

Skin Barrier Properties in Patients with Recessive X-linked Ichthyosis

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Patients with X-linked recessive ichthyosis (RXLI) were studied as a model of the effect of disturbed epidermal lipid composition on skin barrier function. Thirteen patients with RXLI and 15 age- and sex-matched controls were patch-tested with sodium lauryl sulphate (SLS) 0.5% for 24 h. Basal skin properties and skin response to SLS were studied by measurement of transepidermal water loss (TEWL), electrical capacitance and erythema index. No statistically significant difference in basal TEWL was found between the two groups. The skin response to SLS was found to be statistically significantly increased in controls compared to ichthyosis patients, when evaluated by TEWL. When evaluated by erythema index a statistically significant increase in redness was found in controls, but not in ichthyosis patients. Electrical capacitance, reflecting skin hydration, was significantly reduced in RXLI patients as compared to controls. The water permeability barrier in RXLI patients was not found to be impaired, and skin reactivity was found to be decreased in RXLI patients as compared to controls. Key words: disorders of cornification; TEWL; erythema index; SLS.

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In the normal stratum corneum lipids are aggregated within intercellular membranes, where they appear to regulate barrier function and desquamation. Cholesterol, cholesterol sulphate as well as ceramides and free fatty acids are components of the intercellular membrane bilayer system (1, 2). Disturbances in the composition of stratum corneum lipids may influence desquamation. In recessive X-linked ichthyosis (RXLI) a steroid sulphatase deficiency in the epidermis (3–5) and increased levels of cholesterol sulphate (6–8) have been proved. In an experimental model, topical application of cholesterol sulphate to the back of hairless mice induced scaling and increased thickness of stratum corneum, indicating that scaliness may be a direct effect of an increased amount of cholesterol sulphate in the epidermis (9). Little is known about the skin barrier properties in patients with RXLI. The present study was undertaken to investigate basal transepidermal water loss (TEWL) as well as skin resistance to an irritant trauma in patients with RXLI. The study of RXLI may provide new insights into the influence of epidermal lipid composition on skin barrier function and penetration properties of stratum corneum.

MATERIAL AND METHODS

Participants

Thirteen patients with RXLI, all men, median age 39 (range 23–50), participated in the study. The patients all fulfilled the clinical criteria of RXLI (5) and all presented clinical symptoms of RXLI. None of the participants had a history of atopic dermatitis or respiratory allergy. In

all the cases diagnosis had been confirmed by the absence of steroid sulphatase activity in cultured skin fibroblasts and/or leukocytes with ³H-dehydroepiandrosterone sulphate and ³H-oestrone sulphate in a previously performed clinical study of 76 patients with RXLI (5, 10). Only patients in the age group of 18–69 living in the Copenhagen area were invited to participate. Nineteen were invited; 6 refused to participate, leaving 13 patients to be included in our study. Fifteen healthy male volunteers, median age 36 (range 26–47) served as controls. Informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Methods

Basal values of TEWL, electrical capacitance and erythema index were obtained by measurement on the flexor aspect of the right forearm 7 cm from the flexure using the following non-invasive methods:

TEWL was measured using an Evaporimeter (Servo Med, EP1, Stockholm, Sweden) (11). The sensors of the Evaporimeter determine the water vapour pressure gradient of the boundary layer between the skin surface and ambient air in order to quantify the diffusion of water through the skin as the TEWL. The probe was hand-held using an insulating glove to avoid heating of the probe. Values were displayed on a pen recorder, and the mean value during the period 30–60 s after application of the probe to the skin was read. A probe protection cover (no. 2107, supplied with the Evaporimeter) was used, and all measurements were performed inside an incubator to avoid convection of air, according to the guidelines of the Standardization Group of the European Society of Contact Dermatitis (12). Variation in quantification of irritant patch test reactions by non-invasive measuring methods of TEWL and comparison between TEWL and other non-invasive methods have been presented elsewhere (13, 14).

Electrical capacitance was measured by a Corneometer CM 420® (GMBH, Köln, Germany) (13), which measures the electrical capacitance of the outer epidermis. The probe of this instrument is a plastic foil-covered brass grid, which functions as one electrode, while the skin functions as the other and registers hydration down to a depth of about 0.1 mm (15).

Erythema index was measured using a DermaSpectrometer (Cortex Technology, Hadsund, Denmark). This method is based on the amount of reflected red and green light from the skin (16). The spectrometer was placed in contact with the site to be measured with minimal pressure on the skin.

Irritant trauma

A 24-h closed patch test with 60 µl of aqueous solution of 0.5% SLS (SLS Sigma, 99% purity) on filter discs was applied to the flexor aspect of the other forearm, corresponding to the site where basal values were measured. Large Finn chambers (diameter 12 mm) on Scanpore tape were used. Reactions to the SLS patches were evaluated 1 h after removal of the Finn chamber by visual scoring, measurement of TEWL and erythema index.

Visual scoring was performed according to the following scale: 0 = no reaction; 1/2 = scaling or very weak erythema; 1 = weak erythema, possibly slight infiltration; 2 = marked erythema, infiltration, possibly vesicles and crusting; 3 = pronounced erythema, infiltration, possibly vesicles, bullae, pustules and/or pronounced crusting.

The study was carried out in the period February to May 1993. Each patient and their matched control were examined within 4 weeks of each other. The relative humidity varied between 18–35%. Measurements were expressed as the mean values of two recordings for evaporimetry and of three recordings for electrical capacitance and erythema index.

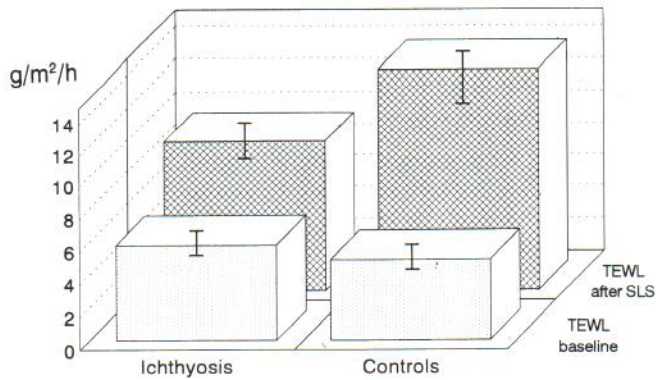


Fig. 1. Results of basal TEWL and TEWL after SLS exposure in RXLI patients as well as in controls are expressed as median values \pm 25/75 percentiles. Values are given in $\text{g}/\text{m}^2/\text{h}$.

Statistics

The Mann-Whitney test for unpaired samples was used for comparison of patients and controls. The Wilcoxon test for paired samples modified according to Pratt was used for comparison of basal and SLS-exposed values (17). The chosen level of significance was $p \leq 0.05$.

Reproducibility of the measurements (i.e. variations between repeated measurements performed within the same area). These were calculated on the basis of the SDs of two measurements for evaporimetry and three for electrical conductance and erythema index from all patients as:

$$SD_{\text{repro}} = \sqrt{(1/n \sum SD^2)}$$

RESULTS

TEWL

Results of baseline TEWL and TEWL after SLS exposure in RXLI patients as well as in controls are presented in Fig. 1. A statistically significant increase in TEWL after SLS exposure, as compared to baseline values, was found in both patients and controls ($p = 0.003$ and 0.001 , respectively). No statistically significant difference in baseline TEWL was found between the two groups ($p = 0.1$). After exposure to SLS, TEWL was significantly increased in control subjects as compared to ichthyosis patients ($p = 0.047$) (Fig. 1). The increase in TEWL after SLS exposure (ΔTEWL) was significantly lower for RXLI patients than for controls ($p = 0.005$).

Electrical capacitance

The electrical capacitance of the skin was significantly reduced in patients with RXLI, median 57.3, as compared to controls, median 83.3 (values in arbitrary units). The p -value was 0.001. Since measurement of electrical values in irritant patch test reactions has been reported to be unreliable, measurement of electrical capacitance was not obtained after SLS exposure (13).

Erythema index

The erythema index, expressed as the median value, increased from 10.0 as baseline value to 11.3 after SLS exposure in the control group. Values are in arbitrary units. The increase was statistically significant ($p = 0.001$). In patients erythema index did not, however, increase from baseline values to SLS exposed skin. No statistically significant difference in erythema index was found between the two groups, in basal values ($p = 0.7$) or in values obtained after SLS exposure ($p = 0.6$).

Visual scoring

No statistically significant differences between the groups were found with respect to visual scoring. A total score of 6 for SLS patch test reactions in the 13 RXLI patients was obtained, compared to a total score of 9 in the 15 controls. Median score for both groups was 0.5 and 25/75 percentiles for both RXLI and controls were 0/0.5.

Reproducibility of measurements

The coefficient of variation (SD) was 0.68, 0.93 and 2.99 for TEWL, erythema index and electrical capacitance measurements, respectively.

DISCUSSION

A decreased response to SLS, as evaluated by measurement of TEWL and erythema, was found in RXLI patients as compared to controls. No difference in basal TEWL was found between the two groups, but electrical capacitance was significantly reduced in RXLI patients. In the present study the diagnosis of RXLI was confirmed by pedigree studies, by the absence of steroid sulphatase activity in cultured fibroblasts and/or leukocytes, and all participants fulfilled the clinical criteria for RXLI (18, 19). The susceptibility of the skin barrier to SLS in patients with RXLI has not been examined before. The decreased increment in TEWL and erythema after SLS exposure may be interpreted as a more resistant skin barrier in RXLI patients than in controls and may reflect either a decreased or delayed response to SLS. TEWL is generally considered to reflect the stratum corneum barrier function integrity, when measured under standardized circumstances (12). The thickness of stratum corneum is known to be correlated to susceptibility to irritants (20), as well as to TEWL (21), and the increased thickness of stratum corneum found in RXLI patients may influence the amount of SLS effectively available for barrier disruption or penetration to viable skin layers. Also the disturbed lipid composition of the stratum corneum may influence the penetration ability of SLS and could, due to a possible chemical binding of SLS in the stratum corneum, influence the normal penetration of SLS through epidermis (22). In a recent study, penetration time for hexyl nicotinate was reported to be accelerated in RXLI patients (23). Due to the dissimilar chemical structure of SLS (anionic detergent) and hexyl nicotinate (ester of nicotinic acid), different penetration characteristics should be expected, and the observations are not conflicting with the present results.

It has been suggested that increase in TEWL after SLS exposure may also reflect an increased water-binding capacity of the stratum corneum (24). The altered water binding in stratum corneum in RXLI patients, as reflected by decreased electrical capacitance, could therefore also influence the response to SLS. More than 25 years ago, TEWL was measured in two different studies on 7 and 5 RXLI patients, respectively (25, 26). Measurements were either taken on washed abdominal skin after inhibition of eccrine sweating (25) or on the upper arm (26). Subjects with atopic dermatitis and other forms of ichthyosis were included in the analysis (25). A ventilated chamber method was used to measure TEWL, and thus the results cannot

be directly compared to results obtained with the method for TEWL measurement more commonly used today (12). In a recent study basal TEWL was measured in 6 subjects with RXLI (23), and 4 of these were reported to have TEWL values above the upper limit of the normal TEWL range. In the present study we also found slightly increased basal TEWL in RXLI patients as compared to controls, but this finding failed to reach statistical significance. The degree of clinical involvement of the examined skin area may also influence the outcome of the measurement.

In subjects without disorders of cornification basal TEWL has been demonstrated to reflect skin susceptibility to at least some irritants. Subjects with high basal TEWL are generally more susceptible to irritants than subjects with low basal TEWL (27). From this observation no increased susceptibility to SLS should be expected in RXLI patients, as was also not found in the present study. Decreased electrical capacitance was found in RXLI patients, illustrating decreased water content of the stratum corneum, and confirming that the patients actually had clinical symptoms on the skin area examined. A negative correlation between electrical capacitance and TEWL has been reported in normal skin and various skin diseases (15, 28). However, our present results illustrate that in RXLI patients, decreased hydration of stratum corneum is not correlated to a seriously disturbed water barrier function.

No difference in erythema index in basal values or in values obtained after SLS exposure was found between the groups. These results were supported by data obtained from visual scoring. In the control group a significant increase in erythema index after SLS exposure was found, an increase which was not present in the RXLI group. These data are in accordance with the observations on TEWL and underline the decreased skin reactivity to SLS in patients with RXLI.

RXLI can be seen as an experimental model provided by nature for the study of the effect of lipid composition on barrier integrity. Functional studies of RXLI skin may provide new information and improve our understanding of the normal barrier function.

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