrambled eggs Adherence criteria Moisturizer: at least 3-5 d/wk for at least 16 wk. Food: Intake of each food for a minimum 3-5 d/wk for at least 5 wk Adherence rate 27% (bath oil + ceridal); 43% (bath oil only); 32% (food) Control Not reported	NA	No effect[b] AD at 12 mo (8% no tx group, 11% in skin tx group, 9% in food intervention gp, 5% - combined intervention group) 3•1% (95% CI, −0•3 to 6•5) in favor of control Neither skin moisturizers nor early complementary feeding reduced development of AD	36 hospital admissions and 9 cases of impetigo evenly distributed across the gps AD presented earlier among skin intervention than those without skin intervention and infants in the combined interventions group had delayed presentation of disease

(*continued*)

Table 1 (*Continued*)

Autho/publication yearCountry(ies) of study	Study design	Population characteristics	Frequency, type, and instructions for moisturizer use	Outcome of skin parameters	Outcome of clinical allergyAllergic sensitization	Other outcome
Chalmers et al,[12] 2020 BEEP United Kingdom	RCT 2014-2016	1394 Neonates High risk (family hx of atopy, first degree) Duration of treatment First 3 wk to 1 y of age Outcome-allergy At 2 y Diagnostic criteria UKWP	Intervention Doublebase gel (Dermal Laboratories, United Kingdom) Or Diprobase Cream (Bayer, United Kingdom). At least once daily. Whole body except scalp. Moisturizer after every bath. Adherence criteria At least 3-4 times per week to most of the body Adherence rate -74% at 1 y, Control-18% at 1 y. 70% at all times Controls No moisturizers Both groups Avoid soap, bubble bath, bath oils, wipes Use fragrance-free cleanser and shampoo	NA	No effect[b] Eczema in (23%) in moisturizer gp vs (25%) in control gp (adjusted RR, 0.95 (95% CI, 0.78-1.16); *P* = .61 (NS) FA – (7% in moisturizer gp vs 5% in control gp) egg - greater risk (NS) AR and wheeze similar in the 2 gps Proportion of allergic sensitization to food and aeroallergens were similar in the 2 gps	Skin infections 15% moisturizer vs 11% in control Mean no of skin infections per child in year 1 (0.23 (SD, 0.68) in moisturizer gp vs 0.15 (0.46) in control gp) adjusted incidence rate ratio 1.55 (95% CI, 1.15-2.09) (S)
Thitthiwong and Koopitakkajorn,[82] 2020 Thailand	RCT 2016-2017	52 infants High risk (Family hx of allergic dx, first degree) Duration of treatment <10 wk to 9 mo of age Outcome 9 mo Diagnostic criteria AD guidelines by Eichenfield et al (2014)	Intervention "Cold Cream" containing white petrolatum, stearyl alcohol, propylene glycol, and glycerin. Applied all over the body except periorbital and perioral areas. At least once daily shortly within 3 to 5 min after bathing and padding dry the baby skin Control No skin care product except using the gentle liquid baby cleansers during bathing and the barrier ointment or cream on diaper areas as needed.	NA	Positive effect[b] At 9-mo-old follow-up, 0% intervention group vs 14.8% in the control group had AD (*P* value = .045). (S)	Mean age of onset of AD was 5.5 ± 0.55 mo Clinical dryness was comparable between groups (*P* = .12)

(*continued*)

Table 1 (*Continued*)

Autho/publication yearCountry(ies) of study	Study design	Population characteristics	Frequency, type, and instructions for moisturizer use	Outcome of skin parameters	Outcome of clinical allergyAllergic sensitization	Other outcome
Techasatian and Kiatchoosakun,[83] 2021 Thailand	RCT 2019-2020	154 High-risk neonates (parental hx of AD/AR/AS) Recruited within 3 wk of birth Outcome 6 mo of age Diagnostic criteria Hanifin and Rajka	Intervention Choose from 5 options: Ezerra lotion, Eucerin Omega Plus Extra Soothing, Eucerin Omega Soothing lotion, Physiogel A.I. restoring lipid balm and Lyl Hydrating moisturizer Emollient and skincare advice Apply at least once daily to entire body surface (excluding the scalp) Adherence criteria low (1-3 d/wk; moderate (4-6 d/wk) Adherence rate Majority had low (40 [54.05%]) to moderate (34 [45.95%]) adherence Control Skincare advice only	NA	Positive effect[b] At 6 mo, cumulative incidence of AD (21.62% in emollient gp vs 54.17% in control gp) RRR - 60.1% (RR, 0.39; 95% CI, 0.24-0.64; $P <$ .001) (S) Low adherence to emollient use associated with lower number of patients with AD ($P = .008$).	Emollient gp developed AD later and had lower severity of AD than control gp ($P < .001$). Cutaneous eruptions more frequent in the emollient gp Exposure to passive smoking associated with development of AD as compared with non-smoking exposure, both during pregnancy and after the child's birth ($P < .001$).

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; CI, confidence interval; BEEP, Barrier Enhancement for Eczema Prevention; FA, food allergy; FS, food sensitization; HR, hazard ratio; NA, not available; (NS), not statistically significant; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; (S), statistically significant; SSO, sunflower seed oil; UKWP, United Kingdom Working Party Criteria.
[a]Published RCTs with at least an arm with moisturizer only intervention and outcome of AD with or without FA.
[b]AD/FA outcome.

whose moisturizer use mirrored the intervention group in some cases. Similarly, Xu et al,[18] who did not find any difference in incidence rate of AD between experimental and control groups in a meta-analysis of prevention studies (OR, 0.7; 95% CI, 0.48-1.01, 9 trials), could not reach a definitive conclusion because of the differences in moisturizers used, sample sizes, and follow-up times across the studies. This raises the question of what qualities a moisturizer needs to have to be effective in prevention and management of AD. It therefore becomes important to look at the evidence supporting early moisturization of the skin to prevent AD and FA, and also the possible reasons why it has not been useful in preventing these allergies.

Skin Barrier and Epicutaneous Sensitization in the Pathogenesis of Atopic Dermatitis and Food Allergy

The SB is made up of layers of corneocytes in the stratum corneum (SC), tightly bound within a highly ordered lipid matrix to form a firm semipermeable membrane preventing excess loss of water from the body and ingress of microbes, irritants, and allergens (Fig 1). The corneocytes are enveloped by insoluble structural proteins such as filaggrin (FLG), loricrin, involucrin, and small proline-rich proteins, which protect the hydrophilic environment within. FLG in particular is important for skin moisturization, because its catabolism yields free amino acids, urocanic acid, lactic acid, and pyrrolidone carboxylic acid, which are major constituents of natural moisturizing factor.[19] These endogenous moisturizers attract water into the corneocytes making them turgid, which contributes to the soft and supple property of healthy skin. The corneocytes are interwoven within a hydrophobic environment formed by a complex arrangement of lipids, including ceramides, fatty acids, cholesterol, and its esters. The composition and structure of these lipids are an important determinant of the skin's permeability barrier to water and hydrophilic agents.[20] The functioning of this barrier is commonly assessed by measuring TEWL; where the higher the water loss the weaker the barrier function of the skin.

AD arises as a result of complex interaction between SB abnormalities and immunologic alterations. These epidermal barrier

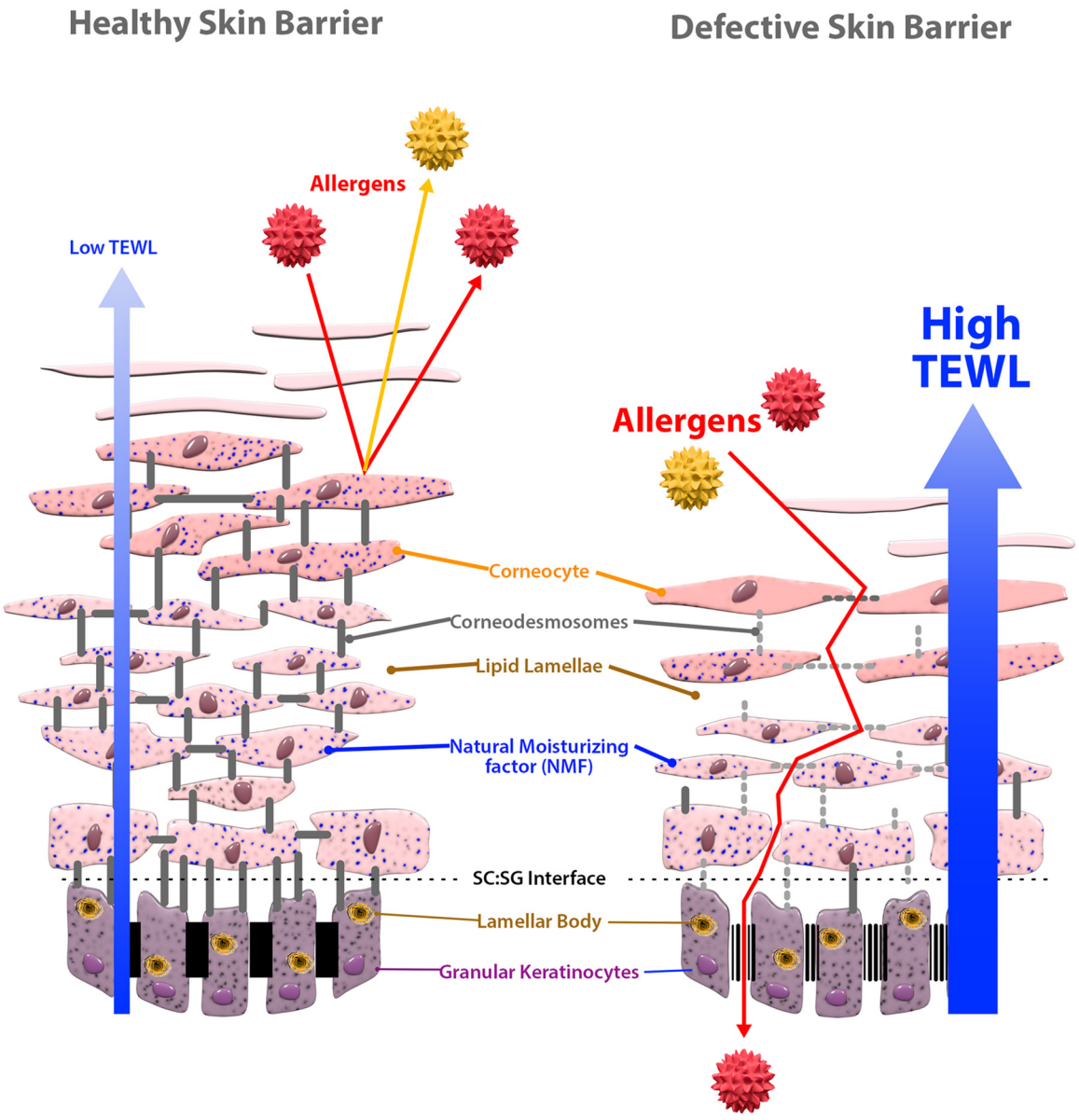

Figure 1. Healthy and defective skin barrier. Healthy skin barrier is composed of corneocytes lined by structural proteins such as filaggrin and interwoven in a lipid matrix. Abnormalities of the SB components make it defective, leading to increased TEWL and permeation of allergens through the skin. SB, skin barrier; SC, stratum corneum; SG, stratum granulosum; TEWL, transepidermal water loss.

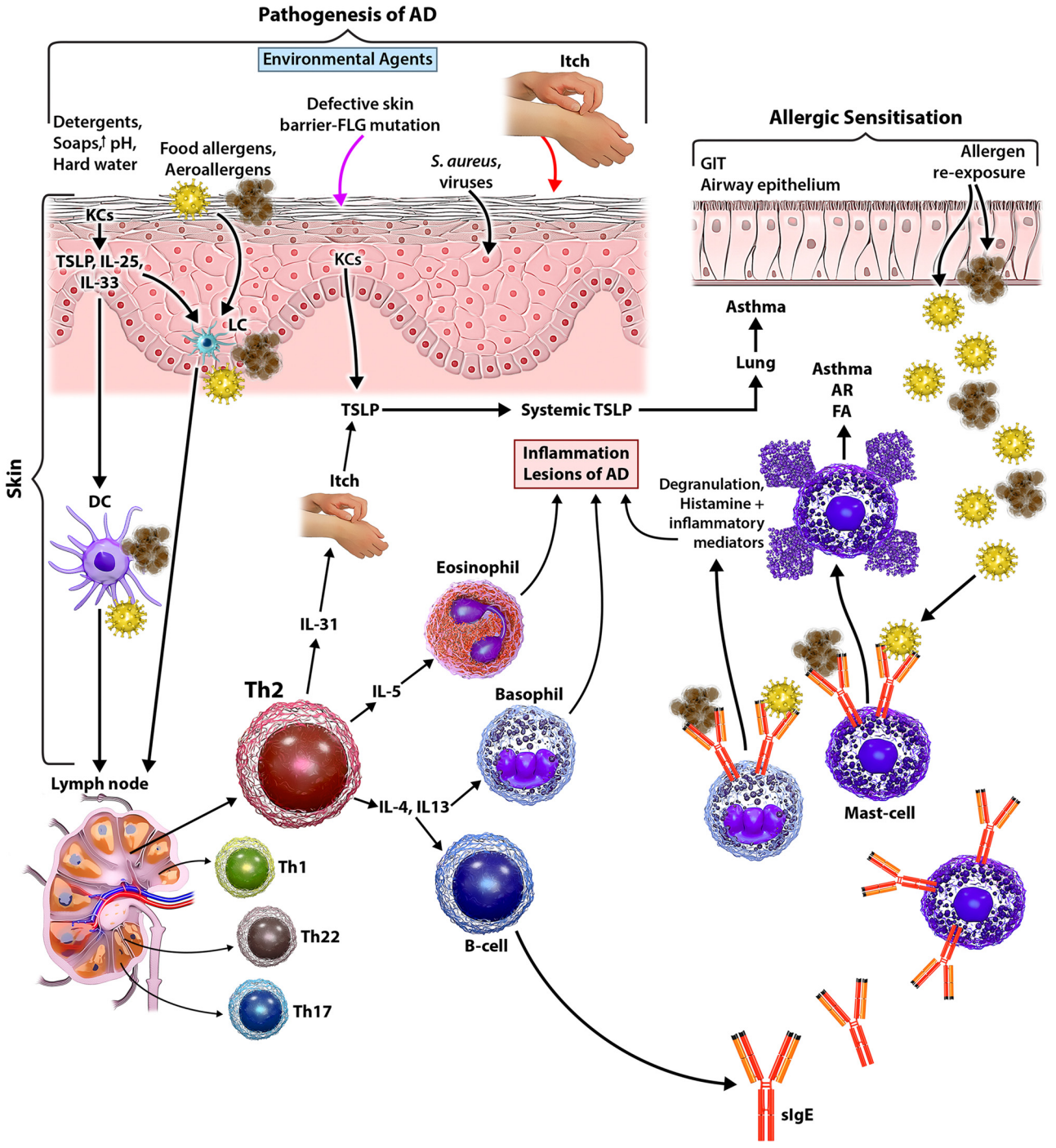

Figure 2. Pathogenesis of AD and epicutaneous sensitization. Allergen exposure through damaged skin barrier stimulates production of T_H2 cytokines, causing inflammation in AD, allergic sensitization, and systemic inflammation. AD, atopic dermatitis; AR, allergic rhinitis; DC, dendritic cell; FA, food allergy; GIT, gastrointestinal tract; IL, interleukin; KC, keratinocyte; LC, Langerhans cell; MC, mast cell; sIgE, allergen-specific immunoglobulin E; *S aureus, Staphylococcus aureus*; TSLP, thymic stromal protein.

abnormalities or damage (Fig 1) can be caused by various factors that include abnormal expression of structural proteins (such as reduced levels of functional FLG owing to *FLG* gene mutations), altered lipid synthesis, cutaneous dysbiosis, increased skin pH, and exogenous environmental factors (eg, house dust mites, detergents, hard water).[19,21,22] Barrier abnormalities are not only important in the pathogenesis of AD; they have also been associated with the development of FA. Flohr et al[23] reported an association between TEWL and food sensitization in exclusively breastfed infants despite adjustment for *FLG* mutation status and AD presence. Although Ashley et al[24] showed that SB gene *SPINK5* mutation is associated with challenge-proven FA, Leung et al[25] reported that lower FLG content and higher TEWL levels were associated with AD FA+ when compared with AD FA−, thus demonstrating a link between epidermal damage and FA.

Enhanced permeation of microbes, allergens, and irritants through a defective SB stimulates immune dysregulation (Fig 2). Antigen-presenting cells (Langerhans cells and dendritic cells) capture and process allergens that prime conversion of naive T-helper cells (T_H0) to T-helper 2 (T_H2) in the lymph nodes. Allergic sensitization occurs with production of allergen-specific IgE (sIgE) from the B-cells stimulated by T_H2 cytokines, interleukin (IL)-4 and IL-13. These sIgEs bind to the FcεRI receptors of mast cells and basophils. A pool of

memory B-cells and allergen-specific T_H2 cells is subsequently produced with facilitated antigen presentation.[26] Following re-encounter with the sensitizing allergen through either the skin, gut, or airway, there is crosslinking of sIgE with activation of mast cells and basophils causing degranulation and release of inflammatory mediators, which in conjunction with cytokines from allergen-specific T_H2 cells causes local and systemic inflammation, hypersensitivity, and target organ damage predisposing to FA, allergic rhinitis, and asthma.[26] This process by which the defective SB facilitates permeation of allergens, stimulating IgE production and predisposing to airway and gastrointestinal allergy, is known as epicutaneous sensitization.

Evidence Supporting Epicutaneous Sensitization in the Development of Allergy

Various animal and human studies have supported the mechanism of epicutaneous sensitization.[27,28] Strid et al[27] demonstrated that epicutaneous exposure to peanut through abraded skin of BALB/c mice induced high levels of peanut-specific IL-4 and IgE and when followed by oral exposure to peanuts, prevented tolerance to the allergen. On further oral exposure, there was increased sensitization, whereas other mice that were previously tolerant became partly tolerant on epicutaneous exposure.[27] Ovalbumin (OVA), a clinically relevant allergen, was applied to the shaved abdominal skin of 3 types of mice—the homozygous flaky tail (*ft/ft*) mice (which have a dry, scaly skin, and a similar genetic mutation to *FLG* mutation in humans), the heterozygous (*wt/ft*) mice, and the wild-type (*wt/wt*) mice. No gross skin lesions were seen in any of the mice. However, there was marked cutaneous inflammation on histopathology and increased TEWL on the site of allergen challenge and raised OVA-specific IgE seen in the *ft*|*ft* mice when compared with that seen in the other mice.[28] In another study, epicutaneous sensitization was carried out with OVA in 1 group of BALB/c mice, whereas another group had oral immunization with OVA and cholera toxin. An oral challenge that was subsequently done increased IL-4 levels, IgE-dependent intestinal mast cell expansion, and anaphylaxis only among the mice who had sensitization through the skin with OVA.[29] This suggests the role of the skin and not gut for sensitization. The observed anaphylaxis suggests systemic hypersensitivity. Tolerogenic T regulatory cell cytokines in the gut have been found to protect against FA. This has led to the dual-allergen exposure theory in FA, whereby food sensitization through an impaired SB leads to cytokine dysregulation and development of FA, whereas early oral exposure to a food allergen induces tolerance thereby preventing FA.[30] The above-mentioned studies in mice were done on disrupted SB, artificially by abrasion and tape stripping for BALB/c mice and genetically predetermined barrier defect for *ft*|*ft* mice, thus demonstrating that sensitization is facilitated through a defective SB. This is further supported by another study which demonstrated that application of peanut or OVA through intact skin of BALB/c mice did not induce allergic sensitization but rather blocked induction of oral sensitization.[31] Other studies in animal models have documented increased airway hyperresponsiveness and inflammation following exposure to inhaled allergen, to epicutaneously sensitized mice compared with control.[32,33]

Clinical evidence of epicutaneous sensitization was found in a longitudinal study (ALSPAC), where development of peanut allergy (PA) among preschool children was associated with eczema and the use of skin preparations containing peanut oil. These oils were mostly used in topical formulations for managing inflammatory lesions, such as diaper rash, eczema, and dry skin. PA was independently associated with oozing, crusted lesions suggesting that a defective SB was important in the development of the allergy.[34] A substantial association between *FLG* mutation and challenge-proven PA was demonstrated following adjustment for AD in a cohort of children from multiple countries.[35] Brough et al[36] demonstrated that among children with *FLG* mutations, there was a dose-dependent increase in PA and sensitization with increased exposure to house dust peanut protein, whereas there was no relevant effect of exposure in children without *FLG* mutations. This was after adjustment had been made for AD and egg allergy.[36] In a study of Japanese women, a substantial relationship between use of wheat-containing facial soap and the development of FA to wheat was found.[37] Increasing food sensitization has also been associated with worsening severity of AD in infants.[23,38] Another study demonstrated that early aggressive treatment of AD in infants with corticosteroids was associated with fewer allergies at 2 years of age. Longer duration of AD before remission with topical steroids was associated with increased risk of FA.[39]

Objective measures have also shown a relationship between defective SB and sensitization or allergy. Boralevi et al[40] found a correlation between high TEWL levels and greater levels of sensitization to aeroallergens in infants with AD. Higher TEWL levels were associated with 2 or more positive results of atopy patch test (APT). Similarly, De Marchi et al[41] found an association between increased allergic sensitization (from skin prick tests) and high TEWL values in nonlesional skin of children with AD.[41] Wärnberg et al,[42] in a recent report, documented that raised levels of TEWL at the age of 3 months increased the risk of food sensitization at 6 months of life. Horimukai et al[43] documented that high TEWL measurements taken within 7 days of life correlated with increased incidence of AD at 32 weeks of life irrespective of *FLG* mutation status. High TEWL was also associated with a nonsubstantial increase in ovomucoid sensitization.[43] Flohr et al[44] reported that infants with *FLG* mutation were more likely to have eczema and higher TEWL at 3 months of age. They also found that TEWL was also elevated in the skin of *FLG* mutation carriers without eczema.[44] These suggest that SB impairment may be an early event that predisposes to AD and other allergies. It therefore appears logical that modification of SB could be important in development and prevention of atopic conditions such as AD and FA.

Effects of Moisturizers on the Skin

Moisturizer Types and Effects on Skin Barrier and Disease

Moisturizers are widely used cosmetic and pharmaceutical products which restore moisture to the skin. They are often referred to as emollients, yet the meaning of these words is subtly different; moisturizers improve skin hydration whereas emollients soften and smoothen the skin. Moisturizers have been found to reduce skin dryness, prolong time to flare, and lessen topical steroid use in AD.[45] Although dryness and SB impairment seem to be linked in disease conditions such as AD, they are different entities with a complex relationship. The outer layers of the SC contribute more to the appearance of surface dryness and little to permeability. Hence, a change in dryness may not always be accompanied by changes in SB function as measured by TEWL. Similarly, the relief of dryness through the use of moisturizers does not necessarily have positive effects on the SB.

Moisturization products are available in various combinations of ingredients, including emollients and humectants, and other excipients which are required to make a cosmetically acceptable topical preparation (Table 2).[46] Occlusive emollient products such as Vaseline (pure petrolatum ointment) form a hydrophobic film over the outer layer of the skin. This transiently reduces TEWL through evaporation, rehydrating the skin passively. This occlusive effect requires frequent and prolonged application of the emollient to sustain it. Petrolatum is one of the most occlusive products that is able to reduce TEWL by 99%, thereby enabling SB repair.[47]

Ointments and oils are greasy in nature and need addition of emulsifiers with water to create creams and lotions to improve cosmetic acceptability. However, some creams and lotions (oil-in-water

Table 2
Ingredients of Moisturizers

Ingredients				Excipients			
Occlusives	Humectants	Physiological lipids (fats and oils)	Natural extracts	Emulsifiers	Antioxidants	Preservatives	Fragrances
Mineral oil Liquid paraffin Petrolatum White soft paraffin Beeswax Silicones Dimethicone Zinc oxide	Urea Glycerol Lactic acid (AHA) Sorbitol Panthenol Propylene glycol Hyaluronic acid	Fatty acids Lauric acid Linoleic acid Linolenic acid Oleic acid Stearic acid Monoglycerides Diglycerides Triglycerides Ceramides Cholesterol	Aloe vera *Avenao sativa* (colloidal oatmeal) Green tea Curcumin	Stearic acid Palmitic acid Cholesterol Sodium lauryl sulfate	Tocopherols, butylated hydroxytoluene (BHT) Alkyl gallates Ascorbic acid Citric acid Tartaric acid EDTA	Isothiazolinone Methylchloroisothiazolinone Imidazolidinyl urea Parabens Butyl paraben Methyl paraben Propyl paraben Ethyl paraben	Farnesol Geraniol Benzyl alcohol Eugenol Limonene Hydroxycitronella

NOTE. Some ingredients belong to more than 1 class.

emulsions) seem to increase TEWL, enhance sodium lauryl sulfate (SLS)-induced irritation, and increase penetrance of drugs such as hydrocortisone.[48] Aqueous cream BP (liquid paraffin and white soft paraffin), which had been widely used as a moisturizer, caused an increase in TEWL to levels associated with onset of disease flares in participants with AD.[49] This was attributed to the presence of a surfactant used to create the emulsion, SLS, which is a known skin irritant and trigger for inflammation in AD.[50] Typically used oil-in-water emulsions, without humectants or harsh surfactants, do not seem to have any relevant effects on the SB (positive or negative) and impart limited skin moisturization.[9] This shows that the surfactants used as emulsifiers in moisturizers is an important consideration and that the emulsification of emollient lipids with water reduces their effectiveness as moisturizers.

Skin humectants hydrate the skin by attracting water from the dermis and the environment into the epidermis. Some of them such as urea and glycerol are naturally found in the skin. Glycerol is a common humectant in moisturizers with excellent hydrating properties which has been attributed to its high accumulation in the SC.[51] Moisturizers comprising emollients and glycerol offer superior skin moisturization compared with emollient only formulations[9,52] and improve skin dryness and disease severity in subjects with AD.[45] Some studies also show that glycerol can help accelerate SB repair after physical disruption.[53,54] This may explain why the addition of humectants such as glycerol to oil-in-water emulsions appears to mitigate the negative effects of the emulsifiers on the SB.[55] However, in practice, glycerol creams have varied effects on the SB providing protection against irritants such as SLS and nickel on one hand and enhancing the penetration of substances such as hexylnicotinate on the other hand.[56,57] Similarly, urea has been found to enhance penetrance of some drugs such as salicylic acid, corticosteroids, and antifungal medications.[58,59] At higher concentrations of 10% or more, urea also has a keratolytic effect.[59] Yet, lower concentrations (3%-5%) of topical urea preparations seem to strengthen the SB (reducing TEWL and skin sensitivity to irritants).[60,61] This is in part because of the ability of urea to enhance the expression of FLG.[62] Moreover, the ability of urea creams to prevent or delay flares of AD is attributed to these improvements in barrier function.[61,63] Humectants therefore seem to have a complex effect on the SB, both enhancing the permeability of substances on one hand and protecting against the effects of these substances on the other hand, depending on the formulation of the vehicle and their concentrations.

Beyond emollients and humectants, a plethora of natural lipids and phytochemicals can be found in moisturizers with a range of purported physiological activities, including antioxidant, anti-

What do we know?

- Skin barrier dysfunction predisposes to, and often precedes AD and FA
- Allergen sensitisation through a defective skin barrier can lead to clinical disease
- Moisturisers are beneficial in AD by prolonging time to flare, reducing the number of flares and the quantity of topical corticosteroids needed to improve eczema
- Moisturisers can have negative or positive effects on the skin barrier depending on their formulation and ingredients
- Some moisturisers may enhance skin permeability, enhancing drug delivery and increasing susceptibility to irritants and potentially allergens depending on their formulation and conditions of use
- There is limited evidence to suggest that skin-barrier enhancing moisturisers may reduce allergen sensitisation

Figure 3. What do we know about moisturizers and allergic disorders?

What do we need to find out?

- Are the differences in outcome of prophylactic moisturisation for atopic dermatitis and other allergies dependent on moisturiser choice?
- Does timing of the start of moisturisation in infancy significantly affect the outcome of prevention?
- Does frequent moisturisation increase contact of allergens with the skin to enhance epicutaneous sensitisation?
- Does continuous moisturiser use delay rather than prevent the development of AD and FA? Could prolonged delay lead to eventual prevention of AD and FA?
- Does increased skin permeability caused by some moisturisers increase the risk of AD and FA?
- Will combination of other prophylactic modalities like environmental modulation with moisturisation have a greater effect on the prevention of AD and FA?
- How does moisturisation prevent or delay relapse (secondary prevention) in established AD?
- Is the effect of prophylactic moisturisation in less developed skin of infants different to that of clinically inflamed skin of older people?

Figure 4. What do we need to find out in relation to moisturizers and allergy?

inflammatory, SB strengthening, and moisturizing. Ceramides, cholesterol, and fatty acids are thought to penetrate the SC and replace the endogenous lipids of the lamellar matrices that are deficient in AD to help restore SB function.[64,65] In a cohort of pediatric patients, a ceramide-dominant, trilipid cream was found to considerably improve clinical lesions of AD, improve SB function, and enhance SC cohesion.[66] Enhanced lamellar membrane formation is seen following treatment with some lipid creams compared with the use of other common moisturizers.[66,67] Other ingredients such as niacinamide, tocopherol, and ascorbic acid are thought to enhance the endogenous production of key SB components.[68] However, as observed with humectants, which themselves often have physiological effects, the overall effects of finished moisturizer products on the SB depend very much on formulation. Natural oils, such as olive oil and sunflower seed oil, are commonly used as moisturizers. Although they are high in physiological lipids, phytochemicals, and glycerol and concordantly impart good moisturization, they have negative effects on the SB and act as good penetration enhancers owing to their high content of fatty acids such as oleic acid. [8,69]

Fully appreciating the contribution of moisturizers to the management of AD is challenging; on one hand, the relief of dryness and the improved penetration of topically applied drugs such as corticosteroids is desirable, and yet on the other hand, the condition is driven by SB disruption with the permeability of irritants and allergens being key triggers. It is evident that some emollients are positive to the SB, whereas some are either neutral or negative to the SB.

Effects of Moisturizers on Allergen Sensitization

Few studies have documented the effect of moisturizers on allergic sensitization. Sindher et al[70] demonstrated superior SB-enhancing properties, reduced total IgE, and increased total IgG4 and peanut-specific IgG4 levels with the use of a trilipid moisturizer in infants, when compared with a paraffin plus petrolatum-based product. The trilipid cream was also associated with higher levels of tolerogenic CD4+ cells and lower proinflammatory IL-4 CD4+ cells, demonstrating reduced allergic sensitization and increased tolerance.[70] The reactions of the APT, a type IV delayed hypersensitivity to intact protein allergens, mimic the early phase of AD microscopically and macroscopically, and it has been used as a model to study the disease.[71] Mias et al[72] documented a preventive effect of moisturizer pretreatment on *Dermatophagoides pteronyssinus* APT. This was characterized by inhibition of inflammatory epidermal dendritic cells and activation of Langerhans cells, thus demonstrating prevention of inflammation by moisturizer. Similarly, eczematous house dust mite APT reactions in patients with AD were prevented with a fatty acid rich moisturizer.[73] A study comparing vehicles in 2 methods of APT found that the petrolatum-based method was associated with increased number of reactions and more severe reactions than the aqueous one.[74] These studies suggest that pretreatment of the skin with SB-enhancing moisturizers can prevent development of AD-like lesions induced by aeroallergens, yet some emollients can also facilitate passage of allergens when applied together. This is likely to be affected by the properties of the topical formulation and the order of application or exposure, a concept widely accepted when viewing moisturizers as vehicles for topical drug delivery.[75]

Overall, some moisturizers seem to improve the SB which may reduce susceptibility to external agents. Paradoxically, increased permeability may sometimes be seen with these agents depending on their formulation and the conditions of use.

Conclusion

Current evidence suggests that the use of moisturizers in preventing AD may be ineffective whereas the possibility of increased risk of AD and FA with this intervention needs to be confirmed. The types of moisturizers being the cause of these observations are plausible but need further investigation. There is good evidence to show that a disrupted SB is important in the development of AD and FA, which is in

part by increasing the risk of epicutaneous sensitization. Some moisturizers strengthen the SB and seem to subsequently prevent or delay relapse (secondary prevention) with clear benefits in the management of AD. Some other moisturizers have limited effects on the SB and in some cases even damage it. There is evidence that some moisturizers can increase permeability of the skin to irritants and drugs and that this may also be the case for allergens (Fig 3). Although the use of barrier-strengthening moisturizers is expected to prevent primary development of AD and FA, there is currently very limited evidence on the effects of these moisturizers on allergen sensitization. Does the use of moisturizers prophylactically and in younger, less developed skin have different effects to use on clinically dry or inflamed skin? How do some of the paradoxical effects of moisturizer products affect allergy prevention? There are still questions that need to be answered to fully determine the usefulness of moisturizers in prevention of AD and FA (Fig 4).

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