Altered Epidermal Permeability Barrier Function in the Uninvolved Skin Supports a Role of Epidermal Dysfunction in the Pathogenesis of Occupational Hand Eczema

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Keywords

Hand eczema · pH · Hydration · Permeability barrier · Transepidermal water loss

Abstract

Although a compromised epidermal permeability barrier can contribute to the development of contact dermatitis, whether subjects with hand eczema display abnormalities in baseline epidermal permeability barrier function in their uninvolved skin remains unknown. The aim of the present study was to assess epidermal permeability barrier function in subjects with and without hand eczema in clothing manufacturers. Upon approval by the institutional review board, volunteers were recruited from clothing manufacturers in Guangzhou City, China. An 11-item questionnaire was used to collect general data from the volunteers. The diagnoses of self-proclaimed hand eczema were further confirmed by a dermatologist. Epidermal biophysical properties, including transepidermal water loss (TEWL) rates, stratum corneum hydration and skin surface pH were measured on the flexural surface of the left forearm in all volunteers. Epidermal biophysical properties were compared among cohorts of subjects with active hand eczema, a prior history of hand eczema and without any history of hand eczema. A total of 650

questionnaires were collected from 462 females and 188 males, with a mean age of 36.7 ± 0.46 years (range 16–69 years; 95% CI 35.8–37.59). Thirty-five subjects (5.4%) currently had hand eczema, while 28 subjects (4.3%) reported a prior history of hand eczema that was inactive currently. The prevalence of hand eczema did not differ significantly between genders. Neither a prior personal nor a family history of allergies was associated with the prevalence of hand eczema, but certain occupations and frequent contact with disinfectants were independently associated with the prevalence of hand eczema. In the overall cohort, males displayed higher TEWL rates and stratum corneum hydration levels than did females. Both skin surface pH and TEWL rates differed significantly among normal controls and subjects with active hand eczema or a prior history of hand eczema ($p < 0.05$). In conclusion, the uninvolved skin site of subjects with hand eczema exhibits abnormalities in epidermal permeability barrier, supporting a pathogenic role of epidermal dysfunction in hand eczema. Whether subjects with hand eczema in other occupations also display altered epidermal function on uninvolved skin remains to be explored.

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Introduction

Defects in the epidermal permeability barrier can provoke cutaneous inflammation [1]. Conversely, improvements in the epidermal permeability barrier can prevent and alleviate some inflammatory dermatoses. Studies showed that improvements in epidermal permeability barrier with a topical lipid mixture markedly improved the severity scoring of atopic dermatitis in children [2]. Likewise, topical applications of a barrier repair emollient in combination with topical glucocorticoid cream reduced psoriasis area severity index scores by approximately 25% in comparison to glucocorticoid cream alone [3]. Moreover, recent studies demonstrated that improvements in epidermal permeability barrier function delayed the relapse of psoriasis [4]. Furthermore, expression levels of proinflammatory cytokines in normal-appearing aged murine skin could also be lowered simply by improvements in epidermal permeability barrier function [5]. Together, disparate types of evidence suggest a regulatory role for the epidermal permeability barrier in the development of cutaneous inflammation.

Hand eczema, a common dermatosis, belongs to the category of contact dermatitis and it is often associated with particular occupations. Studies suggest that a defective epidermal permeability barrier function could contribute to the development of contact dermatitis. First, mutation in filaggrin, a structural protein required for the epidermal permeability barrier, decreases thresholds for both irritant and allergic contact dermatitis in mice [6]. Likewise, filaggrin mutations are associated with an enhanced tendency to develop both irritant and allergic contact dermatitis in humans [7, 8]. Moreover, reductions in filaggrin content were found in lesional skin of hand eczema, supporting a possible role for the epidermal permeability barrier function in the pathogenesis of hand eczema [9]. Second, while deficiency in caspase 14 impairs the epidermal permeability barrier [10], the uninvolved skin of hand eczema subjects displays a lower expression of caspase 14 [11]. Third, deficiencies in late cornified envelope proteins, LCE3B and LCE3C, other structural proteins of the barrier, are associated with allergic contact dermatitis [12].

Collectively, these studies suggest a pathogenic role for defects in the epidermal permeability barrier in the development of hand eczema. However, there is still a lack of sufficient, direct evidence to support that a defective permeability barrier predisposes to the development of hand eczema. If the development of hand eczema is attributed to the defective epidermal permeability barrier, unin-

involved skin sites should exhibit elevations in transepidermal water loss (TEWL) rates, an indicator of permeability status. Therefore, we compared here the epidermal permeability barrier function in a large cohort with or without hand eczema.

Subjects and Methods

This study was carried out in clothing manufacturer workers in Guangzhou City during the months of November and December. An 11-item questionnaire was used to collect general information of volunteers (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000506425). This questionnaire focused primarily on work-related questions. Subjects with self-proclaimed hand eczema were further examined by a dermatologist, who confirmed the diagnosis of hand eczema, according to its clinical features. No effort was made to distinguish between allergic and irritant contact dermatitis. Except for regular bathing and washing, no moisturizer lotion or cream was applied to measurement sites for at least 24 h prior to measurements. Epidermal biophysical properties, including TEWL rates and stratum corneum hydration were measured with GPskin Barrier® (GPower Inc., Seoul, South Korea) [13], while skin surface pH was measured with a portable skin pH meter (Hanna Instruments, Smithfield, RI, USA) on the flexor side of the left forearm. This study was approved by the institutional review board of the Dermatology Hospital of Southern Medical University (GDDHLS20180505). Informed consents were obtained from all subjects prior to the study.

Statistics

GraphPad Prism 5 software was used for all statistical analyses. The two-sided Fisher's exact test or χ^2 test was used when comparing qualitative variables. The Mann-Whitney test was used to determine the significance between groups, while one-way ANOVA was used to determine significances among more than two groups. Data are expressed as means $\pm$ SEM. *p* values are indicated in tables, the figure or figure legend.

Results

Basic Characteristics of Subjects

A total of 650 questionnaires were obtained from 462 females and 188 males, with a mean age of 36.7 ± 0.46 years (range: 16–69 years; 95% CI: 35.8–37.59). Subjects with current hand eczema were 38.69 ± 1.90 years of age (median: 40; 95% CI: 34.83–42.54) while subjects with past hand eczema (not now) were 36.61 ± 2.17 years of age (median: 35; 95% CI: 32.16–41.06). A majority of these volunteers (73%) worked in the production line. Over 80% of subjects in these cohorts did neither routinely use detergents to wash their hands nor moisturizers after hand washing. Fifty-five (8%) subjects had a family history of allergy, while 29% of subjects had a personal his-

Table 1. Demographic characteristics of subjects

	Females (<i>n</i> = 462)	Males (<i>n</i> = 188)
Mean age ± SEM (median, range), years	36.86±0.84 (35, 17–67)	36.63±0.54 (37, 16–69)
Hand eczema at present time	26 (6)	9 (5)
History of hand eczema, but not currently	19 (4)	9 (5)
Other dermatitis (excluding hand eczema and psoriasis)	0	0
Occupation		
Production lines	337 (73)	137 (73)
Warehouse workers	14 (3)	9 (5)
Management	3 (1)	1 (1)
Others	108 (23)	41 (22)
Substances that your hands frequently contact		
Disinfectants	6 (1)	1 (1)
Detergents	96 (21)	17 (9) ^b
Hair dye products	1	0
Cosmetics	16 (3)	0
Lubricants	20 (4)	14 (7)
Others	7 (2)	6 (3)
Wet work	5 (1)	6 (3)
Washing hands		
Mean frequency ± SEM, times/day	7±0.16	7±0.46
Washing with detergents	31 (7)	24 (13) ^d
Using moisturizers after washing hands		
Most times	24 (5)	0 ^a
Occasionally	97 (21)	7 (4) ^c
Never	341 (74)	181 (96) ^c
A personal history of allergy/atopic dermatitis	131 (28)	55 (29)
A family history of allergy/atopic dermatitis	39 (8)	16 (9)

Results are given as numbers with percentages in parentheses unless indicated otherwise. The two-sided χ^2 test was used to assess the significant differences between genders. ^a*p* = 0.0018, ^b*p* = 0.0003, ^c*p* < 0.0001, ^d*p* = 0.0119.

tory of allergy. Thirty-five subjects (5.4%) currently had hand eczema while 28 subjects (4.3%) only had a prior history of, but no current, hand eczema. Lifetime prevalence of hand eczema was 9.7% (63/650). Prevalence of hand eczema did not differ significantly between genders in this cohort although female dominance has been documented [3, 14]. Characteristics of these cohorts are summarized in Table 1.

Occupation Dominates the Prevalence of Hand Eczema

Because routine occupational and/or household activities are often associated with the development of hand eczema, we first analyzed which of these activities are possible risk factors for hand eczema. The prevalence of hand eczema varied greatly with occupation (*p* < 0.0001, Table 2). Subjects working either at a production line or warehouse appeared to be at a higher risk for the development

of hand eczema in comparison to other occupations (Table 2).

The prevalence of hand eczema varied greatly with exogenous substances or materials that hands frequently contacted (*p* = 0.0408). Among the substances and materials, disinfectants were most strongly associated with hand eczema (relative risk = 0.1727, *p* < 0.05; Table 2). Although wet work is considered as a major contributor to hand eczema [15], the prevalence of hand eczema did not differ significantly between wet and nonwet workers in this study. Likewise, the frequency of daily washing hands did not influence the development of hand eczema. Subjects with hand eczema washed their hands 7.9 ± 0.7 times per day (median: 7; 95% CI: 6.40225–9.42632) while subjects without hand eczema washed their hands 7.2 ± 0.2 times per day (median: 7; 95% CI: 6.85185–7.59789). Finally, the prevalence of hand eczema was comparable in subjects with or without a prior or family history of al-

Table 2. Possible risk factors of hand eczema

Factors	N	Hand eczema, n (%)	p value (odds ratio, 95% CI)
Occupation			
Production	474	27 (5.7)	0.0059 (0.1119, 0.01506–0.8307) <0.0001 (0.01802, 0.002038–0.1593)
Services	23	7 (30.4)	
Management	4	0	
Others	149	1 (0.7)	
Substances and materials that your hands frequently contact			
Disinfectants	7	2 (28.6)	0.0479 (0.1298, 0.02388–0.7055)
Detergents	113	6 (5.3)	
Hair dye products	1	0	
Cosmetics	16	0	
Lubricants	34	3 (8.8)	
Others	13	1 (7.7)	
None of these	466	23 (4.9)	
Wet work (ns)			
Yes	11	1 (9.1)	
No	639	34 (5.3)	
Frequency of washing hands (ns)			
≥10 times/day	133	7 (5.3)	
<10 times/day	517	28 (5.4)	
Washing hands with detergents (ns)			
Yes	55	2 (3.6)	
No	595	33 (5.5)	
Using moisturizers after washing hands (ns)			
Most times	24	1 (4.2)	
Occasionally	104	7 (6.7)	
Never	522	27 (5.2)	
History of allergy/atopic dermatitis (ns)			
Neither personal nor family history of allergy	444	21 (4.7)	
Only a personal history of allergy	151	12 (7.9)	
Only a family history of allergy	20	1 (5)	
Both personal and family history of allergy	35	1 (2.9)	

Two-sided Fisher's exact test was used to assess the significant differences. ns, not significant.

lergies (Table 2). Taken together, only occupation and materials that frequently contact hands appear to be risk factors for hand eczema in this occupational setting.

Uninvolved Skin Site of Subjects with Hand Eczema Displays Compromised Permeability Barrier Function

Previous studies have shown that a defective permeability barrier can enhance the percutaneous penetration of substances into the skin, predisposing to the development of contact dermatitis [16]. We next assessed the epidermal permeability barrier function in these subjects. In agreement with previous findings [17], males exhibited higher basal TEWL rates in comparison to females

(Fig. 1a). Similarly, stratum corneum hydration levels in males were also significantly higher than those in females (Fig. 1a, $p < 0.0001$). Moreover, TEWL rates were significantly higher in subjects with current and a prior history of hand eczema altogether than in subjects without hand eczema (Fig. 1b, $p < 0.01$). Although skin surface pH did not differ significantly either between subjects with current and a prior history of hand eczema altogether, and subjects without hand eczema (Fig. 1b), subjects with active hand eczema displayed higher skin surface pH in comparison to subjects with either a prior history of hand eczema ($q = 5.029$, $p < 0.01$) or without a history of hand eczema (Fig. 1c, $q = 6.09$, $p < 0.001$). Stratum corneum

Fig. 1. Comparison of epidermal function in subjects with and without hand eczema. **a** Comparison of epidermal function between males and females in this cohort. Because of nonnormality of the data, an unpaired *t* test (Mann-Whitney test) was used for comparisons between the two groups. **b** Comparison of epidermal function between subjects without hand eczema and subjects with either current or a prior history of eczema. Because of nonnormality of the data, an unpaired *t* test (Mann-Whitney test) was used for comparisons between the two groups. **c** Comparison of epidermal function among subjects without hand eczema, with current

eczema or those with a history of eczema. Data are expressed as means $\pm$ SEM. A Kruskal-Wallis test was used to determine the significant differences among groups, and the differences between hand eczema and normal controls were determined using one-way ANOVA with post hoc Dunnett's multiple comparison test. *p* values above the columns vary significantly between groups (^a *p* < 0.05 and ^b *p* < 0.01) while *p* values in the columns are versus subjects without hand eczema (^c *p* < 0.01 and ^d *p* < 0.001). *n* = 61 for hand eczema and *n* = 587 for subjects without hand eczema.

hydration levels were 14% lower in subjects with active hand eczema than those without hand eczema (Fig. 1c, 27.46 ± 2.85 vs. 31.94 ± 0.52 , *p* = 0.0635). Striking differences were found in TEWL rates among subjects without a history of hand eczema, with active or a prior history of hand eczema (Fig. 1c, *F* = 5.806, *p* = 0.0032). Furthermore, in subjects currently without active hand eczema but a prior history of hand eczema, their TEWL rates were 18% higher than in those without a history of hand eczema at all (10.42 ± 1.55 vs. 8.56 ± 0.24). Finally, subjects with and without a family history of hand eczema or allergy displayed comparable levels of TEWL, stratum corneum hydration and skin surface pH. These results demonstrate that subjects with hand eczema exhibit defects in epidermal permeability barrier and stratum corneum acidity on the involved skin site.

Discussion

While hand eczema is a common dermatosis in the USA and Europe, information about the prevalence of hand eczema in China is limited. We show here that the lifetime prevalence of hand eczema was 9.7%, while point prevalence was 5.4% in this cohort, which both were low-

er than that reported in European populations [14]. Although no efforts were made to differentiate allergic from irritant contact dermatitis, hand eczema in this cohort likely was, at least to a large extent, irritant contact dermatitis because (1) the majority of occupational hand eczemas are irritant rather than allergic contact dermatitis [15, 18] and (2) the prevalence of hand eczema was comparable in subjects with and without a history of allergies.

Regarding risk factors, many factors can contribute to the development of hand eczema. Occupational wet work and frequent hand washing have been considered as major contributors to hand eczema at least in the health care industry [18, 19]. However, the present study did not reveal any link between hand eczema and either wet work or frequent hand washing. The discrepant results between the present study and others could be due to the relatively small sample size in the present study, where there were only 13 wet workers. Regarding a possible link between atopic dermatitis and hand eczema, it is inconclusive. While subjects with atopic dermatitis display a higher prevalence of hand eczema compared to those without atopic dermatitis [20], the rates of allergic contact dermatitis on the hands were comparable between atopic and nonatopic subjects [21]. Moreover, it is no surprise that no subjects with atopic dermatitis were present in

this cohort, possibly because of the low overall prevalence of adult atopic dermatitis (<1%) in China [22]. The link between topical use of disinfectant and hand eczema is also uncertain. While previous studies showed no association of disinfectants with hand eczema, the present study demonstrated that over 28% (2/7) of subjects with hand eczema frequently contacted disinfectants, but our sample size was too small to draw any conclusions. That occupation markedly influenced the prevalence of hand eczema is consistent with prior observations [19]. In this cohort, subjects working in production lines and warehouses exhibited the highest risk for hand eczema, possibly because they repeatedly contact the same or similar substance(s) daily. In such cases, occasional contact with substances at low concentration may not be harmful, but repeated contact could eventually provoke hand eczema. Finally, other studies have shown that single nucleotide polymorphisms of inflammation-related genes are associated with hand eczema [23]. Whether such genes were altered in these subjects is unknown.

A pathogenic role for a defective epidermal permeability barrier in hand eczema has long been proposed, because (1) expression levels of barrier-related proteins, including filaggrin and caspase 14, decline in the lesional skin of hand eczema [9, 11], (2) TEWL rates increase in lesional skin and adjacent nonlesional skin [11], (3) topical barrier repair strategies delay the relapses of and/or improve hand eczema [24, 25] and (4) skin disorders, such as atopic dermatitis, with a defective permeability barrier are risk factors of hand eczema [26]. However, direct evidence to support the role of epidermal permeability dysfunction in hand eczema is far less sufficient. In most, if not in all studies, measurements of TEWL rates were performed on lesional or their adjacent sites. Here, we showed that TEWL rates also elevated in the uninvolved skin sites of subjects with hand eczema, but the underlying mechanisms are unclear. Although filaggrin mutations, a presumed cause of barrier dysfunction, are associated with hand eczema, particularly irritant contact dermatitis [27, 28], the following evidence does not support a role of filaggrin mutations in the elevated TEWL rates in the present cohort: (a) not all hand eczema has been associated with filaggrin mutations, while environmental factors largely account for the development of hand eczema [29, 30]; (b) humans with and without filaggrin mutation display comparable basal barrier function [31, 32]; and (c) in mice with filaggrin mutations, elevations in TEWL rates were observed only in aged, but not young mice [6], while our subjects were under 40 years of age. Therefore, filaggrin mutations

likely did not contribute to the increased TEWL rates in this cohort. Nonetheless, doubtlessly elevated TEWL rates play a significant role in the pathogenesis of hand eczema. A number of previous studies have shown that disruption of the epidermal permeability barrier not only induces production and release of proinflammatory cytokines [1, 33], but also stimulates T-cell proliferation [32], leading to reductions in thresholds of response to external stimuli [34]. Whereas hand eczema belongs to the category of contact dermatitis, results of the present study support the notion that pre-existing dysfunction of the epidermal permeability barrier predisposes to the development of hand eczema. Although the skin surface pH in subjects with hand eczema was significantly higher than that in subjects without hand eczema, it still falls within a normal range. Thus, the marginal elevation in skin surface pH likely did not contribute to the development of hand eczema.

Prior studies have demonstrated the importance of measuring epidermal permeability barrier function in evaluating the status and therapeutic efficacy of certain dermatoses. In both adults and children with atopic dermatitis, TEWL rates positively correlate with disease severity [35–37]. Moreover, measurement of TEWL rates is a reliable approach to evaluate the therapeutic efficacy of the treatments for both atopic dermatitis and psoriasis [2, 3, 38]. In addition, infants with higher TEWL rates during the first week of life predict a higher risk of atopic dermatitis later in the life independently of filaggrin mutations [39]. Likewise, TEWL rates predict the relapse of psoriasis, i.e., psoriasis relapses sooner in subjects with higher TEWL rates [4]. We showed here that uninvolved skin sites of subjects with hand eczema displayed higher TEWL rates, suggesting that TEWL rates could possibly serve as a proxy in predicting the risk of developing hand eczema, a notion which requires further studies. Notably, the TEWL rates were 2 g/m²/h higher in males than in females in this cohort. However, we did not observe the difference in the prevalence of hand eczema between males and females, probably because males and females commonly have different occupations, which can influence the development of eczema. However, whether the gender differences in TEWL rates can contribute to the different prevalences of hand eczema between males and females remains to be determined, ideally in a large cohort that both males and females have the same or similar occupation.

In conclusion, the uninvolved skin sites of patients with hand eczema exhibit defects in epidermal permeability barrier function, which could contribute to the de-

velopment of hand eczema. Conversely, improvements in the epidermal permeability barrier could prevent and/or treat hand eczema.

Limitations

There are several limitations in the present study, including (a) data using questionnaires to obtain participants' history of skin disorders may not be accurate, (b) whether and how much prior and/or current skin disorders contribute to the development of hand eczema remains to be determined and (c) because of the low prevalence of hand eczema, studies in large cohorts are required to confirm the results of the present study.

Statement of Ethics

This work was reviewed and approved by the Institutional Review Board of Dermatology Hospital (Approval No. GDDHLS-20180505).

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Author Contributions

Wang X., Ye L., Lai Q., Wen S., Long Z. and Qiu X. performed experiments. Man M.-Q. and Yang B. designed experiments. Man M.-Q. analyzed and interpreted data, and wrote the draft. Elias P.M. and Yang B. interpreted data and critically reviewed the paper.

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