49 Measuring Disturbed Barrier Function in Atopic Eczema

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Both clinical and instrumental studies on patients with atopic eczema (AE) have demonstrated some abnormalities in barrier function and skin hyperirritability.

In epidemiological studies, AE subjects showed a high incidence of hand eczema induced by irritant substances. In particular, they prove to run a significant risk of developing contact dermatitis when exposed to occupational factors, i.e., chemicals, water, soil, or wear. Several authors observed that cutaneous atopy amplifies the effects of irritant exposure in occupations at risk such as hairdressers, cleaners, metalworkers, mechanics, nurses, etc. [1–10].

Moreover, atopy is not only considered a predisposing factor for irritant contact dermatitis, but it also seems to influence the course of the disease. In fact, it has been reported that individuals with a history of childhood atopic eczema are affected by hand dermatitis earlier, more frequently, and more severely than healthy controls [11, 12].

49.1 Transepidermal Water Loss in Patients with Atopic Eczema

Transepidermal water loss (TEWL) values, reflecting skin barrier function, are considered to be a predictive factor for the development of irritant contact dermatitis, correlating with skin susceptibility to irritants [13–16]. Most authors reported increased TEWL values in AE subjects, both adults and children, at eczematous, but also at apparently unaffected skin areas [17–20].

In a study performed on AE children and controls, we found significant alterations in TEWL, measured at different body sites, on uninvolved skin of atopic patients [19, 20] (Table 49.1). When dividing our study population into two groups according to the presence of skin lesions, we observed significantly higher TEWL values at healthy skin sites in patients with current eczema compared to those without lesions (Table 49.2) [20]. Others studies showed that an increase in TEWL values, more pronounced in atopic patients with active manifestations, was also present in subjects without clinical evidence of the disease, suggesting that this modification may be a functional marker of AE [12, 21, 22]. The presence of active eczematous lesions seems to

Table 49.1. Baseline TEWL and capacitance values (mean ± SD) in 66 AE children and 21 healthy subjects at eight different skin sites

	TEWL	Capacitance
Eczematous skin of AE children	30.48 ± 19.64[a]	42.04 ± 11.36[a]
Uninvolved skin of AE children	8.01 ± 4.38[b]	56.50 ± 12.98[b]
Healthy skin of controls	5.52 ± 3.10	57.63 ± 10.39

[a] Significant compared to uninvolved skin of AE children
[b] Significant compared to healthy skin of control children

Table 49.2. TEWL and capacitance values on uninvolved skin of AE children with current eczema, AE children without skin lesions, and controls

	TEWL	Capacitance
104 AE patients with lesions	9.02 ± 5.32[a]	54.32 ± 13.76[a]
96 AE patients without lesions	7.56 ± 4.54[b]	56.86 ± 13.86[b]
45 controls	5.38 ± 2.96	58.50 ± 11.39

[a] Significant compared to AE children without lesions
[b] Significant compared to control subjects

impair barrier function at skin sites clinically uninvolved. When investigating barrier function in AE, the severity of the dermatitis should be taken into account: TEWL values vary according to the course of the disease and the presence or absence of skin lesions. Moreover, in AE patients the skin barrier impairment appears to be reversible. Long-lasting absence of eczema makes water barrier restoration possible: no differences were found in baseline TEWL on the flexor side of the forearm between atopic individuals without active dermatitis for the past two years and healthy volunteers [23]. Also in patients with past history of AE, but without clinical signs other than hand eczema in adult life, TEWL proved normal on the upper arm [24].

49.2 Skin Hydration and TEWL in Patients with Atopic Eczema

The horny layer water content is known to influence skin barrier function. In fact, occlusion of the skin surface induced an increase in water content favoring percutaneous absorption. In an *in vitro* study, the water content was found to be about 24% of the wet weight of the stratum corneum in dry atopic skin, 37% in clinically uninvolved skin of AE patients and 41% in healthy skin of controls [25]. Comparing AE patients and healthy volunteers, Loden et al. observed lower capacitance values in atopics, especially with an increasing degree of dryness and higher TEWL values [26]. These findings were confirmed by other authors, reporting elevated TEWL and reduced capacitance values in AE patients, both in eczematous and in uninvolved skin, with respect to healthy controls [19, 20, 22, 25–29]. Like TEWL, stratum corneum water content depends on the activity of the disease. Tanaka et al. observed a lower hydration state of the horny layer in patients with severe AE compared to subjects with mild disease [30]. In 200 AE children, we found that capacitance values were significantly lower on eczematous skin areas than uninvolved atopic skin and normal skin of controls (Fig. 49.2) [20]. These alterations were more marked in patients with active disease (Table 49.1). Tanaka et al. also observed a lower hydration state of the horny layer in patients with severe AE than in those with mild disease [30].

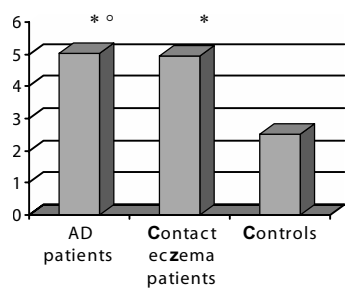

Fig. 49.1. Baseline TEWL values on forearm skin in 20 subjects affected by contact eczema, 14 AE patients, and 20 healthy controls. * = significant compared to healthy controls; ° = significant compared to patients with contact eczema

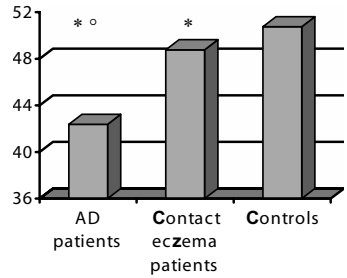

Fig. 49.2. Baseline capacitance values on forearm skin in 20 subjects affected by contact eczema, 14 AE patients, and 20 healthy controls. * = significant compared to healthy controls; ° = significant compared to patients with contact eczema

Stratum corneum hydration depends both on the ability to bind and the ability to retain water [31]. In an *in vitro* study on specimens of dry skin of the back, Werner et al. found that the horny layer from dry atopic skin shows a lower capacity to bind water than that from healthy controls [32].

Investigating the hydration and water-retention capacity of unaffected skin in patients with AE, Berardesca et al. [29] reported that atopic skin presents significantly lower capacitance and higher TEWL values in comparison to control skin. Moreover, in atopic patients the stratum corneum water retention capacity, represented by the skin surface water loss profile, was significantly reduced.

Dynamic methods, such as the sorption-desorption test (SDT) and the moisture accumulation test (MAT), were developed in order to study the horny layer hydration kinetics.

We performed these tests on 45 subjects, aged 4–12 years, comprising 15 individuals with active AE, 15 atopics without eczematous lesions for at least 1 month, and 15 healthy children [33]. The stratum corneum of uninvolved atopic skin appeared to be less hydrated, but more easily hydrated, by water coming both from the deeper layers and from the environment, with respect to the skin of healthy subjects. On the contrary, the eczematous areas showed an increased avidity to retain water, but a reduced absorption capacity.

49.3 Skin Lipids and Transepidermal Water Loss in Patients with Atopic Eczema

Skin lipids, in particular ceramides, proved to play an essential role in the regulation of stratum corneum barrier function and in its water-holding properties [34, 35]. Depletion of lipids from the stratum corneum by solvent extraction leads to a pronounced increase in TEWL, expressing a defect in the integrity of skin function and representing a stimulus to barrier repair and increased synthesis of lipids by keratinocytes [36]. In AE patients, the barrier impairment coincides with marked alterations in the amount and composition of epidermal lipids [22, 37 – 40]. The extrusion of lamellar bodies is delayed and incomplete [41] and levels of enzymes involved in ceramide metabolism [42, 43] are altered as well in unaffected skin of AE subjects. Surprisingly, the recovery of cutaneous barrier function, after tape stripping or acetone treatment, was found to be faster or normal in atopics in comparison with controls, and this may be caused by a persisting mild disturbance of barrier function with consequent permanent activation of repair mechanisms [44, 45]. However, a complete restoration of skin barrier function is not achieved and this can be explained by the decrease in the amount of stratum corneum ceramides observed in atopic skin [22, 40].

When investigating the relationship between different lipid classes and barrier impairment in 47 patients with AE [22], we observed a significant reduction in ceramide 1, ceramide 3, cholesterol sulphate levels, and in the ceramide/cholesterol ratio, associated with a significant increase in the amount of free cholesterol. In particular, atopic patients without lesions at the moment of the investigation had a normal barrier function and intermediate lipid values in comparison to subjects with active signs of the disease and to healthy controls. Moreover, we found an inverse correlation between TEWL and ceramides and a direct correlation between the increase in free cholesterol and the reduction in ceramide 3 levels.

These findings confirm those of other investigators [37] and suggest that a decrease in stratum corneum ceramides is involved in barrier impairment of atopic skin, whereas the increase in free cholesterol values and the reduction in the cholesterol/ceramide ratio may be a response to increased TEWL levels. In fact, the lower amount of cholesterol sulphate, functioning as an intercellular cement in the stratum corneum, which has been described in atopic skin, is associated with its desquamation.

The amount of skin lipids is an important factor in susceptibility to irritation. Investigating the relationship between baseline ceramide composition and the intensity of SLS-induced irritant dermatitis, Di Nardo et al. observed a correlation between colorimetric a* values and ceramide-6I and between TEWL and ceramide-1 levels [46]. In order to induce acute irritation, they also employed a 24-h application of xylene and toluene [47]. On comparing values of the different classes of lipids with clinical irritation parameters, a negative correlation was obtained. Based on clinical observations, two populations were selected: less reactive and hyper-reactive, which also differed in the total weight of lipids, ceramides, and triglycerides. From these findings, skin lipids, and especially ceramide levels, play a protective role with respect to irritant substances.

49.4 Reactivity to Irritants in Atopic Eczema Subjects

Both clinical and instrumental data demonstrated a cutaneous hyper-reactivity in subjects with active AE, experimentally exposed to irritants. Moreover, skin irritability proved to be related to the degree of severity and the extension of the dermatitis. As regards atopic subjects with no active lesions, conflicting findings on cutaneous reactivity have been reported. Whereas some investigators did not observe statistically significant differences in susceptibility to irritants between atopics without current dermatitis and nonatopics [23, 48 – 50], Van der Valk et al. demonstrated that atopic patients without active eczematous lesions responded more to SLS than controls by measuring water vapor loss [51]. Tupker et al. investigated skin irritability by repeated applications of different irritants and found increased TEWL values, both before and after exposure, in subjects with a history of AE compared to subjects with a history of allergic contact dermatitis or controls [18].

These findings were confirmed by other investigators, who found enhanced reactivity to SLS applied to the forearm in individuals affected by AE in comparison to normal controls [52]. Agner challenged the skin

of the flexor side of the upper arm with SLS for 24 h [17] and observed greater reactions in atopic patients compared to controls, as assessed both clinically and instrumentally. Moreover, postexposure TEWL, correlating with baseline values, was significantly higher in atopics than in controls.

After SLS challenge, we observed both an increase in TEWL and a decrease in capacitance, which were more marked in subjects with AE than in controls [53, 54]. In a study conducted on 20 healthy volunteers and 34 subjects with localized eczema in a chronic phase, comprising 14 atopic patients and 20 individuals with contact dermatitis, cutaneous reactions to 30 min 0.5% SLS on the forearms were investigated by measuring TEWL, capacitance, and skin echogenicity at 30 min, 24 h, and 72 h after SLS exposure [54]. Baseline TEWL was significantly higher in atopic or contact dermatitis patients than in healthy subjects, but no differences were observed between the two eczema groups (Fig. 49.1). On the contrary, significant differences were recorded in baseline capacitance values, not only between controls and dermatitis subjects, but also between atopics and patients with contact eczema (Fig. 49.2). Reactivity to SLS, as assessed by TEWL and capacitance, showed no variations between the two eczema groups. On the contrary, the 24-h echographic assessment of SLS-exposed areas showed a significant decrease in epidermal reflectivity, indicating barrier function damage [55], in atopic subjects, but not in contact dermatitis patients. Moreover, hyper-reactivity to irritant stimuli may be responsible for enhanced contact reactions in sensitized atopic subjects, who may also respond to very low concentrations of contact allergens. We observed that SLS pretreatment of nickel patch test sites induced an earlier and more pronounced cutaneous damage in atopic nickel-sensitive patients than in nickel-sensitive nonatopics, followed by a more intense allergic response, probably due to an increased allergen penetration and/or the summation of immune and nonimmune mechanisms [28]. These findings were in agreement with skin echogenicity data, indicating an enhanced response to SLS in atopics [28].

49.5 Barrier Function in Atopic Patients Without Dermatitis

In most epidemiological studies, mucosal atopy did not seem to influence the appearance or course of irritant contact dermatitis [2, 9, 11, 56]. Experimental data regarding the cutaneous barrier function and the susceptibility to irritants in patients affected by mucosal atopy are scarce and contradictory. In subjects with allergic asthma and/or rhinitis, we observed normal baseline capacitance and TEWL values [21, 53, 57], whereas Tanaka et al. demonstrated a decreased hydration state of the stratum corneum and a reduced amino acid content of the skin surface [30]. Nassif et al. found an increased skin susceptibility to 48 h SLS-challenge, assessed by visual scoring, in patients with respiratory atopy, and attributed their results to the influence of cytokines and other mediators circulating in the skin [58]. On the contrary, Löffler did not find differences in the TEWL response to 48-h SLS exposure between individuals with rhinoconjunctivitis or atopic asthma with no symptoms at the time of testing and controls [23]. We also reported that postexposure TEWL, capacitance, and echogenicity values did not differ between subjects with mucosal atopy and healthy volunteers [53]. Moreover, in patients affected by respiratory atopy, baseline and postexposure biophysical cutaneous parameters were not influenced by the season of assessment and the possible aeroallergen burden associated with the release of phlogistic mediators circulating in the skin. In fact, challenging the skin of patients with seasonal allergic rhinitis with SLS during the active phase of the disease, the cutaneous response proved to be as intense as during the remission phase [57].

49.6 TEWL and Topical Agents for Atopic Eczema

Objective monitoring of barrier impairment in AE, performed by transepidermal water loss measurements, is of considerable interest in studies evaluating the efficacy of topical agents for AE skin, both anti-inflammatory drugs and moisturizing creams [59 – 64]. It has been demonstrated that certain moisturizers improve water barrier function, as reflected by TEWL, and skin susceptibility to irritants in atopic patients [60 – 62]. In fact, topical agents for AE differ not only in

their composition, but also in their influence on the skin as a barrier to water, as can be evaluated by TEWL readings. Loden et al. compared instrumentally and clinically the effects on AE patients of a cream containing 20 % glycerin and a cream with 4 % urea. The latter proved superior as regards the improvement in skin barrier function in dry atopic skin. Moreover, a significant relationship was noted between the reduction in TEWL and the clinical improvement of dryness [63]. By treating 24 AE children for 20 – 21 weeks with a ceramide-dominant, physiologic lipid-based emollient, Chamlin et al. demonstrated that TEWL measurement is more sensitive than SCORAD values both for detecting subtle fluctuations in AE activity and for predicting potential relapse [64].

References

1. Nilsson E, Mikaelsson B, Andersson S (1985) Atopy, occupation and domestic work as risk factors for hand eczema in hospital workers. Contact Dermatitis 13:216 – 223
2. Rystedt I. Hand eczema in patients with history of atopic manifestations in childhood. Acta Derm. Venereol (Stockh) 1985; 65:305 – 312
3. Rystedt I (1990) The role of atopy in occupational skin disease. In: Adams RM (ed) Occupational skin disease. Saunders, Philadelphia, pp 215 – 222
4. Seidenari S, Manzini BM, Danese P, Motolese A (1990) Patch and prick test study of 593 healthy subjects. Contact Dermatitis 23:162 – 167
5. Svensson Å (1988) Hand eczema: an evaluation of the frequency of atopic background and the difference in clinical pattern between patients with and without atopic dermatitis. Acta Derm Venereol (Stockh) 68:509 – 513
6. Meding B, Swanbeck G (1990) Predictive factors for hand eczema. Contact Dermatitis 23:154 – 161
7. Stingeni L, Lapomarda V, Lisi P (1995) Occupational hand dermatitis in hospital environments. Contact Dermatitis 33:172 – 176
8. Cronin E (1987) Dermatitis of the hands in caterers. Contact Dermatitis 17:265 – 269
9. Pigatto PD, Polenghi MM, Altomare GF (1987) Occupational dermatitis in bakers: a clue for atopic contact dermatitis. Contact Dermatitis 16:263 – 271
10. Bauer A, Bartsch R, Stadeler M, Schneider W, Grieshaber R, Wollina U, Gebhardt M (1998) Development of occupational skin diseases during vocational training in baker and confectioner apprentices: a follow-up study. Contact Dermatitis 39:307 – 311
11. Susitaival P, Hannuksela M (1995) The 12-year prognosis of hand dermatosis in 896 Finnish farmers. Contact Dermatitis 32:233 – 237
12. Meding B, Swanbeck G (1989) Epidemiology of different types of hand eczema in an industrial city. Acta Derm Venereol (Stockh) 69:227 – 233
13. Pinnagoda J, Tupker RA, Coenraads PJ, Nater JP (1989) Prediction of susceptibility to an irritant response by transepidermal water loss. Contact Dermatitis 20:341 – 346
14. Freeman S, Maibach HI (1988) Study of irritant contact dermatitis produced by repeat patch testing with sodium lauryl sulfate and assessed by visual methods, transepidermal water loss and laser Doppler velocimetry. J Am Acad Dermatol 19:496 – 502
15. Wilhelm KP, Maibach HI (1990) Susceptibility to irritant dermatitis induced by sodium lauryl sulfate. J Am Acad Dermatol 23:122 – 124
16. Goh CL, Chia SE (1988) Skin irritability to sodium lauryl sulphate–as measured by skin water vapour loss–by sex and race. Clin Exp Dermatol 13:16 – 19
17. Agner T (1991) Susceptibility of atopic dermatitis patients to irritant dermatitis caused by sodium lauryl sulphate. Acta Derm Venereol (Stockh) 71:296 – 300
18. Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP (1990) Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. Br J Dermatol 123:199 – 205
19. Seidenari S, Giusti G (1995) Objective assessment of the skin of children affected by atopic dermatitis: a study on pH, capacitance and TEWL in eczematous and clinically uninvolved skin. Acta Derm Venereol (Stockh) 75:429 – 433
20. Giusti G, Seidenari S (1998) La barriera cutanea nei bambini con dermatite atopica: valutazione strumentale in 200 pazienti e 45 controlli. Riv Ital Pediatr 24:954 – 959
21. Conti A, Di Nardo A, Seidenari S (1996) No alteration of biophysical parameters in the skin of subjects with respiratory atopy. Dermatology 192:317 – 320
22. Di Nardo A, Wertz P, Giannetti A, Seidenari S (1998) Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. Acta Derm Venereol (Stockh) 78: 27 – 30
23. Löffler H, Effendy I (1999) Skin susceptibility of atopic individuals. Contact Dermatitis 40:239 – 242
24. Agner T (1991) Skin susceptibility in uninvolved skin of hand eczema patients and healthy controls. Br J Dermatol 125:140 – 146
25. Werner Y (1986) The water content of the stratum corneum in patients with atopic dermatitis. Measurement with the Corneometer CM 420. Acta Derm Venereol (Stockh) 66:281 – 284
26. Lodén M, Olsson H, Axéll T, Werner Linde Y (1992) Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. Br J Dermatol 126:137 – 141
27. Gollhausen R (1991) The phenomenon of irritable skin in atopic eczema. In: Ruzicka T, Ring J, Przybilla B (eds) Handbook of atopic eczema. Springer-Verlag, Berlin Heidelberg New York, pp 306 – 318
28. Seidenari S (1994) Reactivity to nickel sulfate at sodium lauryl sulfate pre-treated sites is higher in atopics: an echographic evaluation by means of image analysis performed on 20 MHz B-scan recordings. Acta Derm Venereol (Stockh) 74:245 – 249
29. Berardesca E, Fideli D, Borroni G, Rabbiosi G, Maibach HI (1990) In vivo hydration and water-retention capacity of stratum corneum in clinically uninvolved skin in atopic

and psoriatic patients. Acta Derm Venereol (Stockh) 70: 400 – 404
30. Tanaka M, Okada M, Zhen YX, Inamura N, Kitano T, Shirai S, Sakamoto K, Inamura T, Tagami H (1998) Decreased hydration state of the stratum corneum and reduced amino acid content of the skin surface in patients with seasonal allergic rhinitis. Br J Dermatol 139:618 – 621
31. Tagami H, Kanamaru Y, Inoue K (1982) Water sorption-desorption test of the skin in vivo for functional assessment of the stratum corneum. J Invest Dermatol 78:425 – 428
32. Werner Y, Lindberg M, Forslind B (1981) The water-binding capacity of stratum corneum in dry non-eczematous skin of atopic eczema. Acta Derm Venereol (Stockh) 62:334 – 337
33. Pellacani G, Seidenari S (2001) Water sorption-desorption test and moisture accumulation test for functional assessment of atopic skin in children. Acta Derm Venereol (Stockh) 81:100 – 103
34. Imokawa G, Akasaki S, Minematsu Y, Kawai M (1989) Importance of intercellular lipids in water-retention properties of the stratum corneum: induction and recovery study of surfactant dry skin. Arch Dermatol Res 281:45 – 51
35. Elias PM, Menon GK (1991) Structural and lipid biochemical correlates of the epidermal permeability barrier. Adv Lipid Res 24:1 – 26
36. Grubauer G, Elias PM, Feingold KR (1989) Transepidermal water loss: the signal for recovery of barrier structure and function. J Lipid Res 30:323 – 333
37. Melnik B, Hollmann J, Hofmann U, Yuh MS, Plewig G (1990) Lipid composition of outer stratum corneum and nails in atopic and control subjects. Arch Dermatol Res 282:549 – 551
38. Yamamoto A, Serizawa S, Ito M, Sato Y (1991) Stratum corneum lipid abnormalities in atopic dermatitis. Arch Dermatol Res 283:219 – 223
39. Schäfer L, Kragballe K (1991) Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. J Invest Dermatol 96:10 – 15
40. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A (1991) Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? J Invest Dermatol 96:523 – 526
41. Werner Y, Lindberg M, Forslind B (1987) Membrane-coating granules in "dry" non-eczematous skin of patients with atopic dermatitis. Acta Derm Venereol (Stockh) 67:385 – 390
42. Jin K, Higaki Y, Takagi Y, Higuchi K, Yada Y, Kawashima M (1994) Analysis of beta-glucocerebridase and ceramidase activities in atopic and aged dry skin. Acta Derm Venereol (Stockh) 74:337 – 340
43. Murata Y, Ogata J, Higaki Y, Kawashima M, Yada Y, Higuki K (1996) Abnormal expression of sphingomyelin acylase in atopic dermatitis: an etiologic factor for ceramide deficiency? J Invest Dermatol 106:1242 – 1249
44. Tanaka M, Zhen YX, Tagami H (1997) Normal recovery of the stratum corneum barrier function following damage induced by tape stripping in patients with atopic dermatitis. Br J Dermatol 136:966 – 967
45. Gfesser M, Abeck D, Rügemer J, Schreiner V, Stäb F, Disch R, Ring J (1997) The early phase of epidermal barrier regeneration is faster in patients with atopic eczema. Dermatology 195:332 – 336
46. Di Nardo A, Sugino K, Ademola J, Wertz PW, Maibach HI (1996) Sodium lauryl sulfate induced irritant contact dermatitis: a correlation study between ceramides and in vivo parameters of irritation. Contact Dermatitis 35:86 – 91
47. Di Nardo A, Sugino K, Ademola J, Wertz PW, Maibach HI (1996) Role of ceramides in proclivity to toluene and xylene-induced irritation in man. Derm Beruf Umwelt 44:119 – 125
48. Stolz R, Hinnen U, Elsner P (1997) An evaluation of the relationship between 'atopic skin' and skin irritability in metalworkers trainees. Contact Dermatitis 36:281 – 284
49. Basketter DA, Miettinen J, Lahti A (1998) Acute irritant reactivity to sodium lauryl sulfate in atopics and nonatopics. Contact Dermatitis 38:253 – 257
50. Hannuksela A, Hannuksela M (1996) Irritant effects of a detergent in wash, chamber and repeated open application tests. Contact Dermatitis 34:134 – 137
51. Van der Valk PGM, Nater JP, Bleumink E (1985) Vulnerability of the skin to surfactants in different groups of eczema patients and controls as measured by water vapour loss. Clin Exp Dermatol 10:98 – 102
52. Cowley NC, Farr PM (1992) A dose-response study of irritant reactions to sodium lauryl sulphate in patients with seborrhoeic dermatitis and atopic eczema. Acta Derm Venereol (Stockh) 72:432 – 435
53. Seidenari S, Belletti B, Schiavi ME (1996) Skin reactivity to sodium lauryl sulfate in patients with respiratory atopy. J Am Acad Dermatol 35:47 – 52
54. Seidenari S (1996) Skin sensitivity, interindividual factors: atopy. In: Van der Valk PG, Maibach HI (eds) The irritant contact dermatitis syndrome. CRC press, Boca Raton, pp 267 – 277
55. Seidenari S, Di Nardo A (1992) B-scanning evaluation of irritant reactions with binary transformation and image analysis. Acta Derm Venereol (Stockh) 175:9 – 13
56. Funke U, Diepgen TL, Fartash M (1996) Risk-group-related prevention of hand eczema at the workplace. Curr Probl Dermatol 25:123 – 132
57. Conti A, Seidenari S (2000) No increased skin reactivity in subjects with allergic rhinitis during the active phase of the disease. Acta Derm Venereol 80:192 – 195
58. Nassif A, Chang SC, Storrs SJ, Hanifin JM (1994) Abnormal skin irritancy in atopic dermatitis and atopy without dermatitis. Arch Dermatol 130:1401 – 1407
59. Aalto-Korte K (1995) Improvement of skin barrier function during treatment of atopic dermatitis. J Am Acad Dermatol 33:969 – 972
60. Loden M (1997) Barrier recovery and influence of irritant stimuli in skin treated with a moisturising cream. Contact Dermatitis 36:256 – 260
61. Held E, Sveinsdottir A, Agner T (1999) Effect of long-term use of a moisturiser on skin hydration, barrier function and susceptibility to irritants. Acta Derm Venereol (Stockh) 79:49 – 51
62. Loden M, Andersson AC, Lindberg M (1999) Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm®). Br J Dermatol 140:264 – 267

63. Loden M, Andersson AC, Andersson C, Frödin T, Öman H, Lindberg M (2001) Instrumental and dermatological evaluation of the effect of glycerin and urea on dry skin in atopic dermatitis. Skin Res Technol 7:209 – 213

64. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW, Williams ML, Elias PM (2002) Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. J Am Acad Dermatol 47:198 – 208