REVISION

Skin barrier in atopic dermatitis

Barreira cutânea na dermatite atópica

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Abstract: Research about the skin barrier and its properties has increased significantly since the 60s, with studies that indicated its resistance when isolated, as well as its particularities in relation to skin permeability. At the same time, description of Odland bodies helped to understand how stratum corneum stability is maintained. The "brick and mortar" model is the most accepted so far. In this analogy, the corneocytes are the bricks and the intercellular lipids are the mortar. Currently, there is concrete evidence that the stratum corneum is an active metabolic structure that holds adaptive functions, interacting dynamically with the underlying epidermal layers. The skin barrier also plays a role in the inflammatory response through melanocyte activation, angiogenesis, and fibroplasia. The intensity of this response will essentially depend on the severity of the injury. Skin barrier abnormalities in atopic dermatitis are clinically observed by the presence of dry skin, a common and significant symptom which constitutes a diagnostic and monitoring parameter. The stratum corneum hydration level and transepidermal water loss are associated with the level of damage to the barrier, representing biophysical parameters. These parameters help doctors monitor patients in a less invasive and more sensitive manner.
Keywords: Dermatitis, atopic; Insensible; Keratinocytes; Water loss

Resumo: O estudo da barreira cutânea e de suas propriedades ganhou impulso a partir da década de 60, com estudos que apontaram sua resistência de forma isolada e suas propriedades com relação à permeação cutânea. Paralelamente, a descrição dos corpos de Odland auxiliou a compreensão da manutenção da estabilidade da camada córnea. O modelo brick & mortar, em que os corneócitos são os tijolos e o cimento são os lipídeos intercelulares, é o mais aceito, até o momento. Atualmente, há evidências consistentes de que o estrato córneo é uma estrutura metabolicamente ativa e exerce funções adaptativas. A barreira cutânea também tem um papel na resposta inflamatória, com ativação de melanócitos, angiogênese e fibroplasia, cuja intensidade depende, basicamente, da intensidade da agressão. As anormalidades da barreira cutânea da dermatite atópica são clinicamente observáveis pela presença de pele seca, achado muito frequente e significativo, que constitui parâmetro diagnóstico e de acompanhamento. O grau de hidratação da camada córnea, assim como a perda de água transepidérmica (transepidermal water loss - TEWL), estão relacionados com o grau de dano à barreira, constituindo parâmetros biofísicos que permitem acompanhar os pacientes de maneira não invasiva e com maior grau de sensibilidade.
Palavras-chave: Dermatite atópica; Queratinócitos; Perda insensível de água

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INTRODUCTION

Atopic dermatitis (AD) is a chronic disease with evolution in outbreaks that predominates in infancy. Its main symptom is pruritus of variable intensity and its main signs are skin xerosis and eczematous lesions. [1] The stimulus for an abnormal response is often external, due to alteration of the skin barrier: there is the development of xerosis, with abnormalities in the stratum corneum, and increase of transepidermic water loss, which also cause an abnormal IL-4 metabolism. [2]

Epidemiologically, AD is one of the most frequent inflammatory dermatoses in infancy, [3] normally with onset in the first years of life. Of the children who develop AD, 50% manifest the disease within the first year of life and 30%, from the first to the fifth year. [4]

Prevalence of AD has increased over the last years, and environmental factors seem to play an important role in this growth. [5,6]

In AD, skin xerosis, a terminology used to describe dry skin, is a very frequent and significant symptom: because it is the clinical expression of the skin barrier abnormality shown by these patients, it is a diagnostic and monitoring parameter.

In the physiopathology of AD, impairment of the skin barrier is associated with a reduction in the levels of ceramide and in the production of profilaggrin, with greater transepidermic water loss (TEWL) and higher predisposition to aggression, which are the trigger for inflammation. [7,8]

Instrumental evaluations of morphological parameters have been investigated to obtain objective reproducible measurements of the skin barrier conditions. Non-invasive techniques have been developed and validated for a few specific parameters. [9]

Two methods that employ instrumental analysis may be used for skin barrier evaluation in AD:

Measurement of the hydric content of the corneal layer (corneometry)

Measurement of transepidermic water loss (TEWL)

These measures identify subtle changes, non-perceptible clinically, with reproducibility in standardized conditions.

3.1. Skin barrier

The idea that the skin barrier would be a simple "mantle" that separated the internal medium from the environment underwent radical changes over the last 50 years. Until the 1960s, it was thought that the skin barrier was in fact in the upper portion of the granulous layer and was not formed by the stratum corneum. The first works to modify this belief were those conducted by Cristopher and Kligman [10], who analyzed the stratum corneum in isolation and showed its resistance. At the same time, studies by Blank [11] and Scheuplein and Blank [12] showed the particularities of the stratum corneum (SC) permeability, whose infiltration is determined by the chemical characteristics of the molecule and thickness of the SC, in addition to its humidity level, according to what was detailed by Sato *et al*. (2002). [13]

Simultaneously, Odland described the organelles that are named after him, also called lamellar bodies, whose structure contains a mixture of ceramides, cholesterol, and free fatty acids. They play a role in the formation of the lipid component of the skin barrier (through exocytosis) and in the maintenance of the stratum corneum stability. [14]

In 1975, Michaels *et al*. [15] suggested a schematic model to explain the permeability of the stratum corneum, called "brick & mortar", where the corneocytes are the bricks and the lipids are the mortar. This model was reviewed and validated by Jonhson *et al.* in 1997. [16] Today this is viewed as the most appropriate model for the understanding of cellular arrangement and the winding ways of skin permeability (Figure 1).

The stratum corneum is a metabolically active structure and it also has adaptive functions, with great interaction with the subjacent epidermal layers.[17]

Physiologically, the stratum corneum is formed by a sequence of events:

1. the keratinocyte cellular membrane of the granulous layer becomes more permeable to ions, especially calcium, which activate peptidases and convert pro-filaggrin into filaggrin: filaggrin is an intermediate filament-associated protein that exists in the granules of kerato-hialine and activates the enzymes trigliceridadase and aggregates keratin filaments with macrofibrils; next, this protein is degraded to free aminoacids that will later be used in the constitution

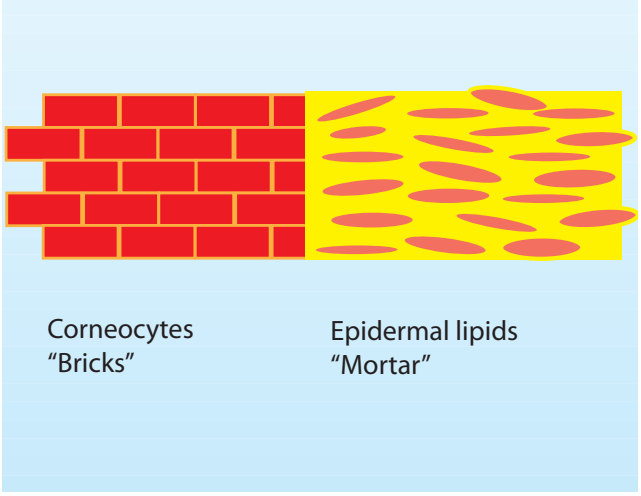
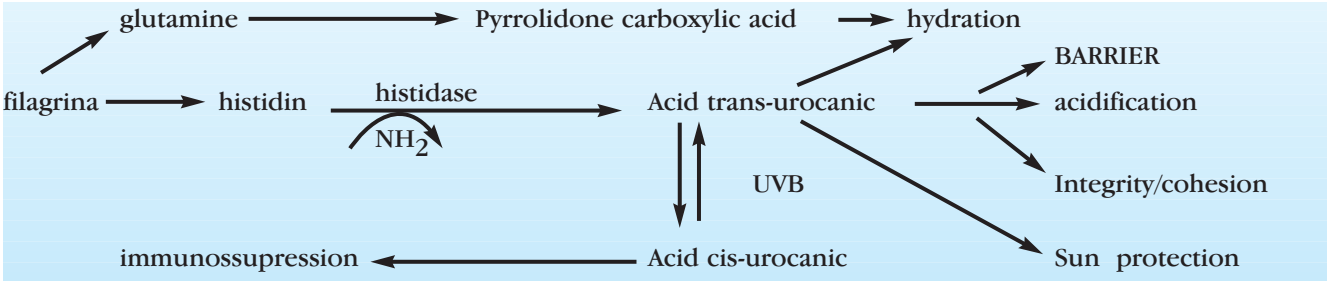


Figure 1: "Brick and mortar" pattern of the stratum corneum (skin barrier)
Source: Michaels AS, et al [15]

Figure 2: Defensive mechanisms of the stratum corneum and influence of filaggrin products



Adapted source: Elias PM, et al. [20]

of the natural moisturizing factor or converted into urocanic acid or pyrrolidone carboxylic acid (PCA). [18]

Filaggrin is responsible for aggregating keratin and other proteins in the superficial layers of the epidermis to form the stratum corneum; [19] the process of conversion of profilaggrin into filaggrin maintains the integrity of the epidermis (Figure 2).

2. With the degeneration of the cellular nucleus, cells become flat and keratin molecules align in parallel, creating a cornified envelope, connected to extracellular lipids. [20] The cohesion power of this layer depends upon the formation of covalent connections of lisyne glutamine, where precursor proteins are incorporated into keratin: involucrin, small proline-rich peptides (SPRP), cornifin, loricrin, keratoline, and desmosomal proteins such as envoplakin and periplakin. [21]

3. Lamellar bodies, originated in the granulous layer, also contribute to the formation of the lipid matrix in which corneocytes are located (Figure 3).[22,23]

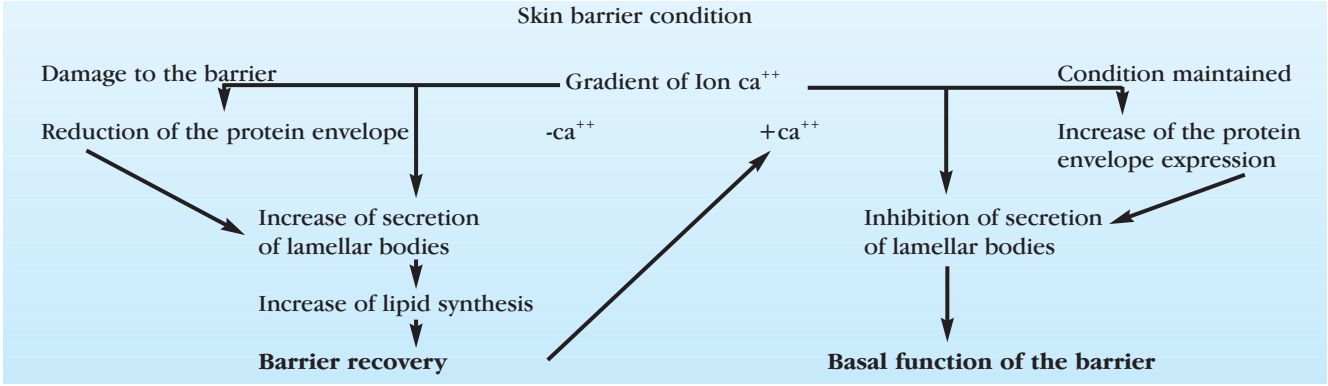
Studies by Elias *et al.* [17,24,25,26] showed that any disturbance of the skin barrier unchains a repair response that may last for days or hours, based on the intensity of the stimulus. Initially, secretion of a pool of pre-formed lamellar bodies occurs, followed by an increase in the synthesis of cholesterol and free fatty acids and ceramides; at the same time, there is an increase in enzymes and levels of RNAm relative to these enzymes, with primary activation by phosphorilation of HMG-CoA reductase and of sterol regulatory element binding proteins (SREBPs) as regulators of the synthesis of cholesterol and epidermal fatty acids. In addition, an increase in the synthesis of epidermal DNA is observed.

Regarding the immunological aspect, there is release of IL1 alpha pools and increase in the synthesis of proteins constituent of cytokines, with the generation of intracellular adhesion molecules (ICAM), and increase of TNF? concentration and granulocyte-macrophage colony stimulating factor (GM-CSF), with consequent activation of Langerhans cells. These phenomena unchain an inflammatory response and activate melanocytes, angiogenesis, and fibroplasia, [27] whose intensity will depend essentially on the intensity of the aggression (Figure 4).

3.2. Skin barrier and atopic dermatitis

Atopic dermatitis is a chronic eczematous dermatitis, characterized by Th2 and Th1 reaction patterns against environmental allergens. In AD, skin

Figure 3: Influence of the barrier condition in the regulation of epidermal differentiation and secretion of lamellar bodies



Adapted Source: Elias PM, et al. [20]

xerosis is a very common and significant finding; because it is the clinical expression of the skin barrier abnormality presented by these patients, it is a diagnostic and monitoring parameter. Studies that correlate skin barrier alterations and AD are summarized in Chart 1.

A study by Bohme *et al*. [28], conducted with 221 atopic children, clearly shows the importance of this small criterion, observed in their sample in 100% of the patients.

Xerosis is associated with a deficiency in the function of the epidermal barrier. [29,30]

Alterations of the barrier function of the stratum corneum are present not only in the affected skin, but also in the apparently normal skin, during the activity of dermatitis.

Di Nardo *et al*. [31] showed a significant reduction in the levels of ceramides 1 and 3 in the stratum corneum; complementarily, a study by Pilgram *et al*. [32] demonstrated a structural imbalance of the extracellular lipid matrix; Murata *et al*.[33] reported an increase in glucosylceramide/esfingomielina deacylase levels as a mechanism of ceramide reduction, occurring in the atopic affected or normal skin. Later, Fartash and Diepgen [34] and Fartash [35] described an alteration in the extrusion of lamellar bodies in the dry skin of atopic patients.

Nonetheless, the organization and maturation of corneocytes are normal in the dry skin of the atopic patient. [36]

Pastore *et al*. postulated that keratinocytes are capable of regulating the immune response in AD, activating, through an increase in the expression of granulocyte-macrophage colony stimulating factor (GM-CSF), epidermal and dermal dendritic cells. [37]

Metabolic alterations of esfingomielina, which lead to a reduction in the levels of ceramides (in particular ceramide 1), also have an important and negative influence on the barrier function, as shown in a study by Hara *et al.* in 2000. [38]

A review by Simpson and Hanifin [39] and studies by Choi and Maibach [40] emphazied the growing interest in the impact of the skin barrier on the evolution of AD, with a strong evidence of its abnormalities.

A recent study by Farwanah *et al*., 2005, [41], comparing psoriasis and AD patients with normal individuals, did not find a significant deficiency in the amount of ceramides in the two groups. Therefore, these authors believe that the parameter ceramide cannot be considered a diagnostic criterion.

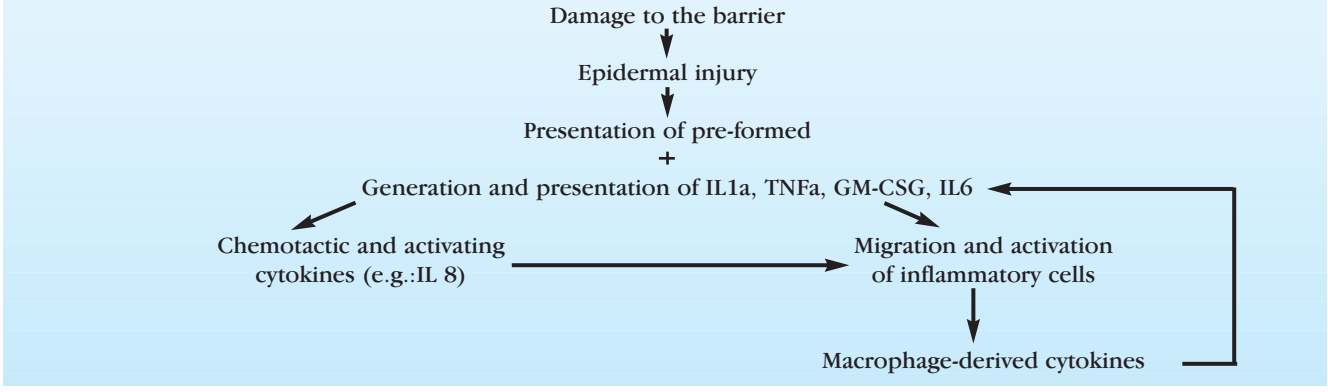
Results from another study conducted in the same year, by Lebwohl and Hermann [42], dispute these findings as even skin without an apparent lesion, but with xerosis, shows alterations related to a reduction in ceramide levels.

The primary barrier damage of atopic dermatitis facilitates the action of irritants and reduces the pruritus threshold, helping the trauma caused by itching and consequent barrier injury. Any trauma to the barrier activates a cascade of cytokines secreted by keratinocytes, aggravating and perpetuating the inflammatory process. [43,44]

Many mediating agents are involved in the genesis of the inflammated skin pruritus; histamine is essential, but not the only one: cytokines, prostaglandines, tachykinins, P substance, and others also play a role in the development of the symptom. [45]

Another factor is the modulation of sensory nerves in the presentation of antigens and skin inflammation. There is evidence that pruritus is a complex sensation, influenced not only by the intensity of the stimulus or severity of the atopic disease, but also by central neurologic stimuli, according to findings by Heyer *et al*. [46] Studies by Seidenari and Giusti attempted to correlate the degree of pruritus with instrumental measurements of the barrier function; these authors observed a progressive reduction of skin hydration values (corneometry) based on pruritus

Figure 4: Aggression to the barrier and development of the inflammatory response



Adapted source: Elias PM, et al. [20]

CHART 1: Studies about the abnormalities of the skin barrier and atopic dermatitis

Authors	Methodology	Conclusion
Di Nardo et al.[31]	Thin layer chromatography of corneal biopsies with cyanocrylate glue	Significant reduction of ceramides 1 and 3 in the stratum corneum
Pilgram et al.[32]	Skin biospy samples examined using electron microscopy	Alterations of the intercellular lipid organization
Murata et al.[33]	Stratum corneum from biopsy samples of AD patients, evaluated by liquid chromatography	Reduction of the levels of ceramides in the atopic affected or normal skin through an increase in the expression of sphingomyelin acylase
Fartasch[35]	Comparative study of biopsies of atopic, psoriatic patients, with lamellar ichthyosis, by ruthenium tetroxide fixation	Alteration of lamellar bodies extrusion in the atopic skin with xerosis
Pastore et al.[37]	Keratinocyte culture under analysis of a reporter gene (chloramphenicol acetyl transferase)	Regulation by the immune response keratinocytes in AD, with greater activity of dermal and epidermal dendritic cells
Hara et al.[38]	Enzymatic measurements of the stratum corneum of AD patients compared with contact dermatitis subjects	Higher expression of sphingomyelin deacylase is responsible for ceramide deficiency in the skin barrier of the atopic patient
Choi MJ, Maibach HI[40]	Enzymatic measurements of the stratum corneum of atopic patients	Increased activity of ceramidase, sphingomyelin deacylase, and glucosylceramide deacylase in AD patients

intensity, even in normal skin area. This may indicate proportionality in the reduction of corneometric values and pruritus intensity, even in normal areas.

There is a progressive increase in transepidermal water loss associated with more severe cases of pruritus. This correlation is described as a factor of predisposition to irritation, even in apparently normal areas. [47,48]

A study by Lee *et al*. [49] with atopic contact dermatitis patients and a control group showed a significant correlation between the highest means of IgE and pruritus intensity, as well as higher levels of TEWL in atopic individuals. The authors conclude that TEWL is a good marker of pruritus intensity and aids in the monitoring of these patients.

Therefore, there is evidence that alterations of the integrity and hydration of the corneum layer facilitate the development of pruritus. The data collected from the sample suggest that biophysical measurements for this parameter, even in normal skin, could act as a predictive or measuring factor influencing tendency to pruritus.

Biophysical parameters for the evaluation of skin barrier in AD:

Clinical examination is an essential tool to the dermatologist for the identification of AD. However, the subjective component may interfere with evaluations for research purposes.

There are still subclinical skin alterations, subtle to inspection, in which there is injury or damage to the barrier that is undetectable in a routine clinical exam. [50]

In the 1960s, laboratory studies about skin physiology, in particular by a German group, analyzed mechanical properties of the structure of the skin. A study by Ridge and Wright, of 1996, was one of the first publications. [51]

The practical applicability of these technologies to measure skin parameters, such as water amount, microcirculation, pigmentation, and elasticity, came with the creation of standardized equipment, which made the establishment of methods and reproducibility of measurements possible.

These methodologies, generically named skin bioengineering techniques, proved to be useful in the evaluation of skin diseases, in addition to providing elements for the consideration of treatments to these disorders.[52,53,54,55]

In the 1980s, a study of biophysical parameters by the groups of Berardesca (Europe) and Maibach (USA) helped the development of bioengineering equipment to measure a few skin parameters.

This equipment allowed the development of methods with the following characteristics:

They are not invasive;

They offer objective measurements with phenomena quantification;

standardization of places, techniques and environmental conditions;

Evaluations without interfering with treatments or with the spontaneous course of the patient's condition. [56]

The standardization of environmental conditions for the collection of measurements is essential so that they can be reproduced. [57]

The correlation between the intensity of AD and the biophysical measurements of lesioned skin has been shown in a study with children and adolescents, conducted by Kim *et al*. [58]

A significant correlation between these measurements in normal skin was confirmed by another study conducted that same year, by Holm *et al*. [59] This study attempted to validate hydration parameters, TEWL, as well as ultrasonography and Doppler in the evaluation of AD in 101 atopic patients and 30 healthy control individuals. Although the authors do not consider these measurements the gold standard for the evaluation of the prognosis of AD, their results showed significant differences between the atopic lesioned skin, normal skin and control group, suggesting a correlation with the level of activity of the disease. This work also shows that even measurements of apparently normal skin are useful for the evaluation of the intensity of the condition.

In 2008, two groups of researchers, Hon *et al*. [60] and Gupta *et al*., [61] showed a correlation between TEWL and SCORAD in children, proving that there is an association between injury to the skin barrier measured by TEWL and the clinical intensity of the disease.

3.3.2 Functional evaluation of the skin barrier: transepidermal water loss

Transepidermal water loss (TEWL) expresses measurements of water diffusion through the skin and it is an important parameter of the skin barrier integrity.

The method described by Nilsson in 1997 [62] uses an open chamber with two sensors in different levels and obtains the degree of evaporation based on the gradient of these measurements. With environmental (humidity and temperature) and patient standardization (resting for acclimation 15 minutes on average before measurement, to reduce the effects of perspiration and vasodilation caused by physical activity), measures can be obtained with reproducibility.

Equipment items were developed based on this principle to obtain these measurements.

In 1995, Barel and Clarys [63] studied equipment for the calculation of transepidermal water loss (Evaporimeter® and Tewamater®). The measurement technique was the evaporation gradient; they collected measurements in normal skin and skin with irritation induced by stripping, in standard laboratory conditions. They achieved a good correlation and reproducibility of the results with this validation.

Transepidermal water loss (TEWL) shows normal levels according to the area of the body. In the trunk, for instance, there is spontaneous water loss through the corneal layer in the amount of 3-6 g/h/m^2; in the face, values range from 1 to 15g/h/m^2. These variations are due to the thickness of the stratum corneum and to the dermal microvasculature.

After the stratum corneum has been injured, the loss may reach 70g/h/m^2. This is a convenient way to measure the extent of the barrier disfunction and constitutes an important instructive element for its evaluation.

The Tewameter ® used is the TM 300 model, by Courage & Khazaka, whose measurements are considered accurate and reproducible if performed in a proper environment by trained personnel. According to Miteva *et al*. [64], who evaluated the available methods of measurement and calibration in standard conditions, concluded that this equipment can achieve reliable measurements that can be reproduced in standard experimential conditions.

Even in the recovery phase, the atopic patient shows dryness or roughness of the skin with increased TEWL. This increase occurs both in the affected and normal skin of atopic patients, as shown by Seidenari and Giusti[47] in a study with 66 atopic and 21 healthy children (without atopy or xerosis).

Measurements obtained of each group were significantly higher for the atopic patients when compared to the control group.

Another study by the same authors [65] with children shows that even without active lesions, the atopic child has a significant increase of TEWL (Chart 2). A total of 200 atopic and 45 non-atopic children (control group) participated in the study.

The averages obtained for each group were significantly higher for the atopic patients, when compared with the control group ($p<0.05$).

With these findings, the authors concluded that the measurement of TEWL is a functional marker of AD, and that it can vary based on the presence of lesions, even in normal skin.

TEWL tends to normalize in the normal skin of atopic individuals in remission of AD. Measurements

of water loss and hydration (capacitance) tend to vary based on the course of the disease, suggesting recovery of the skin barrier or that these alterations are reversible. A study with normal individuals without clinical signs of AD shows normal levels of TEWL in the forearm, according to Loffler and Effendy.[66]

Patients without lesions for over two years showed similar values of TEWL in the forearm to those of non-atopic individuals, according to a study by Agner. [67]

Simultaneously, Conti *et al*. [68] studied a probable correlation between the biophysical parameters and the presence of other atopies, but they did not find any change in the measurements associated with respiratory alterations.

3.3.3 Evaluation of water content in the corneal layer: capacitance

The amount of water in the corneal layer may influence the skin barrier function: greater hydration increases percutaneous absorption.

The amount of water retained in the stratum corneum depends on the capacity of water retention, which maintains the skin soft and flexible, even in dry environmental conditions; this water also helps enzymatic reactions in the maturation and scaling of corneocytes.

Water reduction leads to fissures in the stratum corneum, which allow greater penetration of heavier molecular substances, including allergens and microorganisms.

Hydration of the skin surface may be measured by electrical methods. Conductance measurements, described by Watanabe, Tagami *et al*. [69] assess only the surface, while other capacitance measurements go deeper. Similar results of comparative studies of methodologies were also found by Agner and Serup, in 1998, [70] and by Fluhr et al. [71] in 1999.

Capacitance values measured by the Corneometer ® were correlated with degrees of dry skin clinically observed in a multicentrical study conducted in Germany with 349 individuals in 6 places [72] (Chart 3).

Loden *et al*. [73] found significantly lower capacitance values in patients with AD, especially those with dry skin observed clinically and with higher values of TEWL.

The same author [74] established a correlation between clinical findings about the skin of patients with AD and the intensity of dryness, measurable through capacitance.

As TEWL, capacitance also changes according to the activity of the disease. To show this, Werner [75] evaluated 40 atopic patients: 20 of them with clinically dry skin and 20 with clinically normal skin. The author found a higher average of measurements for the normal skin, with a significant value difference ($p<0.01$).

Biophysical methods have had various applications in AD: they provide elements to measure the improvement of the barrier function and water content in the corneum stratum after treatment with drugs and moisturizers. [76,77,78]

The correlation between non-invasive biophysical parameters of the skin barrier and signs and symptoms of AD has been investigated. Sugarman *et al*. [79] developed a scale based on measurements of corneometry and TEWL, added to the clinical notes of the SCORAD scale, to determine the severity of the condition. However, studies that investigate the correlation between measurements of water content in the corneal layer and TEWL and clinical, epidemiological, and biochemical parameters are still limited in the literature.

Determination of the hydric content of the corneal layer can be accomplished through electrical measurements of the skin surface. The mechanism is the following: water has a higher dielectric constant than the skin. An increase in the hydric content will increase capacitance values, that is, the capacity to maintain a gradient of electrical charge. The equipment that allows this measurement is based on dielectric constant changes, which in turn alter the capacitance.

The measurement of TEWL is based on the passive diffusion of water through the stratum corneum, whose gradient is measured by the open probe of the equipment.

In both situations, the accuracy of the measurements and their reproducibility will essentially depend on a standardized environment in relation to temperature and humidity, excluding variables such as perspiration and products applied to the skin. [80,81,82,83,84]

There is a reduction in the capacitance values of the atopic skin compared to the non-atopic, as well as a significantly greater TEWL in the skin of these

Chart 2: Measurement of TEWL in active atopic children, non-active, and non-atopic

Non-eczematous skin of atopic individuals with activity	9,02 ± 5,32
Non-eczematous skin of atopic individuals without activity	7,56 ± 4,54
Non-atopic individuals (control)	5,38 ± 2,96

Adapted source: Giusti G, et al. [65]

CHART 3: Determination of the degree of xerosis in the skin surface using the corneometer®

Clinical degree of xerosis	Measurement (corneometer units)
Normal (without clinical xerosis)	>40
Dry	40-30
Very dry	<30

Adapted source: Werner Y [75]

patients in comparison with normal skin. The authors also noticed that the presence of respiratory atopy did not lead to significant alterations of these measurements. [85,86]

CONCLUSION

Atopic dermatitis is a chronic disease in which abnormalities in the immune response and constitution of the skin barrier play a fundamental role in the outbreaks of the disorder. The skin barrier may show genetic alterations, but it may also suffer influence of neurologic, immunological, and environmental order.

Changes in the skin barrier affect its function; when its barrier function is damaged, the condition tends to worsen, as the pruritus threshold falls, leading to a concomitant aggravation of the inflammatory process.

This inflammatory condition appears to be present in the atopic patient even in areas of clinically normal skin, since the biophysical measurements of TEWL and corneometry are altered in these areas. Some studies have shown a significantly increased TEWL in the non-lesioned skin of the atopic patient, attributed to a disturbance in the maturation of lamellar bodies.

Biophysical measurements of the non-lesioned skin of AD patients appear to have a correlation with the clinical severity of the disease. With remission of the skin condition, the tendency is the normalization of measurements, according to the literature.

This finding may show that the biophysical parameters of evaluation of the skin barrier may be a reliable indicator of AD activity, even if, at the time of the clinical examination, there is absence of detectable lesions. ❑

REFERENCES

1. Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med. 2005;352:2314-24.
2. Hanifin JM. Immunobiochemical aspects of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1989;144:45-7.
3. Sturgill S, Bernard LA. Atopic dermatitis update. Curr Opin Pediatr. 2004;16:396-401.
4. Freiberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith L, Katz SI, et al. Fitzpatrick's Dermatology in general medicine. 6th ed. New York: McGraw Hill; 2003, v. 1. p.1464.
5. Williams HC. On the definition and epidemiology of atopic dermatitis. Dermatol Clin. 1995;13:649-57.
6. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ. 1992;304:873-5.
7. Leung DY, Boguneiwicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest. 2004;113:651-7.
8. Lai-Cheong JE, McGrath JA. Avanços no entendimento da base genética de doenças hereditárias monogênicas da barreira epidérmica: novas pistas para os principais genes que podem estar envolvidos na patogênese da dermatite atópica. An Bras Dermatol. 2006;81:563-68.
9. Serup J. Characterization of contact dermatitis and atopy using bioengineering techniques. A survey. Acta Derm Venereol Suppl (Stockh). 1992;177:14-25.
10. Cristopher E, Kligman AM. Visualization of the cell layers of the stratum corneum. J Invest Dermatol 1964;42:406-7.
11. Blank IH. Cutaneous barriers. J Invest Dermatol. 1965;45:249-56.11
12. Scheuplein RJ, Blank IH. Permeability of he skin. Physiol Rev. 1971;51:702-47.
13. Sato J, Denda M, Chang S, Elias PM, Feingold KR. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. J Invest Dermatol. 2002;119:900-4.
14. Odland G, Reed T. Epidermis. In: Zelickson A, ed. Ultrastructure of normal and abnormal skin. Philadelphia: Lea & Fabiger; 1967. p.54-75.
15. Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: theory and in vitro experimental measurement. Am Inst Chem Eng J. 1975;21:985-96.
16. Johnson ME, Blankschtein D, Langer R. Evaluation of solute permeation through the stratum corneum: lateral bilayer diffusion as the primary transport mechanism. J Pharm Sci. 1997;86:1162-72.
17. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permaeability barrier. Adv Lipid Res. 1991;24:1-26.
18. Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol. 2003;4:771-88.
19. Tsai K, Valente NY, Nico MM. Inflammatory peeling skin syndrome studied with electron microscopy. Pediatr Dermatol. 2006;23:488-92.
20. Elias PM. Defensive functions of the stratum corneum. In: Elias PM, Feingold KR. Skin barrier. New York: Taylor & Francis; 2006. p.07
21. Steinert PM, Candi E, Tarcsa E, Marekov LN, Sette M, Paci M, et al. Transglutaminase crosslinking and structural studies of the human small proline rich 3 protein. Cell Death Differ. 1999;6:916-30.
22. Feingold KR. The regulation and role of epidermal lipid synthesis. Adv Lipid Res. 1991;24:57-82.
23. Fartasch M, Williams ML, Elias PM. Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implications. Arch Dermatol. 1999;135:823-32.
24. Proksch E, Holleran WM, Menon GK, Elias PM, Feingold KR. Barrier function regulates epidermal lipid and DNA synthesis. Br J Dermatol. 1993;128:473-82.
25. Elias PM. The stratum corneum revisited. J Dermatol. 1996;23:756-8.
26. Wood LC, Elias PM, Calhoun C, Tsai JC, Grunfeld C, Feingold KR. Barrier disruption stimulates interleukin-1 alpha expression and release from a pre-formed pool in murine epidermis. J Invest Dermatol. 1996;106:397-403.
27. Elias PM, Wood LC, Feingold KR. Epidermal pathogenesis of inflammatory dermatoses. Am J Contact Derm. 1999;10:119-26.
28. Bohme M, Svensson A, Kull I, Wahlgren CF. Hanifin's and Rajka's minor criteria for atopic dermatitis: which do 2-year-olds exhibit? J Am Acad Dermatol. 2000;43 (Pt 1):785-92.
29. Proksch E, Jensen JM, Elias PM. Skin lipids and epidermal differentiation in atopic dermatitis. Clin Dermatol. 2003;21:134-44.
30. Linde YW. Dry skin in atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1992;177:9-13.
31. Di Nardo A, Wertz P, Gianetti A, Seidenari S. Ceramide and cholesterol composition of the skin patients with atopic dermatitis. Acta Derm venereol. 1998;78:27-30.
32. Pilgram GS, Vissers DC, Van der Meulen H, Pavel S Lavrijsen SP, Bouwstra JA, Koerten HK. Aberant lipid organization in stratum corneum of patients with atopic dermatitis and lamellar ichtiosis. J Invest Dermatol. 2001;117:710-7.
33. Murata Y, Ogata,J, Higaki Y, Kawashima M, Yada Y, Higuchi K, et al. Abnormal expression of sphingomielin acylase in atopic dermatitis: an etiologic factor for ceramide deficienency? J Invest Dermatol. 1996;106:1242-9.
34. Diepgen TL, Fartasch M. Recent epidemiological and genetic studies in atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1992;176:13-8.
35. Fartasch M. Epidermal barrier in disorders of the skin. Microsc Res Tech. 1997;38:361-72.
36. Hirao T, Terui T, Takeushi I, Kobaiashi H, Okada M, Takahashi M, et al. Ratio of immature cornified envelopes does not correlate with parakeratosis in inflammatory skin disorders. Exp Dermatol. 2003;12:591-601.

37. Pastore S, Giustizieri ML, Mascia F, Giannetti A, Kaushansky K, Girolomoni G. Dysregulated activation of activator protein 1 in keratinocytes of atopic dermatitis patients with enhanced expression of granulocyte/macrophage-colony stimulating factor. J Invest Dermatol. 2000;115:1134-43.
38. Hara J, Higuchi K, Okamoto R, Kawashima M, Imokawa G. High expression of sphingomyelin deaclase is an important determinant of ceramide deficiency leading to barrier disruption in atopic dermatitis. J Invest Dermatol. 2000;115:406-13.
39. Simpson EL, Hanifin JM. Atopic dermatitis. Periodic synopsis. J Am Acad Dermatol. 2005;53:115-28.
40. Choi MJ, Maibach HI. Role of ceramides in barrier function of healthy and diseased skin. Am J Clin Dermatol. 2005;6:215-23.
41. Farwanah H, Raith K, Neubert RH, Wohlrab J. Ceramide profiles of the uninvolved skin in atopic dermatitis and psoriasis are comparable to those of healthy skin. Arch Dermatol Res. 2005;296:514-21.
42. Lebwohl M, Herrmann LG. Impaired skin barrier function in dermatologic disease and repair with moisturization. Cutis. 2005;76(6 Suppl):7-12.
43. Hägermark O. Peripheral and central mediators of itch. Skin Pharmacol. 1992;5:1-8.
44. Sehra S, Barbé-Tuana FM, Holbreich M, Mousdicas N, Kaplan MH, Travers JB. Clinical correlations of recent developments in the pathogenesis of atopic dermatitis. An Bras Dermatol. 2008;83:57-73.
45. Arai I, Takaoka A, Hashimoto Y, Honma Y, Koizumi C, Futaki N, et al. Effects of TS-022, a newly developed prostanoid DP1 receptor agonist, on experimental pruritus, cutaneous barrier disruptions and atopic dermatitis in mice. Eur J Pharmacol. 2007;556:207-14.
46. Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine induced itch and alloknessis (icthy skin) in atopic eczema patients and controls. Acta Derm Venereol. 1995;75:348-52.
47. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. Acta Derm Venereol. 1995;75:429-33.
48. Pinnagoda J, Tupker RA, Coenraads PJ, Nater JP. Prediction of susceptibility to an irritant response by transepidermal water loss. Contact Dermatitis. 1989;20:341-6.
49. Lee CH, Chuang HY, Shih CC, Jong SB, Chang CH, Yu HS. Transepidermal water loss, serum IgE and beta-endorphin as important and independent biological markers for development of itch intensity in atopic dermatitis. Br J Dermatol. 2006;154:1100-7.
50. Zink P. [Methods for the determination of mechanical properties of the skin of the human corpse]. Dtsch Z Gesamte Gerichtl Med. 1965;56:349-70.
51. Ridge MD, Wright V. Mechanical properties of skin: a bioengineering study of skin structure. J Appl Physiol. 1966;21:1602-6.
52. Tupker RA. Baseline transepidermal water loss (TEWL) as a prediction of susceptibility to sodium lauryl sulphate. Contact Dermatitis. 1989;20:265-9.
53. Rudolph R, Kownatzki E. Corneometric, sebumetric and TEWL measurements following the cleaning of atopic skin with a urea emulsion versus a detergent cleanser. Contact Dermatitis. 2004;50:354-8.
54. Kolbe L, Kligman AM, Schreiner V, Stoudemayer T. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. Skin Res Technol. 2001;7:73-7.
55. Yilmaz E, Borchert HH. Effect of lipid-containing, positively charged nanoemulsions on skin hydration, elasticity and erythema - an in vivo study. Int J Pharm. 2006;307:232-8.
56. Serup J. A three-hour test for rapid comparison of effects of moisturizers and activeconstituents (urea). Measurement of hydration, scaling and skin surface lipidization by noninvasive techniques. Acta Derm Venereol Suppl (Stockh). 1992;177:29-33.
57. Agache P, Humbert P. Measuring the skin, non-invasive investigations, physiology, normal constants. Berlin Heidelberg: Springer-Verlag; 2004.
78. Kim DW, Park JY, Na GY, Lee SJ, Lee WJ. Correlation of clinical features and skin barrier function in adolescent and adult patients with atopic dermatitis. Int J Dermatol. 2006;45:698-701.
59. Holm EA, Wulf HC, Thomassen L, Jemec GB. Instrumental assessment of atopic eczema: validation of transepidermal water loss, stratum corneum hydration, erythema, scaling, and edema. J Am Acad Dermatol. 2006;55:772-80.
60. Hon KL, Wong KY, Leung TF, Chow CM, Ng PC. Comparison of skin hydration and evaluation sites and correlations among skin hydration, transepidermal water loss, SCORAD index, Nottinghan Eczema Severity Score and quality of life in patients with atopic dermatitis. Am J Clin Dermatol. 2008; 9:45-50.
61. Gupta J, Grube E, Ericksen MB, Stevenson MD, Lucky AW, Sheth AP, Assa'ad AH, Khurana Hershey GK. Intrinsically defective skin barrier function in children with atopic dermatitis correlates with disease severity. J Allergy Dermatol. 2008;121:725-730.
62. Nilsson GE. Measurement of water exchange through the skin. Med Biol Eng Comput. 1997;15:209-18.
63. Barel AO, Clarys P. Study of the stratum corneum barrier function by transepidermal water loss measurements: comparison between two commercial instruments: Evaporimeter and Tewameter. Skin Pharmacol. 1995;8:186-95.
64. Miteva M, Richter S, Elsner P, Fluhr JW. Approaches for optimizing the calibration standard of Tewameter TM 300. Exp Dermatol. 2006;15:904-12.
65. Giusti G, Seidenari S. La barriera cutânea nei bambini com dermatite atopica: valutazione instrumentale in 200 pazienti e 45 controlli. Riv Ital Pediatr. 1998;24:954-9.
66. Loffler H, Effendy I. Skin susceptibility of atopic individuals. Contact Dermatitis. 1999;40:239-42.
67. Agner T. Skin susceptibility in unvolved skin of hand eczema patients and healthy controls. Br J Dermatol. 1991;125:140-6.
68. Conti A, Di Nardo A, Seidenari S. No alteration of

biophysical parameters in the skin of subjects with respiratory atopy. Dermatology. 1996;192:317-320.
69. Watanabe M, Tagami H, Horii I, Takahashi M, Kligman AM. Functional analyses of the superficial stratum corneum in atopic xerosis. Arch Dermatol. 1991;127:1689-92.
70. Agner T, Serup J. Comparison of two electrical methods for measurement of skin hydration. An experimental study on irritant patch test reactions. Bioeng Skin. 1988;4:263-9.
71. Fluhr JW, Kuss O, Diepgen T, Lazzerini S, Pelosi A, Gloor M, et al. Testing for irritation with a multifactorial approach: comparison of eight non-invasive measuring techniques on five different irritation types. Br J Dermatol. 2001;145:696-703.
72. Agache P, Mary S, Muret P, Matta AM, Humbert P. Assessment of the water content of the stratum corneum using a sorption-desorption test. Dermatology. 2001;202:308-13.
73 Loden M, Olsson H, Axell T, Linde YW. Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. Br J Dermatol. 1992;126:137-41.
74 Loden M, Andersson AC, Lindberg M. The number of diagnostic features in patients with atopic dermatitis correlates with dryness severity. Acta Derm Venereol. 1998;78:387-8.
75 Werner Y. The water content of the stratum corneum in patients with atopic dermatitis. Measurement with the Corneometer CM 420. Acta Derm Venereol. 1986;66:281-4.
76 Loden M, Andersson AC, Andersson C, Frodin T, Oman H, Lindberg M. Instrumental and dermatologist evaluation of the effect of glycerine and urea on dry skin in atopic dermatitis. Skin Res Technol. 2001;7:209-13.
77 Fuchs M, Schliemann-Willers S, Heinemann C, Elsner P. Tacrolimus enhances irritation in a 5-day human irritancy in vivo model. Contact Dermatitis. 2002;46:290-4.
78. Aoki T. Serum antidiuretic hormone is elevated in relation to the increase in average total body transepidermal water loss in severe atopic dermatitis. Br J Dermatol. 2005;153:359-63.
79 Sugarman JL, Fluhr JW, Fowler AJ, Bruckner T, Diepgen TL, Williams ML. The objective severity assessment of atopic dermatitis score: an objectivemeasure using permeability barrier function and stratum corneum hydration with computer-assisted estimates for extent of disease. Arch Dermatol. 2003;139:1417-22.
80 Vilaplana J, Coll J, Trullas C, Azon A, Pelejero C. Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. Acta Derm Venereol. 1992;72:28-33.
81 Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. Br J Dermatol. 1990;123:199-205.
82. Lee CH, Maibach HI. Study of cumulative irritant contact dermatitis in man utilizing open application on subclinically irritated skin. Contact Dermatitis. 1994;30:271-5.
83. Loden M. Biophysical properties of dry atopic skin and normal skin with special reference of skin care products. Acta Derm Venereol Suppl (Stockh). 1995;192:1-48.
84. EEMCO guidance for the assessment of stratum corneum hidration: electrical methods. Berardesca,E; EEMCO (european group for efficacy measurements on cosmetics and other topical products). Skin Res Technol.1997;3:126-32.
85. Seidenari S, Belletti B, Schiavi ME. Skin reactivity to sodium lauryl sulfate in patients with respiratory atopy. J Am Acad Dermatol. 1996;35:47-52.
86. Thune P. Evaluation of the hydration and water holding capacity in atopic skin and so called dry skin. Acta Derm Venereol Suppl (Stockholm). 1989;144:133.

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