The epidermal barrier function and antimicrobial peptides in atopic dermatitis: the role of topical modulation

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**Abstract**

**Introduction**

The epidermal barrier is a crucial component of the defensive function of the skin. The main skin protective functions are related to water loss modulation/prevention, UV-protection, anti-oxidant and antimicrobial actions. It is well established that epidermal barrier function is abnormal in subjects suffering from atopic dermatitis. Several evidences have shown that this alteration could be considered as the initial pathogenic factor starting the pathological process of atopic dermatitis. The aim of this review was to discuss the role of topical modulation in the epidermal barrier function and antimicrobial peptides in atopic dermatitis.

**Conclusion**

The use of emollients has shown to reduce the risk of atopic dermatitis flares and to reduce the need for topical corticosteroid. New emollient and moisturizing products seem promising not only in controlling symptoms and signs of atopic dermatitis but also in improving the skin barrier functions acting specifically in the ceramide component and in normalizing antimicrobial peptides production of keratinocytes.

**Introduction**

Atopic dermatitis (AD) is characterised by reduced skin hydration and an impaired skin barrier mainly due to a deficit in moisturizing property, alteration in lipid content and in the production of antimicrobial substances. It is important to note that in AD subjects' epidermal barrier dysfunction could be observed also in the skin not involved in active lesions. Skin barrier defect in AD is mainly due to reduced lipid (i.e. ceramide) content of the epidermis; a reduced or genetically altered filaggrin synthesis and finally a reduced synthesis of antimicrobial peptides (AMPs). The deficit of the innate immunity could explain the increased risk of pathogenic bacterial colonisation and infection observed in AD subjects. For these reasons, treatments with the aim to improve skin barrier properties of AD subjects could be a relevant approach in the strategic treatment of this skin condition. In view of the fact that AD is a chronic condition, caring for atopic skin must be a day-to-day task. Efficient skin care may reduce acute flares by improving the compromised skin barrier and reducing trans-epidermal water loss (TEWL). The mainstay of basic AD management, supported by several international guidelines, is the regular use of moisturisers together with good hydration of skin and the avoidance of known triggers. New moisturising products could contain additional compounds helping in the recovery of the normal skin barrier (i.e. ceramide topical supplementation) or showing anti-inflammatory action. When used as mono-therapy, the use of moisturising creams is associated with a clinical improvement in AD. A particular interest could be found in the use of topical anti-inflammatory and moisturising products containing compounds, which could improve the innate immunological system of the skin such as isoleucine. Topical isoleucine has shown to increase production at the skin level of AMPs. Therefore, the use of these kinds of products could have a strong rationale in AD coadjuvant treatment. In patients with mild to moderate AD chronic lesion, the use of non-steroidal cream containing L-isoleucine has shown to significantly reduce the eczema area and severity index (EASI) score of children with AD of the face with a clinical efficacy significantly greater than the control emollient cream. These data, therefore, suggest that it could be possible to modulate and improve the defective skin barrier system in AD patients through topical specific compounds. This paper discusses topical modulation in the epidermal barrier function and AMPs in AD.

**Discussion**

Epidermal barrier alteration in AD: focus on filagrin

The superficial layer of the skin (epidermis) plays an important role in several physiologic critical functions such as control and modulation of water loss, antimicrobial defence, the hydration of skin, UV defence, anti-oxidant defence and the formation of a mechanical barrier. The normal epidermal barrier is formed mainly by flattened keratinocytes, holding together by cornodeomesosomes, a water resistant layer of lipid lamellae which prevent water loss, and finally by natural moisturizing factor, a mixture of aminoacids, urea and other substances, which are contained inside the keratinocyte cell. It is well known that atopic dermatitis is a clinical condition characterised by a deficit of the barrier function of the skin. In AD subjects' epidermal barrier dysfunction could be observed also in the skin not involved in active lesions. Skin barrier defect in AD is mainly due to reduced lipid (i.e. ceramide) content of the epidermis; a reduced or genetically altered filaggrin synthesis and finally a reduced synthesis of antimicrobial peptides (AMPs). The deficit of the innate immunity could explain the increased risk of pathogenic bacterial colonisation and infection observed in AD subjects. For these reasons, treatments with the aim to improve skin barrier properties of AD subjects could be a relevant approach in the strategic treatment of this skin condition. In view of the fact that AD is a chronic condition, caring for atopic skin must be a day-to-day task. Efficient skin care may reduce acute flares by improving the compromised skin barrier and reducing trans-epidermal water loss (TEWL). The mainstay of basic AD management, supported by several international guidelines, is the regular use of moisturisers together with good hydration of skin and the avoidance of known triggers. New moisturising products could contain additional compounds helping in the recovery of the normal skin barrier (i.e. ceramide topical supplementation) or showing anti-inflammatory action. When used as mono-therapy, the use of moisturising creams is associated with a clinical improvement in AD. A particular interest could be found in the use of topical anti-inflammatory and moisturising products containing compounds, which could improve the innate immunological system of the skin such as isoleucine. Topical isoleucine has shown to increase production at the skin level of AMPs. Therefore, the use of these kinds of products could have a strong rationale in AD coadjuvant treatment. In patients with mild to moderate AD chronic lesion, the use of non-steroidal cream containing L-isoleucine has shown to significantly reduce the eczema area and severity index (EASI) score of children with AD of the face with a clinical efficacy significantly greater than the control emollient cream. These data, therefore, suggest that it could be possible to modulate and improve the defective skin barrier system in AD patients through topical specific compounds. This paper discusses topical modulation in the epidermal barrier function and AMPs in AD.
Epidermal barrier alteration in AD: the role of moisturizing topical treatment

Caring for atopic skin must be continuous as long as the disease is a chronic condition. Efficient skin care may reduce acute flares by improving the compromised skin barrier and reducing TEWL. The mainstay of basic AD management, supported by several international guidelines, is the regular use of moisturisers together with good skin hydration and the avoidance of known triggers. As stated by international guidelines, emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. This statement is supported by several clinical studies demonstrating the therapeutic role of emollient in AD. The multicentre barrier enhancement for eczema prevention (BEEP study) has shown that once-daily application of an emollient from birth through to the age of 6 months is able to prevent atopic dermatitis flares. The 6-month cumulative incidence of eczema was 21.8% in the emollient group, in comparison with 43.3% in the control group. This means a 67% reduction in risk. In children with moderate AD, Szczepanowska et al. have evaluated whether adding emollients to the standard topical corticosteroid therapy could influence the clinical outcome. Concomitant usage of emollients significantly improves xerosis and pruritus during corticosteroid treatment of atopic dermatitis, and enables to maintain clinical improvement after therapy discontinuation. Therefore, dry-skin care is very beneficial for patients with AD reducing trans-epidermal water loss and reducing skin barrier compromise.

Antimicrobial peptides in AD: is it possible to modulate their production with topical product?

Pharmacological induction of AMPs at epithelial barriers could have
therapeutic utility. It has been recently reported that the discovery of substances with low molecular weight can induce epithelial antimicrobial peptide production in cell-based assays. In particular L-isoleucine and its analogues are highly specific β-defensin inducers in epithelial cells. In 2000, Fehlbaum et al. have demonstrated that L-isoleucine, in a dose-dependent manner, could induce defensin production in AMPs constitute an important component of the mammalian innate immune response. These results were confirmed by Santiago et al. In an animal model, they found that Isoleucine is an inducer of Beta-defensin production. This action of Isoleucine was observed when the aminocid was applied directly on thracheal epithelia mucosa. Therefore, Isoleucine could be considered an AMP-producer at skin level. In a recent multicentre trial conducted in children with mild-moderate AD of the face, Marseglia et al. have shown that a topical anti-inflammatory moisturising cream containing rhamnosof, ceramides and L-Isoleucine was able to significantly reduce the EASI score by 71% in comparison with baseline after 6 weeks of treatment. This clinical effect was statistically superior to the effect on EASI score obtained in the control group treated with a simple emollient cream.

Conclusion
Atopic eczema (AE) is a very common skin condition mainly seen in the paediatric population. AD affects 1 out of 10 children, and is associated with significant morbidity. AD is characterised by a chronic impairment of skin barrier functions. Defective permeability and defective antimicrobial barrier are in fact a well-known aspect of AD. Skin barrier alteration and a reduction of innate immune mechanisms (low production of AMPs) are considered the hallmarks of AE. It is recognised that skin barrier dysfunction precedes eczema development, and this alteration even exists in non-lesional skin. In addition, barrier dysfunction results in an increase in protein allergen penetration through the epidermis and predisposes to secondary skin infections, commonly seen in AD. This is supported by the fact that the majority (i.e. 80%) of AD patients classified as “no-atopic” subsequently showed an increase in IgE, developing a “true” AD. Skin barrier alteration in AD is manifested mainly with xerosis, inflammation and an increase in tendency to pathogen bacteria colonisation and infections due to the innate immune mechanisms alteration. From a molecular point of view, defective epidermal barrier function is correlated, at least in 1 out of 3 AD patients, with reduced or defective synthesis of the filament-aggregating protein filaggrin. Other alterations responsible of the skin barrier defect could be found in a reduction of ceramide levels in the skin and increased levels of endogenous proteolytic enzymes. These alterations cause an increased trans-epidermal water loss. Skin xerosis is a common clinical manifestation, together with eczema, of AD. Daily emollient treatment is considered a mainstay of AD treatment alone or in combination with other therapies. The use of emollients has shown to reduce the risk of AD flares and to reduce the need for topical corticosteroids. New emollient and moisturising products seem promising not only in controlling symptoms and signs of AD but also in improving the skin barrier functions acting specifically in the ceramide component and in normalising AMP production of keratinocytes.

References