

## CLINICAL REPORT

# No Increased Skin Reactivity in Subjects with Allergic Rhinitis During the Active Phase of the Disease

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**Data on skin reactivity in patients with respiratory atopy without atopic dermatitis are scarce and controversial. Our purpose was to assess whether skin reactivity in patients with seasonal allergic rhinitis varies according to the phase of the disease and the possible release of inflammatory mediators acting on the skin during the pollen season. The volar forearm skin of eleven patients with seasonal allergic rhinitis without atopic dermatitis was challenged with a single exposure to sodium lauryl sulfate. The skin response was evaluated instrumentally over 72 h by transepidermal water loss, capacitance and echogenicity measurements for the assessment of skin damage and the inflammatory response. Tests were performed in winter and repeated in spring in seasonal allergic rhinitis patients, when they showed respiratory symptoms. Fifteen subjects with atopic dermatitis underwent the same experimental procedure in winter as a control population. Baseline and postexposure values were similar both in winter and in spring in seasonal allergic rhinitis patients. After sodium lauryl sulfate challenge, atopic dermatitis patients showed a higher degree of skin barrier damage and inflammation compared to patients with seasonal allergic rhinitis. These findings suggest that subjects with seasonal allergic rhinitis without atopic dermatitis have normal epidermal barrier function and normal skin reactivity during both the inactive and the active phase of the disease. Inflammatory mediators possibly released by mucous membranes during active allergic rhinitis do not influence skin barrier function. Key words: skin reactivity; sodium lauryl sulfate; allergic rhinitis; atopy.**

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Many environmental and individual factors contribute to the development of irritant contact dermatitis. Patients with atopic dermatitis (AD) show a high incidence of hand eczema based on susceptibility to irritant substances and alterations of cutaneous barrier function (1–4). In these patients, skin hyper-reactivity is present also on healthy skin and it is more marked during the active phase of the disease (5–7). Both epidemiological and experimental data referring to liability to hand dermatitis in atopic subjects without AD are scarce and controversial (8–10). Employing 48-h testing with graded dilutions of sodium lauryl sulfate (SLS), a model irritant, assessed by visual scoring, Nassif et al. observed lower irritancy thresholds both in AD and in mucosal atopic patients compared to healthy controls (11). Tanaka et al. observed a decreased hydration state of the stratum corneum and reduced amino acid content of the skin in patients with

seasonal allergic rhinitis in the active disease season (12). On the contrary, we showed that subjects with respiratory atopy alone have normal cutaneous baseline biophysical parameters and skin reactivity to SLS, as assessed instrumentally, similar to those of healthy subjects (13, 14). In order to confirm our previous data and ascertain if skin reactivity in subjects with seasonal allergic rhinitis may vary according to the phase of the disease, we exposed patients with seasonal allergic rhinitis to SLS both during winter time, when no symptoms were present, and during spring time at the height of the grass pollen season in Italy.

## PATIENTS AND METHODS

Eleven patients (7 women and 4 men) with allergic rhinitis but no asthma, without a personal history of dermatitis and with positive prick test responses to grass pollen but not to house dust mites, showing symptoms exclusively during the pollen season, participated in the study after informed consent. Mean age was  $28 \pm 3$  years. Subjects were selected for not being skin-atopics employing the Diepgen criteria (15). Only volunteers scoring less than 10 points ( $\text{mean} \pm \text{SD} = 5.56 \pm 1.51$ ) were recruited. As a control population, 15 subjects with AD with a limited number of skin lesions ( $\text{mean} \pm \text{SD} = 21.32 \pm 4.10$ ) were included after informed consent.

During the winter season (January) all subjects underwent one 30-min patch test with 40  $\mu\text{l}$  5% SLS on the volar surface of the right forearm (5 cm below the elbow crease). The solution was pipetted onto a filter paper disk, put in a large Finn Chamber (11 mm in diameter), and fixed to the skin by Scanpor tape. After the 30-min and the 24-hour assessments the test site was covered with an empty chamber until the next examination (16, 17). In the patients with seasonal allergic rhinitis, tests were repeated during spring (May), when they showed respiratory symptoms.

### *Instrumental measurements*

All measurements were performed at baseline and after 24 and 72 h. All evaluations were carried out after a 30-min acclimatization period in an air-conditioned room. Room temperature was kept at  $21^\circ - 22^\circ\text{C}$  and humidity at 45–50%, to prevent environmental influences from affecting the results.

### *Evaporimetry*

Transepidermal water loss (TEWL) was measured with an Evaporimeter EP1 (Servo Med, Stockholm, Sweden). This instrument records TEWL using the vapour pressure gradient estimation method as described in detail by Nilsson (18). Evaluations were carried out according to guidelines of the standardization group of the ESCD (19).

### *Corneometry*

Capacitance, as a measure of stratum corneum hydration, was recorded using a Corneometer CM 820 (Courage and Khazaka, Koln,

Germany). This device consists of a main housing and a measuring probe which works as a condenser. Its capacitance is influenced by a change in the dielectrical constant of the material in contact with the probe. The probe is applied on the skin with a standard pressure of 3.5 N (Newton). The values are expressed in arbitrary units (AU).

#### Ultrasound

The echographic evaluations were performed with a 20 MHz B-scanner (Dermascan C, Cortex Technology, Hadsund, Denmark), which records images representing a cross section of the skin (20). The images were elaborated by a dedicated program by means of 2 different amplitude bands. As parameters for assessing the intensity of the reaction, the extension of the hypoechogenic dermal areas (0 to 30 pixel values) was employed, whereas the extension of the superficial hyper-reflecting band (201 to 255 pixel values) was used for the assessment of epidermis integrity (21).

#### Statistical analysis

The analysis of variance (ANOVA) test for repeated values and the paired sample *t*-test were used to compare differences between baseline values and 24-h and 72-h values. To compare instrumental values referring to the 2 different populations and the seasonal differences in subjects with seasonal allergic rhinitis, Student's *t*-test for unpaired values was employed. A level of  $p < 0.05$  was considered statistically significant.

## RESULTS

#### Baseline biophysical parameters

In patients with seasonal allergic rhinitis, no variations were observed between values referring to the examination performed in 2 different seasons for instrumental measurements (data not shown). However, for capacitance baseline values in patients with seasonal allergic rhinitis (mean  $\pm$  SD =  $48.45 \pm 5.83$  and  $52.10 \pm 9.60$  AU in winter and spring respectively) significantly differed from those of patients with AD (mean  $\pm$  SD =  $42.68 \pm 8.71$  AU).

#### Post challenge measurements

**Evaporimetry (Fig. 1a).** After exposure to SLS, a significant increase in TEWL as compared to baseline was observed at 24 h and 72 h in all patients. In subjects with seasonal allergic rhinitis, post-exposure TEWL values were similar during winter and spring seasons, but in patients with AD this increase was significantly higher compared to subjects with seasonal rhinitis.

**Corneometry (Fig. 1b).** In all groups of subjects, capacitance values were lower after exposure to SLS. In seasonal allergic rhinitis patients, a significant reduction compared to baseline was recorded only in winter at all evaluation times.

**Ultrasound (Fig. 2).** A significant increase in skin thickness after SLS exposure was recorded both during winter and spring time at 72 h in seasonal allergic rhinitis patients and at all measurement times in patients with AD. Post-exposure, 24-h and 72-h values were significantly higher in subjects with AD compared to seasonal allergic rhinitis patients (Fig. 2a).

Values referring to the extension of hypoechogenic dermal areas (0–30 values), evaluating dermal oedema, were higher

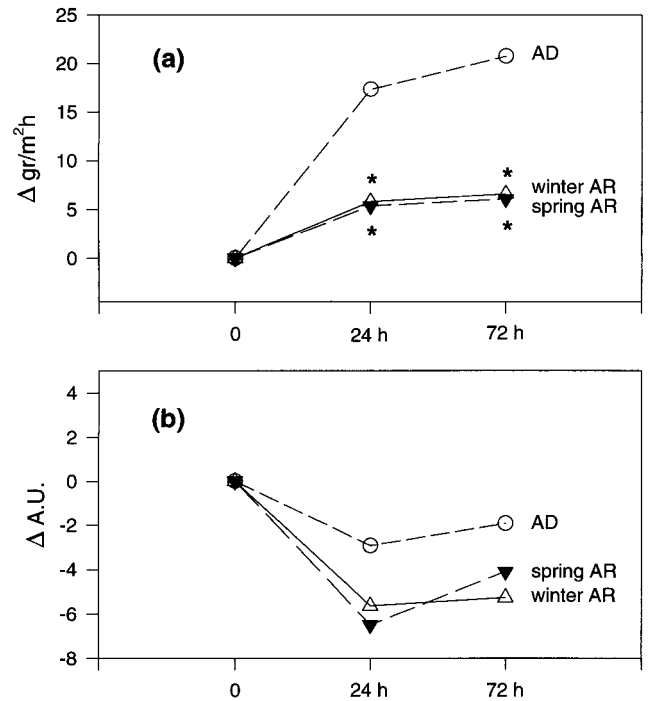


Fig. 1. (a) TEWL and (b) capacitance values of the skin in patients with atopic dermatitis (AD) (○) and subjects with seasonal allergic rhinitis (AR) during spring (▼) and winter (△) after exposure to 5% SLS: differences compared to baseline values (Delta Δ) are presented. Significant differences at 24 and 72 h were observed for TEWL for spring and winter and for capacitance for winter values in both patient groups. \* significant compared to AD.

compared to baseline at all measurement times, but differences were statistically significant only in patients with AD (Fig. 2b). Moreover, in patients with AD the exposure to SLS induced a significant reduction in the extension of hyper-reflecting epidermal areas (201–255 values) at 24 and at 72 h. The difference in the decrease compared to seasonal allergic rhinitis subjects was significant at 24 h (Fig. 2c).

## DISCUSSION

Atopy has been defined a familiar hyper-sensitivity of skin and mucous membranes to environmental substances, associated with increased IgE production and/or altered non-specific reactivity (22). Clinically, it is characterized by cutaneous and/or mucosal involvement, which may be concomitant in the same individuals. However, apart from immunological alterations, a specific organ reactivity is required to develop an atopic disease. Abnormalities in skin barrier function, as assessed instrumentally, in subjects with AD, both adults (5–7, 23) and children (24), are well known. These alterations correspond to higher baseline TEWL values at apparently healthy skin sites (5–7, 23, 24) and to lower capacitance values (24–26). Moreover, both an increased inflammatory response and enhanced barrier damage are observable in patients with AD after challenge with detergents (5–7, 14). While cutaneous hyper-reactivity in subjects with AD has been documented both by clinical contributions and experimental data, little is known about cutaneous barrier function in atopic subjects without dermatitis. The skin of

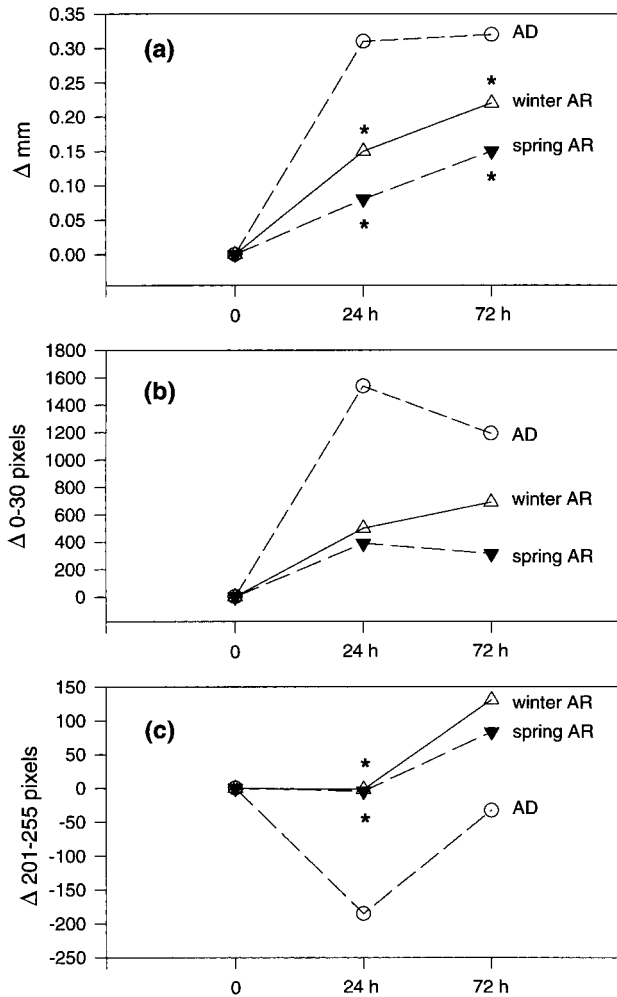


Fig. 2. Ultrasound evaluation of the skin in patients with atopic dermatitis (AD) (○) and subjects with seasonal allergic rhinitis (AR) during spring (▼) and winter (△) after exposure to 5% SLS: differences compared to baseline values (Delta  $\Delta$ ) are presented. The increase in skin thickness was significant at 72 h in all patients and at 24 h in subjects with atopic dermatitis (a). Values referring to dermal areas (0–30 pixels) were significantly increased in patients with atopic dermatitis (b). Values referring to epidermal areas (201–255 pixels) were significantly reduced at 24 h in patients with atopic dermatitis also compared to those with allergic rhinitis (c). \* significant compared to AD.

subjects with respiratory atopy does not seem as dry as the skin of subjects with AD (27). Few studies on hand eczema assess the importance of respiratory atopy as a risk factor, and their results are controversial (8–10). Lammintausta & Kalimo described a significantly higher frequency of hand dermatitis in hospital wet workers affected by allergic rhinitis and/or asthma without AD compared to non-atopics (8). On the contrary, Rystedt did not notice any difference in the frequency of hand eczema between subjects with atopic asthma and/or rhinitis and healthy controls (9). The latter's observations were confirmed by those of Funke et al., who, in a study considering risk factors for hand eczema in 2100 apprentices in the automobile industry, identified a history of hand eczema, AD and dyshidrosis as predisposing causes, whereas the personal and family history of respiratory atopy

was only moderately associated with irritant dermatitis of the hands (10). The barrier in mucosal atopics has been studied both under baseline conditions and after challenge by Nassif et al. (11), by Tanaka et al. (12) and by us (13, 14). Baseline capacitance, TEWL and pH values were found to be normal in subjects with allergic asthma/rhinitis in our study evaluating 30 subjects with respiratory atopy, 60 healthy subjects and 38 patients with AD (13). On the contrary, Tanaka et al. observed decreased baseline hydration values, as assessed by conductance measurements, in seasonal allergic rhinitis patients during the active phase of the disease (12). Employing a 48-h challenge with concentrations of SLS ranging from 0.0625 to 0.31%, Nassif et al. observed increased skin irritancy as assessed by visual scoring in patients affected by mucosal atopy without dermatitis (11). The authors attributed the decreased irritancy threshold in atopic individuals to the influence of circulatory cytokines and other mediators on the skin (11). These data were not confirmed by us in a study comparing skin reactivity to SLS in patients with respiratory atopy without cutaneous involvement, to patients with AD and non-atopics (14). In fact, post-exposure TEWL, capacitance and echogenicity values in subjects with respiratory atopy did not differ from those referring to healthy subjects (14).

So far, the skin of respiratory atopics has been investigated without comparing the different phases of the disease, and no attention has been paid to the presence of symptoms at the moment of investigation and the possible influence of inflammatory mediators released by mucous membranes on the skin's immune system and barrier function. In order to clarify these aspects, we studied subjects affected by seasonal allergic rhinitis during different phases of the disease, i.e. both during winter time and the pollen season, and compared them to patients with AD. Instrumental measurements, enabling a precise and objective evaluation, were employed. Both parameters of hydration of the skin, i.e. capacitance, TEWL and epidermal echogenicity, and those assessing inflammatory changes, i.e. skin thickness and dermal echogenicity, were used for the quantification of SLS-induced damage. In patients with AD, SLS induced a marked increase in TEWL values (Fig. 1a), dermal oedema and skin thickness and a decrease in hyper-reflecting epidermal areas (Fig. 2). In seasonal allergic rhinitis patients, notwithstanding the use of methods enabling the assessment of minimal variations and subclinical changes, no increase in skin reactivity was observed during the active phase of the disease (Figs. 1 and 2). On the contrary, during winter time, we observed a slight reduction in capacitance values at baseline. Moreover, 30 min after SLS challenge, an enhanced reduction in capacitance values was observed in winter, confirming data by Tupker et al., who found a reduced pre-exposure barrier function and an increased susceptibility to SLS in November compared to July, both in patients with AD and in healthy controls, probably due to the influence of environmental agents such as UV light, temperature and relative humidity on the skin (28).

These data confirm our previous observations obtained testing patients with AD and healthy subjects, and show that skin biophysical parameters are similar in patients with seasonal allergic rhinitis and healthy subjects, whereas marked alterations are observable only in patients with AD indicating that susceptibility to irritant substances in patients with AD is based on specific alterations of their skin (13, 14, 16, 17, 24).

This is confirmed by our data, which show that skin barrier function and reactivity in patients with seasonal allergic rhinitis, accurately selected according to criteria enabling the exclusion of subjects with a tendency to develop AD, are normal and are not influenced by the possible release of inflammatory mediators from the mucous membranes during the active phase of respiratory atopy.

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