Original paper

# Evaluation of selected skin barrier functions in atopic dermatitis in relation to the disease severity and pruritus

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Postep Derm Alergol 2012; XXIX, 5: 373-377
DOI: 10.5114/pdia.2012.31491

## Abstract

**Introduction:** Atopic dermatitis (AD) is an inflammatory pruritic dermatosis, which is characterized by an impaired skin barrier function manifested as an increased transepidermal water loss (TEWL).
**Aim:** Presentation results of instrumental evaluation of the skin barrier function in AD patients in relation to the disease severity as well as pruritus.
**Material and methods:** Fifty-five AD patients aged from 8 to 60 years were enrolled to the study. Epidermal barrier function (TEWL measurement and corneometry) as well as erythema measurement were determined in each patient within the same affected skin region, antecubital fossa. Clinical evaluation was performed using the W-AZS scoring system.
**Results:** There was a statistically significant difference in the mean TEWL values between groups of patients with different degrees of skin inflammation expressed by the W-AZS index, while no significant differences were observed in relation to the skin hydration and ertyhema measurement. There was a statistically significant correlation between the W-AZS index and TEWL as well as between the W-AZS I index and TEWL.
**Conclusions:** Selected parameters of the skin barrier function (TEWL, skin hydration) and the level of erythema are useful in evaluation of AD. Transepidermal water loss measurement presents a good correlation with W-AZS and with intensity of patients itching. Instrumental assessment provides us with a fast and objective evaluation of the eczema status, what seems to be very important in the era of evidence-based medicine.

**Key words:** atopic dermatitis, skin barrier, transepidermal water loss.

## Introduction

Atopic dermatitis (AD) is considered a multifactorial and complex skin disorder, where symptoms in the form of intense itching and eczematous skin lesions arise from complex interactions between genetic and environmental factors [1, 2]. A cardinal sign of AD is very dry skin, which is observed not only within the affected regions, but also within the whole body surface. According to pathogenesis of AD, much interest in recent years has been associated with structural and functional abnormalities of the epidermal barrier as an important and underlying cause involved in the formation of skin lesions in patients with AD. This concept, which supports the defective epidermal barrier as the primary event in development of AD is called an "outside-inside" hypothesis [1-6]. In the 1980s and 1990s, the barrier defect in AD was explained mainly by a deficiency of lipids, especially ceramides. Further studies showed also abnormal keratinocyte differentiation in AD. In recent years the connection with mutations of filaggrin gene, altered homeostasis and lack of the natural moisturizing factor (NMF) has revealed new aspects of this issue. The consequence of all causative factors mentioned above is an increased water loss (transepidermal water loss – TEWL), poor hydration and propensity toward development of flares of AD, even after a long period of remission [1-5].

The epidermal barrier, which protects the organism against an extensive water loss and the entry of external environmental stressors is referred to the most superficial and structurally heterogeneous layer of epidermis –

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stratum corneum (SC). Stratum corneum is composed of terminally differentiated anucleate keratinocytes, called corneocytes, and lipid-rich extracellular matrix [4, 5]. The condition of this layer nowadays can be easily evaluated with the use of noninvasive bioengineering techniques, such as measurement of TEWL and SC hydration. These methods allow for precise and objective quantification of the SC function and have been constantly evolving [7].

It would seem that there is a need for broader appraisement of these methods in relation to the disease severity as well as pruritus, which has not been evaluated before. An instrumental assessment of AD patients in the form of TEWL measurement and skin hydration, expanded by erythema measurement was performed in a group of 55 AD patients. The data presented in this paper are a part of a large study on noninvasive assessment in AD, with special emphasis on skin sonography as well as nonlesional skin in AD, and will be published in the nearest future.

## Material and methods

### Participants

Fifty five AD patients (26 women, 29 men) treated at the Department of Dermatology, Poznan University of Medical Sciences, aged from 8 to 60 years (mean age: 25.9 ±11.8 years) were enrolled to the study. Informed consent was obtained from all patients, and the study was approved by the local ethical committee.

### Clinical evaluation

Clinical evaluation was performed before the instrumental assessment using the W-AZS scoring system [8]. The W-AZS index allows for a detailed assessment of both objective (severity and extent of skin inflammation) and subjective (pruritus) symptoms. The itching sensation is evaluated on a scale of 0-34 points with respect to extent, frequency and severity. Also sleep disturbances (including difficulty in falling asleep, awakening or insomnia) are taken into account. The extent of skin lesions is determined using the "rule of nines". Severity of the disease is rated in terms of the presence of both acute and chronic skin lesions (erythema/papule, vesicles/erosions, crusts/exfoliation and lichenification/discoloration). As a result of inflammatory process evaluation, the patient may achieve max. 178 points. The total value of the W-AZS index (212 points) is a sum of subjective and objective symptoms. In this paper, we evaluated the total W-AZS index as well as separately we analyzed only subjective symptoms of W-AZS describing them as W-AZS I.

### Instrumental assessments

Transepidermal water loss was determined by Tewameter TM 300 (Courage-Khazaka, Cologne, Germany) according to the guidelines of the standardization group of the European Society of Contact Dermatitis [9]. At least 20 measurements given as a mean value and expressed in SI units ($g/m^2/h$) were carried out (normal range: 0-25 $g/m^2/h$).

Hydration of SC (corneometry) was obtained with the use of Corneometr CM 825 (Courage-Khazaka, Cologne, Germany), whose main principle is based on the fact that the dielectric constant of water is 81 and of dry skin is below this. A normal value of SC hydration was accepted as higher than 40 u [10]. Five measurements given as a mean value in arbitrary units (range: 0-130) were determined in accordance with guidelines [11].

Erythema was evaluated on the basis of reflectance spectroscopy, where the redness is calculated by subtracting the absorbance due to melanin from the absorbance of the green filter, using Color Meter II (Cortex Technology, Hadsund, Denmark) [12]. Three independent measurements were made at an interval of 30 s, on the basis of which the average value was determined.

Instrumental assessments were performed in the same room conditions (temperature 20-22°C, humidity 20-40%) after 15-30 min acclimatization by the same trained physician. All bioengineering assessments were conducted within the same affected skin region, antecubital fossa, always in the same order: TEWL, corneometry, erythema.

### Statistical analysis

Statistical analysis was performed with the use of statistical package Statistica v 10.0. and the chosen level of significance was $p < 0.05$. The compatibility of assessed parameters with normal distribution was checked and Bartlett's test of homogeneity of variance was performed. For characteristics consistent with a normal distribution for comparison between groups, an analysis of variance was used. When compatibility with the normal distribution was not confirmed, a nonparametric test, Mann-Whitney or Wilcoxon tests were used. The relationship between indexes and TEWL was calculated with the Spearman rank correlation coefficient.

## Results

The median of the W-AZS index in the group of 55 patients with AD was 74.5 points (min. 7.8 points, max. 169 points), while median of W-AZS I was 16.1 points (min. 0 points, max. 34 points).

To compare the severity of the clinical status with the results of instrumental methods (TEWL, corneometry, erythema), patients were divided into 2 groups differing in the value of the indexes (W-AZS and W-AZS I). An analysis of the W-AZS allowed to distinguish group I - patients with a mild and moderate clinical status (W-AZS < 70 points) and group II with moderately severe and severe

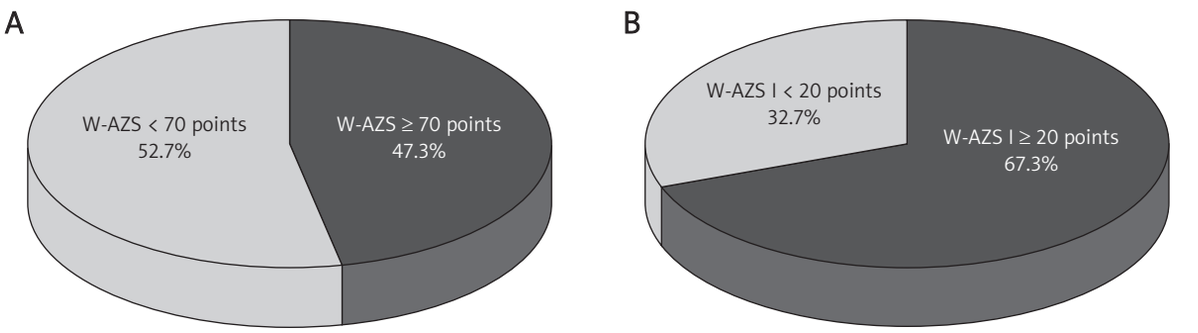


**Figure 1.** Evaluation of objective and subjective symptoms on the basis of W-AZS (**A**) and W-AZS I (**B**) indexes

skin inflammation (W-AZS ≥ 70 points). Group I included 26 patients (47.3%) and group II – 29 patients (52.7%) (Figure 1). Based on the analysis of the W-AZS I index, 2 groups with different severity of subjective symptoms were formed. Group I consisted of 37 patients (67.3%), who obtained less than 20 points. Group II included 18 patients (32.7%) with the W-AZS I index ≥ 20 points (Figure 1). Severity of subjective symptoms in group I was defined as mild and moderate, whereas in group II – as significant.

A mean TEWL value was 33.5 ±12.4 g/m$^2$/h (min. 13.4 g/m$^2$/h, max. 65.5 g /m$^2$/h). Transepidermal water loss values within the normal range were observed in 16 patients (29.1%), whereas TEWL values ≥ 25 g/m$^2$/h were detected in 39 patients (70.9%). There was a statistically significant difference in the mean TEWL values between groups of patients with different degrees of skin inflammation expressed by the W-AZS index ($p$ = 0.013). In group I (patients with a mild and moderate clinical status), mean TEWL was 21.9 ±2.3 g/m$^2$/h (min. 11.3 g/m$^2$/h, max. 37.9 g/m$^2$/h), while in group II (patients with a moderately-severe and severe clinical status) it was 37.2 ±15.0 g/m$^2$/h (min. 13.4 g/m$^2$/h, max. 65.5 g/m$^2$/h) (Figure 2). There was no statistically significant difference in mean TEWL values between groups of AD patients differing in severity of subjective symptoms. Patients with mild and moderate itching sensations obtained 31.5 ±3.1 g/m$^2$/h, while a group with significant pruritus reached 38.1 ±7.9 g/m$^2$/h.

A mean value of skin hydration (skin capacitance, corneometry) was 19.9 ±7.9 u (min. 2.6 u, max. 37.9 u) and none of the patients reached 40 u, adequately to healthy skin hydration [9]. There was no statistically significant difference in the skin hydration measurement between groups of AD patients differing in disease severity and pruritus, expressed on a scale of W-AZS and W-AZS I. In a group with W-AZS < 70 points mean that the corneometry value was 19.6 ±5.3 u, while in patients with W-AZS ≥ 70 points was 18.1 ±8.5 u. Comparable mean corneometric values were observed in relation to W-AZS I (20.8 ±5.3 u and 19.2 ±3.1 u).

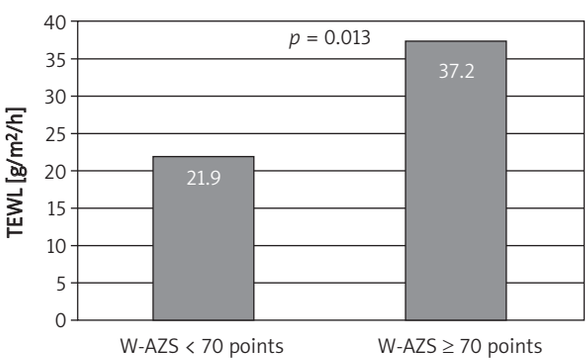


**Figure 2.** Mean TEWL values in relation to the disease severity (W-AZS index)

A mean erythema value was 16.7 ±3.4 (min. 9.0, max. 23.0). No statistically significant differences were obtained between groups of AD patients with different severity of skin inflammation and pruritus. In patients with W-AZS < 70 points mean erythema level was 19.1 ±4.2, while in patients with W-AZS ≥ 70 was 17.9 ±4.5. Comparable mean erythema values were detected in relation to W-AZS I (16.1 ±5.5 and 18.1 ±3.7).

There was a statistically significant correlation between the W-AZS index and TEWL ($R$ = 0.33, $p$ = 0.01) as well as between the W-AZS I index and TEWL ($R$ = 0.36, $p$ = 0.006). No significant variations were observed for skin hydration and erythema measurement.

## Discussion

Assessment of disease severity in AD seems to be quite complicated due to the variable lesional morphology, poorly marginated lesions and the presence of lesions in different stages within the same patient. Several different scoring systems have been proposed in recent years and still new indexes have been regularly introduced to the clinical practice [13]. However, they appear to provide poor intraobserver and interobserver reproducibility. Thus,

there is a need for searching for bioengineering instrumental assessment, which will simplify and provide an objective evaluation of the disease process [7, 9-11]. In this field especially the measurement of TEWL and water content of SC (skin capacitance, corneometry) are in routine clinical usage, however evaluation of erythema and the measure of specific parameters with the use of high-frequency ultrasonography (HF-USG) may also enhance the assessment [7, 14-16].

In this paper we used 3 noninvasive methods of clinical evaluation of AD in relation to the disease severity and pruritus. The first assessed parameter was TEWL, which for years has served as a useful indicator of the skin barrier function. According to available literature data, the measurement of TEWL is characterized by extraordinary sensitivity in detecting even subclinical deviations and its elevated levels are observed also within nonlesional AD skin [5, 17]. It is also perceived as a predictive factor for the development of skin irritation in patients with AD [18]. Loss of water through the epidermis takes place primarily via two mechanisms: evaporation by passive diffusion and secretion by the eccrine glands. The concept of TEWL is mainly based on evaporation of water through the skin and its appendages, with the process of sweating limited to a minimum [19].

Intact skin is characterized by a low TEWL, which generally does not exceed 25 g/m$^2$/h [18]. Although within different skin regions, a variation in TEWL values may be observed, what may be related to the SC thickness and the differences in skin microcirculation. In the case of severe destruction of SC, TEWL may reach even 70 g/m$^2$/h [17]. In our study, only in 29.1% of cases TEWL was within normal ranges (0-25 g/m$^2$/h), while its mean value was 33.5 ±12.4 g/m$^2$/h with a maximum of 65.5 g/m$^2$/h. Such parameters confirm significant disturbances in homeostasis of the skin barrier function. In the presented study, we detected also a statistically significant difference in the average TEWL values between groups of patients with different degrees of skin inflammation (patients with more severe skin lesions presented an enhanced water loss) as well as we observed a good correlation between TEWL and severity of skin lesions. This confirms previous reports on the relationship between TEWL and patients' clinical status [4, 7, 20]. On the other hand, analysis of subjective symptoms (W-AZS I) did not reveal any difference in mean TEWL values in a group with mild and significant pruritus. However, we found a significant correlation between TEWL and W-AZS I. This points to the complexity of the problem of itching in AD and should be evaluated in future studies.

Another analyzed parameter was the measurement of the SC hydration. It is well known that inadequate hydration causes impairment of the barrier function and increases the likelihood of skin irritation. The water content in the epidermis is mostly associated with the presence of NMF and the appropriate composition and structure of lipids [7]. Hygroscopic properties of NMF make act as an effective humectant and help to maintain normal SC hydration. The decrease in water content (less than 10%) clinically presents as dry skin in the form of its roughness and scaling [21]. The most commonly applied method to assess skin hydration is electrical conductance (capacitance), where the measure concerns superficial layers of the epidermis with a thickness of 10-20 microns [11]. There is an inverse relationship between TEWL and the degree of hydration of the epidermis and high TEWL values are usually associated with a reduced water content [7].

According to Werner, healthy skin is characterized by the corneometric measurement higher than 40 u [10]. None of the patients in the presented study reached such level and mean SC hydration was approximately 20 u. We did not observe a relationship between W-AZS and W-AZS I and electrical conductance, which is in contradiction to other clinical data. Holm *et al.* detected the connection between severity of skin lesions measured with the use of 3 independent scores (SCORAD, EASI and ADSI) and skin water content [22].

In the presented study we also evaluated skin color on the basis of erythema measurement. Erythema is a well-known sign of skin inflammation and accompanies the acute and chronic stages of AD. Although noninvasive assessment seems to be more objective than the naked eye evaluation, we did not detect a relationship between the degree of erythema and W-AZS as well as the severity of pruritus.

For the integral evaluation of the skin barrier function, beside such parameters like TEWL, SC hydration, measuring of skin acidity is also essential [5, 7]. Skin surface pH measurement provides information on barrier homeostasis, function of antimicrobial skin defense and may serve as a marker of epidermal restoration after exposure to harmful external factors (for example alkaline soaps and other detergents). In AD, pH is increased and alkaline pH may induce or exacerbate the disease. Another relevant components of SC, which may also be investigated, are lipids. As regards AD, with a prominent role of the ceramide profile [4, 7, 19, 23].

In this study we examined selected parameters of the skin barrier function (TEWL, SC hydration) and the level of skin erythema in relation to the disease severity and pruritus. We investigated their usefulness in evaluation of AD. However, SC hydration and skin erythema provided substantial and objective information on the patient's clinical status, only TEWL measurement had a good correlation with W-AZS and what should be emphasized, also with intensity of patients itching. Pruritus in AD, like dry skin is a hallmark feature of this disorder, and in fact, is difficult to evaluate due to many psychological aspects influencing its sensation. It is possible that certain parameters of the skin barrier function

(like TEWL) may contribute to a better understanding of the pathogenesis of itching in AD. For sure, instrumental assessment provided us with a fast and objective evaluation of the eczema status, what seems to be very important in the era of evidence-based medicine, where reproducible techniques, which allow for quantification of the disease severity in communication between different scientific groups are in special need.

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