

Report

Atopic dermatitis: correlation between non-damaged skin barrier function and disease activity

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Abstract

Background Atopic dermatitis (AD) is a chronic dermatosis, predominant in childhood, characterized by pruritus and eczematous-type lesions with xerosis as the prominent clinical sign.

Objectives To analyze the correlation between biophysical measurements of skin barrier function and other assessment criteria of clinical severity according to Rajka and Langeland's criteria.

Methods Biophysical measurements [transepidermal water loss (TEWL) and corneometry] were obtained from 120 patients with the diagnosis of AD. Serum levels of IgE were also evaluated.

Results A significant correlation between corneometry, TEWL, and clinical severity of AD was found. Data showed an inverse correlation between corneometry, TEWL, and AD severity, and a significant difference ($P < 0.001$) between mean of corneometry and TEWL and AD severity (mild, moderate, and severe). As for IgE levels, corneometry had significant negative correlation, in contrast with TEWL, which showed a significant positive correlation ($P < 0.001$).

Conclusion Biophysical measurements of skin barrier in non-lesional skin of AD may work as an evaluation factor for AD severity.

Introduction

Atopic dermatitis (AD) is a chronic dermatosis that progresses in episodes and mainly affects children. Its main symptom is a variable pruritus and signs are cutaneous xerosis and eczematous pattern lesions. The prevalence of AD has been increasing in recent years, probably due to the role of environmental factors.¹

The pathophysiology of AD is complex, involving many immune and non-immune phenomena. Genetic factors determine the expression of atopy, which may be complete (atopic triad: dermatitis, asthma, and rhinitis) or incomplete; abnormalities of immune responses mediated by T-helper 2 lymphocytes are triggered by airborne allergens, microbial products, or contact allergens. In addition to immune dysfunction, there are abnormalities to skin barrier formation, which are present not only in the damaged areas but also in clinically unaffected skin.^{2,3}

Abnormalities of barrier function favor contact with antigens and other environmental stimuli; therefore, activation of interleukins and cytokines starts, culminating in enhanced inflammatory response.⁴

In AD pathophysiology, skin barrier defect is associated with reduced ceramide levels and profilaggrin production, leading to greater transepidermal water loss (TEWL) and to an enhanced predisposition to aggression, triggering inflammation.³

Determination of AD severity and monitoring of disease progression have been attempted with various criteria. Currently, patient history and clinical presentation are the main tools that physicians use to diagnose and follow-up in patients with AD; however, due to variability in medical examinations, reproducing information may be problematic, which is aggravated by the multiplicity of criteria regularly proposed.⁵

In AD, xerosis is a frequent and significant finding, which may be the clinical expression of skin barrier abnormality, and it is a diagnostic and follow-up parameter.⁶ Bohme *et al.*,⁷ studying 221 atopic children, clearly show the importance of xerosis in AD, observed in 100% of the subjects. In order to obtain objective and reproducible measurements of skin barrier conditions, non-invasive instruments, assessment of hydration level, and integrity of skin barrier function may be used.^{8,9} Such assessments

can also detect underlying clinical skin infections, which are imperceptible to clinical routine examination but may be evidenced by careful inspection of damage to skin barrier function.¹⁰

In 2003, Sugarman *et al.*¹¹ developed an equation to define the correlation between AD severity and TEWL parameters and measurement of water in stratum corneum [objective severity assessment of atopic dermatitis (OSAAD)] compared with scoring atopic dermatitis – (SCORAD), resulting in a good correlation.

Even though SCORAD is a widely used criteria to follow up patients with AD, its applicability in darker-skinned subjects has been discussed. Bem-Gashir *et al.*,¹² studying AD severity in African-American and Caucasian children, demonstrated that SCORAD results underestimate AD in African-American children because it considers erythema.

This paper analyzes the correlation between biophysical measurements of skin barrier function and other assessment criteria of clinical severity according to Rajka and Langeland.¹³

Materials and methods

Subject selection

We studied 120 patients with AD that were followed up at the Atopic Dermatitis Outpatient Clinic from the Department of Dermatology, Hospital das Clinicas, University of Sao Paulo Medical School, Brazil. The clinical diagnosis of AD was established according to the Hanifin and Rakja's¹⁴ criteria, between March 2006 and March 2007.

All patients were informed of the study objectives and voluntarily agreed to participate, signing an informed consent form.

Methodology

To assess skin presentation severity, patients or their guardians answered a survey based on the criteria of Rajka and Langeland, which classifies dermatitis into mild, moderate, and severe, as provided below.

Sum of grades was expressed in:
extension + progression + intensity:

- 1 3–4: mild.
- 2 4.5–7.5: moderate.
- 3 8–9: severe.

To calculate extension, authors recommended the use of the “rule of nine,” used to calculate burnt areas, in which each area represents a percentage of body area.

Upon the first medical visit, the following measurements were made:

- 1 Hydration level of stratum corneum, with equipment model Corneometer MPA 580® by manufacturer Courage + Khazaka Electronic GmbH (Germany).¹⁵

- 2 TEWL, with equipment model Tewameter TM300® by manufacturer Courage + Khazaka Electronic GmbH (Germany).¹⁶

All measurements were taken within standardized climate conditions, with control of temperature and humidity monitored by thermohygrometer. For standardization purposes, the temperature during measurement ranged from 18 to 22 °C, whereas humidity was within 40–60 °C; collected measures that fell outside of these parameters were not included in the study. The collection area chosen in all patients was the flexural region of the mid-third forearm.

Patients that had applied topical products or had washed the region within four hours were not included in the study. Similarly, patients with active lesions on the standardized collection area were not included. IgE circulating levels were also measured.

Statistical analysis

Analyses were conducted using SPSS (version 15; SPSS Inc., Chicago, IL, USA). Means of corneometric measurements and TEWL according to AD severity were compared using analysis of variance. To assess the difference between means of severity (variable with more than two categories), a Tukey test was applied.

Variance analyses were used to compare means of measurements of corneometry, TEWL, and IgE according to severity of AD. Assessment of the association between levels of corneometry, TEWL, and IgE was performed using the Pearson correlation coefficient.

Results

We assessed 120 patients, distributed according to clinical severity (Rajka and Langeland scale) into:

- 1 Mild grade (up to 4): 34 patients (28.3%).
- 2 Moderate grade (4.5–7.5): 45 patients (37.5%).
- 3 Severe grade (8–9): 41 patients (34.1%).

Concerning gender, 55% of the sample was formed by female patients (66) and 45% by male patients (54). As to age, distribution ranges was as follows:

- 1 0–10 years: 55 patients (45.8%).
- 2 11–17 years: 22 patients (18.3%).
- 3 18 years or older: 43 patients (35.8%).

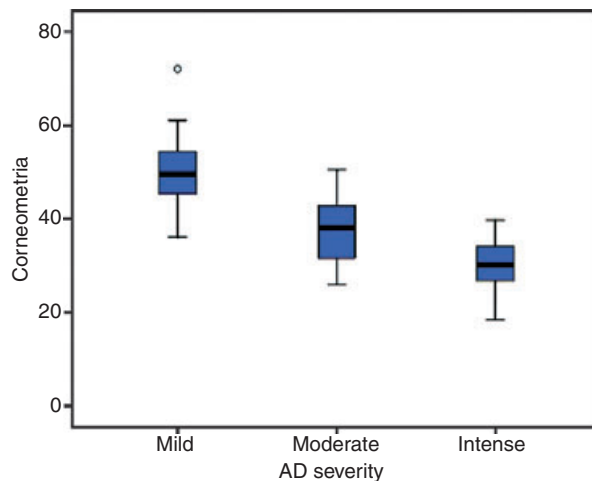
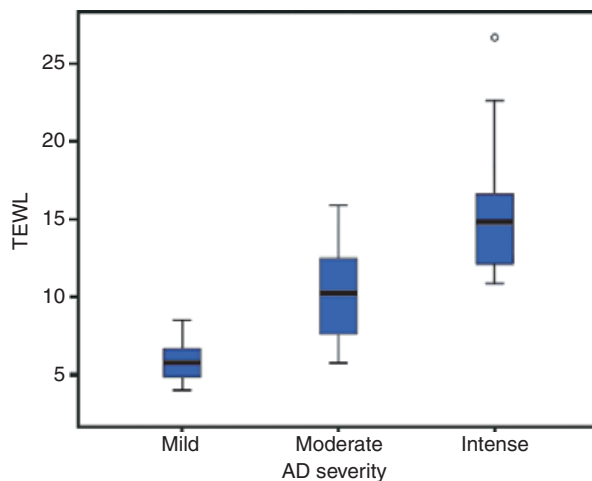
Means of corneometric measurements and TEWL obtained for each group were the following (Table 1): There was a significant difference between mean of corneometry measurements, TEWL, and clinical severity of the presentation ($P < 0.001$).

Means of IgE serum levels obtained in each group according to the severity ranged from 142.4 UI/ml (mild), 310.48 (moderate), to 3644.22 (severe). There was a significant difference for IgE levels between mild and severe

Table 1 Mean biophysical measurements based on clinical severity of atopic dermatitis, according to Rajka and Langeland

Biophysical measurements	Mild grade	Moderate grade	Severe grade
Corneometry ^a	49.8 ± 9.3 ^b	37.3 ± 10.4 ^b	29.7 ± 11.7 ^b
TEWL ^a	5.8 ± 2.3 ^b	10.2 ± 4.1 ^b	15.2 ± 3.5 ^b

TEWL, transepidermal water loss.

^a $P < 0.001$.^bMean ± SD.**Figure 1** Corneometry and atopic dermatitis severity**Figure 2** TEWL and atopic dermatitis severity

AD and moderate and severe AD ($P < 0.001$). There was no statistical difference for IgE levels between mild and moderate AD.

Data showed that there was significant and an inversely proportional correlation between corneometry and TEWL; the mean of corneometry and TEWL and level of AD differed significantly (mild, moderate, and severe). These data are shown in a boxplot for corneometry (Fig. 1), TEWL (Fig. 2) and IgE levels (Fig. 3).

Correlation between IgE means and biophysical means

There was a significant negative correlation between corneometry levels and TEWL; corneometry and IgE levels had a significant negative correlation. However, TEWL and IgE had a significant positive correlation; there was a linear correlation between the three variables, and the correlation between TEWL and IgE was directly proportional (Table 2). There was dependence between the level of corneometry, TEWL, and IgE.

Discussion

The inflammatory status is present in atopic patients even in clinically normal skin areas, where altered biophysical measurements of TEWL and corneometry are detected. Some studies^{17,18} have demonstrated significantly increased TEWL on non-damaged skin of atopic subjects, which is attributed to a maturation disorder of lamellar bodies, associated with a genetic predisposition of high protease production, leading to an early break of the corneum desmosomes¹⁹ with consequent disorders of the epidermal barrier. However, the same measurements taken in normal adults with a history of AD in childhood showed no abnormalities. This finding is consistent with Matsumoto,²⁰ who showed that the water content measured by corneometry, such as in TEWL, is normal in patients without atopic manifestations.

Biophysical measurements of non-damaged skin in patients with AD in activity seem to correlate with clinical severity, once measurements tend to restore to the normal range as the AD skin lesions remit. This finding may indicate that biophysical parameters of the barrier assessment are reliable indicators of AD activity, even when there is no detectable damage in the clinical examination.

The correlation between AD severity and biophysical measurements of damaged skin has been shown in a study with children and adolescents.²¹ The significant correlation of these measurements of non-damaged skin was confirmed by Holm *et al.*,²² who intended to validate the parameters of hydration, TEWL, ultrasound, and Doppler to assess AD. Even though these authors did not consider these measurements as the “gold standard” to assess AD severity and to define prognosis of AD, their results showed significant differences between damaged atopic

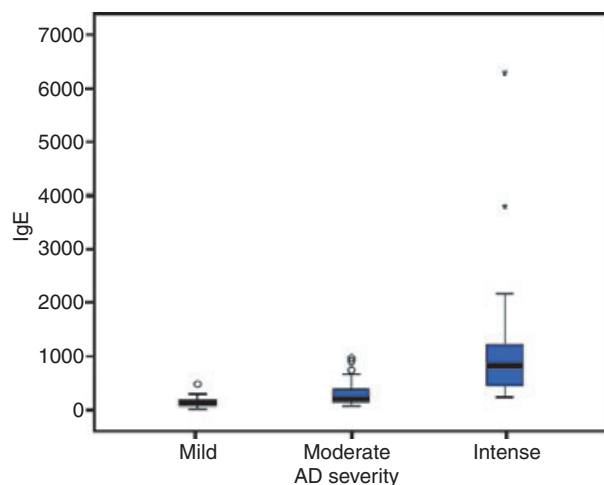


Figure 3 Serum IgE levels according to atopic dermatitis (AD) severity

Table 2 Corneometry, transepidermal water loss (TEWL) and IgE correlation in atopic dermatitis

	Pearson correlation coefficient	*P value
Corneometry and TEWL	−0.640	<0.001
Corneometry and IgE	−0.319	0.001
TEWL and IgE	0.358	<0.001

Significant value: * $P < 0.001$.

skin, non-damaged skin, and the controls, suggesting a correlation with levels of disease activity. The study has also demonstrated that samples collected from apparently non-damaged skin can be used to assess disease severity.

Even during remission periods, atopic patients show cutaneous xerosis or rashes and TEWL increases. The increase is present both on the damaged skin and non-damaged skin of atopic patients, as shown by Seidenari and Giusti,¹⁷ whose study included 66 atopic and 21 healthy children. The means obtained in each group were significantly higher for atopic patients than for the controls. Another study by Giusti²³ showed that the atopic child has significant increases in TEWL, even without active lesions. Based on these findings, the authors concluded that TEWL measurement was a functional marker of AD, which may vary based on the presence of skin damage, despite absence of clinical lesions.

In our study, there was significant TEWL increase in non-damaged skin in atopic patients, in accordance to AD clinical level; the corneometry levels were proportionally reduced to the AD clinical intensity; moreover, there

was an inverse proportional correlation between corneometry and TEWL in non affected skin of atopic patients. These findings suggest that biophysical measures could play a role in AD follow-up, even in patients with few apparent lesions.

IgE measurements

Although no significant linear relation between clinical severity grading and IgE levels was detected, our data showed that corneometry measurements and IgE levels had a significant negative correlation, whereas TEWL and IgE had a significant positive correlation.

Lower corneometry and higher TEWL means in atopic patients with high levels of IgE lead to a correlation between barrier compromise and IgE level; possibly, affected corneometry and TEWL levels are manifested before pruritus or function as a sign indicating that the skin is more predisposed to pruritus, but there is no evidence to this effect. It is not known whether IgE increases because of the barrier defect shown by the measurements or whether increased IgE promotes the barrier defect, even in non-affected atopic skin. Likewise, IgE levels seem to be correlated with AD severity.²⁴

Conclusion

Atopic dermatitis is a chronic skin disease in which immune response abnormality and skin barrier function play a relevant role, especially during severe flares. When the skin barrier function is harmed, the clinical presentation tends to worsen, leading to an augmented inflammatory process.

Transepidermal water loss and corneometry, two biophysical non-invasive measurements of the skin barrier status, are related to severity of AD, once they represent skin barrier and stratum corneum integrity.

Our study demonstrates a significant correlation between corneometry, TEWL, and AD severity. Moreover, augmented TEWL correlated with high IgE levels, pruritus, and asthma. Therefore, noninvasive biophysical measurements of skin barrier such as corneometry and TEWL, even in non-damaged AD skin, may represent useful tools to evaluate disease severity and pruritus. However, ethnic diversity should be considered when analyzing data, as these features may modify the interpretation of the results.

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