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Review Article

Steroid-sparing effect of emollients in atopic dermatitis and psoriasis

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ABSTRACT

The aim of the present article is to analyze the role of emollients in the topical management of atopic dermatitis and psoriasis and also to review the clinical studies available on the beneficial effect of co-therapy of emollients and topical corticosteroids. Understanding the stratum corneum's key involvement in the pathophysiology of atopic dermatitis and psoriasis has led to the development of new therapeutic approaches for treating not just inflammation but also restoring a healthy skin barrier. While topical corticosteroids are the cornerstones of treatment for atopic dermatitis and psoriasis, the potential risks of overuse (including atrophy, striae, dyspigmentation, and loss in epidermal barrier homeostasis) must be weighed against the benefits. These risks futher increase the necessity of finding non-steroidal treatments. Emollients aid the epidermal barrier function as they improve the oil and lipid levels and restore its protective function. Used regularly, emollients may reduce flare-ups and may also have a direct anti-inflammatory effect and may reduce the need to use topical corticosteroids, i.e. they have a 'steroid sparing effect'.

INTRODUCTION

Many chronic skin diseases, such as atopic dermatitis and psoriasis, are associated with impaired skin barrier function.[1] The lack of an intact skin barrier has been associated to decreased filaggrin expression in atopic dermatitis and hyper-proliferation and poor keratinocyte differentiation in psoriasis.[2] With the recognition of the critical role of the epidermal barrier in disease pathogenesis and associated allergic comorbidities, several studies have investigated emollient treatment aimed at restoring barrier function as well as a safe and efficient strategy for disease prevention and flare risk.[3] Corticosteroids are the most commonly used topical therapy for inflammatory dermatoses such as atopic dermatitis and psoriasis, notably for the quick clearance of acute flares.[4] However long-term continuous application of topical corticosteroid (TCS) can cause cutaneous atrophy, telangiectases, purpura, and striae formation, as well as systemic absorption if used on a large surface area can cause hypothalami-pituitary-adrenal (HPA) axis suppression, growth retardation in children, and cataract and glaucoma formation in adults.[5] Thus, intermittent topical corticosteroid (TCS) therapy should be complemented with emollient adjunct therapies to prevent localized adverse effects and address epidermal barrier dysfunction. The therapeutic effects of emollients for atopic dermatitis and psoriasis have been linked to improvements in epidermal function, such as epidermal permeability, stratum corneum hydration, and stratum corneum pH.[6]

Pathogenesis of atopic dermatitis and psoriasis

Despite the clinical differences between atopic dermatitis and psoriasis, multiple investigations have demonstrated that, in addition to immunological mechanisms and genetic variation, loss of skin barrier integrity is a

significant cause.[7] The underlying pathological mechanism of atopic dermatitis is suggested to be abnormal T helper 2 (Th2) lymphocyte activation with subsequent secretion of a variety of pro-inflammatory cytokines, such as interleukin (IL)-4, IL-5, IL-22, and others, which leads to the destruction of the epidermal barrier. On other hand aberrant activation of Th1 and Th17 cells with simultaneous release of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), IL-17, and IL-23 is assumed to be the pathological mechanism of psoriasis.[8] Although both diseases share similar barrier defects, such as epidermal hyperplasia and defective terminal differentiation, there are significant distinctions, including psoriasis's extensive parakeratosis.[9] Also some patients with atopic dermatitis have loss-of-function mutations in the FLG (Filaggrin) gene, which encodes the intermediate-filament protein filaggrin. In contrast, filaggrin mutations are not thought to influence psoriasis susceptibility. The morphology of corneocytes changes when filaggrin is absent from human skin, which may impair the organization of extracellular lamellae and the overall barrier.[10] With the emergence of stratum corneum, a formidable skin barrier, as a target tissue has added invigorating dimensions in the on-going research to find plausible explanation for the sequence of events in atopic dermatitis and psoriasis.[11]

Changes in the epidermal barrier seen in people with atopic dermatitis and psoriasis.

The stratum corneum employs an array of strategies to maintain the epidermal barrier, such as: enzymatic responses, commensal bacterial colonization, immune signaling, antimicrobial lipids and peptides, low pH, and natural moisturizing factor. The complex lauer of the stratum corneum supports execution of these strategies and is composed of corneocytes and a matrix of intercellular lipids (ceramide, cholesterol, and free fatty acids), both of these components are derived from the terminal differentiation process of keratinocytes. Changes in this process of epidermal differentiation and lipid composition lead to a disturbed skin barrier.[12] Atopic dermatitis skin abnormalities include epidermal hyperproliferation, increased skin pH, enhanced protease activity, and increased sodium concentration. A number of studies have found lipid abnormalities in the skin of people with atopic dermatitis. The stratum corneum lipids are loaded with cholesterol (about 25% by weight), free fatty acids (about 25% by weight), and ceramides (about 50% by weight) under homeostatic conditions, with a small amount of cholesterol sulfate and phospholids. These lipids form a three-dimensional structure of stacked lipid layers or lamellae that are properly positioned around protein elements. The synthesis and structure of epidermal lipids are both essential for proper skin barrier function. Subjects with atopic dermatitis exhibit abnormalities in both lipid composition and architectural organization. Researchers are now focused on atopic dermatitis lipid-related ceramide anomalies and are developing a slew of ceramide-containing moisturizers in the hopes of improving dry skin and barrier function.[13] It is not surprising that epidermal barrier abnormalities have been associated in psoriatic lesions given the nature of psoriasis etiology. The main alterations seen in psoriatic skin are a decrease in ceramide levels as well as a change in the quality and composition of ceramide species. Changes in the extracellular matrix lipid quantity and quality have also been described, with sphingosine levels considerably higher in psoriatic lesional skin. A modification of cholesterol and fatty acid levels are also observed in psoriatic lesions as well as a modification of the cornified lipid envelope structure and its components. Transepidermal water loss (TEWL) is significantly increased in psoriasis, and its increment is direcly dependent on the severity of the lesions.[14]

Side-effects of topical corticosteroids when used for long term

With the introduction of topical corticosteroids (TCS) of different potency, the treatment of inflammatory cutaneous illnesses has become more effective and less time-consuming. However, their utility has become a double-edged sword, with increasing incidences of abuse and misuse that result in substantial local, systemic, and psychological side effects.[15] Many types of steroid-induced adverse effects can arise through mechanisms such as cell proliferation suppression, immunosuppression, or hormonal activity. An upsurge in the frequency of steroid-induced dermatological disorders has been noted recently.[16] Atrophy of the skin, perioral dermatitis, striae, telangiectasia, rosacea, and hypertrichosis are the most frequent side effects of topical corticosteroid. There are also systemic consequences such as glaucoma, inhibition of the hypothalamus, pituitary, and adrenal glands, and hyperglycemia.[17] Disease recurrence as a result of a rebound effect after therapy is discontinued is among other less frequently noticed adverse effects. The masking or stimulation of some cutaneous infections, such as tinea incognito, as well as tachyphylaxis or regression of clinical improvement after a period of use can be obseved with topical corticosteroid.[18]

Topical corticosteroid withdrawal appears to be a clinical adverse effect distinct from other well-described topical cortico steroid adverse effects. It results from prolonged, inappropriate, and frequent use of moderate- to high-potency topical corticosteroids. The most commonly reported symptoms are burning and stinging sensations, with erythema being the most prevalent manifestation. Signs and symptoms occur days to weeks after the discontinuation of topical corticosteroid.[19] Topical corticosteroid withdrawal is divided into 2 distinct morphologic syndromes: Papulopustular and Erythema oedematous. Erythematoedematous type is more often in patients with chronic dermatoses such as atopic dermatitis and it is characterized by redness, scaling, wheel formation with or without burning sensation.

Papulopustular type is more common in patients who are using topical corticosteroid for pigmentary disorders and acneiform conditions. The papulopustular variation is distinguished from the erythema oedematous subtype by the presence of pustules and papules in addition to erythema, but less frequently by swelling, oedema, burning, and stinging.[20]

Effects of topical corticosteroids on epidermal barrier structure and function

Morphological, physiochemical, and functional changes have been demonstrated to affect epidermal barrier functions in relation with topical corticosteroid use. These include epidermal atrophy, keratinocyte size reductions, ceramide, free fatty acid, and cholesterol declines, and an increase in trans epidermal water loss (TEWL).[21] Subclinical unfavorable alterations in the epidermis were observed as early as 3 days after topical corticosteroid administration on both human and mouse skin, indicating deterioration in epidermal barrier homeostasis.[22] These included delayed barrier recovery, aberrant stratum corneum integrity and cohesion, and global lipid synthesis inhibition. Disturbed skin barrier function is a major pathophysiological factor in atopic dermatitis and psoriasis, and further aggravation induced by topical corticosteroids might result in a worsening of basal skin conditions.[23] In addition to the topical steroid, appropriate use of emollient moisturizers is considered a baseline therapy for atopic dermatitis and psoriasis, as they can improve and reinforce the skin barrier function.[24, 25]

Role of emollients in restoring healthy skin barrier

Emollients, also known as moisturisers, are the mainstay of treatments for dry skin conditions like atopic dermatitis and psoriasis. The terms ‘moisturiser’ and ‘emollient’ are often used interchangeably and describe their two main actions on the skin: to soften and increase skin hydration.[26] Following the application of a moisturizer (emollients) to injured skin, the skin barrier is rebuilt in four steps. The oily component of the moisturizer forms a thin film on the skin, signaling the start of barrier repair; the skin moisture distribution coefficient changes; moisture diffuses from the dermis to the epidermis; and water distribution to the epidermis is controlled by skin lipid synthesis and intercellular lipid secretion.[27] Emollients also alter the physical properties of the stratum corneum; the added water increases the extensibility, pliability and plasticity of the stratum corneum. This is especially important in atopic dermatitis and psoriasis in which the aberrant and inflammatory epidermis is brittle, resulting in severe fissuring. Other less easily explained pharmacological activities include an anti-inflammatory effect, antimitotic effect and antipruritic effect. Used regularly, emollients may reduce flare-ups and may also have a direct anti-inflammatory effect and may reduce the need to use topical corticosteroids, i.e. they have a ‘steroid sparing effect’.[28]

NEWLY DEVEOLPED EMOLLIENTS WITH ANTI-INFLAMMATORY BENEFITS

It is recognised that regardless of the substantial effectiveness of emollients in maintaining the condition of the skin, the majority of atopic dermatitis and psoriasis patients will experience, more or less frequently, flares in their condition where additional anti-inflammatory medication is necessary. This is generally in the form of corticosteroids which, because of the well documented adverse effects on the skin resulting from long term use, clinicians need to prescribe itcarefully avoiding its abuse.[29] Some of active ingredients with anti-inflammatory property are also added into moisturizers with claims of being suitable for atopic or psoriatic skin lesion. The use of these anti-inflammatory agents may reduce or substitute for the use of topical corticosteroids, thus minimizing their side effects.[30] Some anti-inflammatory compounds found in anti-inflammatoty skin moisturizers are reviewed here.

Aloe vera gel

Aloe vera contains glucomannan, an emollient polysaccharide that act as a moisturizer. Mannose-6-phosphate found in the mucilaginous gel of Aloe vera is considered to be the active ingredient with anti-inflammatory action.[31]

Chamomile derived bioactives

α-bisabolol is an active derived from german chamomile flower, also known as levomenol, accounts for its potent anti-inflammatory effects. Bisabolol down-regulate the inflammatory cytokines and hence reduce inflammation, soothe and calm the skin.[32]

Comfrey derived bioactive

Commonly known as comfrey, Symphytum officinale L. is a perennial herb commonly found in United Kingdom. Its anti-inflammatory activities are attributed to its bioactive constituents allantoin and rosmarinic acid.[32,33]

Niacinamide

Niacinamide (vitamin B3) reduces inflammation by decreasing histamine release from mast cells[34]. It also improves epidermal barrier function by increasing ceramide production and other stratum corneum lipids.[35]

Palmitoylethanolamine (PEA)

N-palmitoylethanolamine (PEA), a member of the functional endocannabinoid system, is abundant in the stratum granulosum of the skin.[36] A cream containing PEA has been demonstrated to minimize transepidermal water loss, enhance PEA levels in treated skin, and exhibit anti-inflammatory activity.[37]

Colloidal oatmeal

Oatmeal contains polysaccharides, proteins, lipids, saponins, enzymes, flavonoids, vitamins, and avenanthramides as active components. Avenanthramides are phenolic compounds present in oats that mediate its anti-inflammatory activity, it decrease activation of nuclear factor kappa B pathway in keratinocytes and diminish the secretion of the pro-inflammatory cytokines and histamine. It also replenishes the skin's natural levels of vital lipids like ceramides, cholesterol, and free fatty acids. It promotes skin barrier repair, preserves skin water content, and inhibits transepidermal water loss.[38]

Butyrospermum parkii (Shea butter)

Shea butter is extracted from the kernels of the sheu tree (Vitellaria paradoxa) and its main actives consist of triterpenes, tocopherol, phenols, and sterols. Shea butter exhibited anti-inflammatory effects through inhibition of iNOS, COX-2, and cytokines via the NF-κB pathway.[39] It has a proven instant moisturisation and skin barrier strengthening effect, making it a suitable emollient for a wide range of advanced skin care treatments.[40]

Ceramides and fatty acids

Ceramides effectively reduce the expression of inflammatory enzymes and cytokines[41]. Regular use of semi-solid formulations containing triple-physiologic lipids in a 3:1:1 molar ratio of ceramide, cholesterol, and free fatty acids has been demonstrated to reduce the requirement for topical steroid application.[32]

Zinc gluconate

Many skin inflammations can be effectively treated with zinc gluconate. Recent research suggests that its anti-inflammatory actions may target at peroxisome proliferator-activated receptors-α (PPARs-α), human β-defensin-2, and psoriasin.[42]

Corticosteroid-sparing effects of emollient in atopic dermatitis and psoriasis

During atopic and psoriasis flares, anti-inflammatory therapies, such as topical corticosteroids, are considered the mainstays of therapy, but relying on these drugs carries potential risks. Topical corticosteroid medication can cause cutaneous atrophy, which is characterized by a thinner epidermis, increased transepidermal water loss, and decreased levels of epidermal ceramides, cholesterols, and free fatty acids. Even short-term (3-day) treatment with strong topical corticosteroids given topically has a negative influence on epidermal structure and function. Furthermore, some researchers contend that the increase in epidermal permeability caused by short-term topical corticosteroid therapy enhances skin sensitization to allergens in the environment, resulting in an inflammatory response.[43]

To restore skin barrier function and to alleviate the lack of epidermal lipid synthesis, emollients are commonly used in atopic dermatitis and psoriasis. They are also used to improve patients quality of life and, presumably, to reduce the amount of topical corticosteroid used.[43] Several studies have been conducted to investigate the steroid-sparing effect of emollients when used in combination with topical corticosteroids. In a 3-week study of children with mild-to-moderate atopic dermatitis, once-daily hydrocortisone 2.5% cream plus an emollient was compared to twice-daily hydrocortisone 2.5%. After 7 days, skin complaints and lesion size improved considerably in both therapy groups, with no significant between-group differences. These data demonstrated that utilizing an emollient can lower topical corticosteroid exposure while providing the same amount of improvement.[44] In a trial of infants (12 months of age) with moderate-to-severe atopic dermatitis, the efficacy of an oat-extract-containing emollient provided in combination with either a moderate or high-potency corticosteroid was studied. Emollient use reduced high-potency corticosteroid use by 42% ($p<0.05$) in this 6 week research.[45] Another study looked at the influence of an oil-in-water-containing emollient on the use of desonide 0.05% in children aged 4 to 48 months with moderate atopic dermatitis. This study discovered that applying a topical corticosteroid every other day as an adjuvant to twice-daily emollient use was just as helpful as using a once- or twice-daily topical corticosteroid alone.[46] The latest emollients, known as 'Emollients plus' in European recommendations, contain vehicle-type chemicals as well as extra active components and non-medicated substances capable of influencing the skin microbiome in atopic dermatitis sufferers. Additional active constituents of 'emollients plus' include flavonoids and riboflavins from protein-free oat plantlet extracts, bacterial lysates from Aquaphilus dolomiaeor Vitreoscilla filiformis species, or a synthetic derivative of menthol. Maintaining the integrity of the barrier that protects the skin is critical for the management of atopic dermatitis, which has been linked to an imbalance of skin microflora, specifically Staphylococcus aureus over colonization.[47]

Emollient 'plus' significantly reduced corticosteroid consumption in mild to severe atopic dermatitis patients receiving corticosteroid treatment when compared to normal treatment with commercial emollients. Despite similar improvements in clinical evaluations, quality of life (QOL), and good tolerability in both groups, the Emollient'plus' group used 31% less corticosteroid, on fewer days, and with fewer applications of corticosteroid per day than the Control's own-emollient group.[47] An open label trial of 96 patients with chronic plaque-type psoriasis found that adding water-in-oil emollients to a topical corticosteroid regimen was effective. The efficacy of betamethasone dipropionate cream applied twice daily and once daily application of betamethasone dipropionate cream and either a water-in-oil based moisturizing cream

or lotion was similar (p=0.05). Once daily application of betamethasone dipropionate cream combined with either a water-in-oil based cream or lotion performed much better than betamethasone dipropionate cream alone (p=0.05). Water-in-oil emollients have a steroid-sparing effect in the treatment of chronic plaque-type psoriasis.[48] A randomized, double-blind, placebo-controlled research with ammonium lactate lotion and halobetasol ointment was conducted on 55 patients with mild-to-moderate psoriasis. Patients used ammonium lactate lotion twice daily and either placebo ointment (N=20) or steroid ointment (N=21) twice daily exclusively on weekends. After two weeks of combination treatment, 41 of 55 patients (74.6%) were assessed as "clear" (0) or "almost clear". When compared to placebo, the combination treatment effectively cleared plaque psoriasis, and ammonium lactate twice daily with weekend-only applications of halobetasol ointment effectively sustained the initial improvement for a significantly longer period of time without demonstrating any significant side effects, such as steroid atrophy, cutaneous irritation, or telangiectasia.[49] 15 patients with mild-to-moderate plaque psoriasis were enrolled. For each patient two symmetrical, target lesions were selected and randomized to receive hydrocortisone valerate 0.1% cream (HVC) + keratolytic, keratoplastic and anti-inflammatory cream (EKC) containing urea 20%, salicylic acid 2% and niacinamide (2%) or hydrocortisone valerate 0.1% cream (HVC) alone for 4 weeks. Combination therapy (HVC+EKC) was as effective as monotherapy (HVC) twice daily with a similar reduction, objectively evaluated, of skin thickness at week 4 in comparisons with baseline. The clinical examination of target lesion Score matched the efficacy outcomes. The results show that using a keratolytic, emollient, and anti-inflammatory cream in conjunction with a topical corticosteroid is effective in plaque psoriasis, with a steroid-sparing effect.[50]

CONCLUSION

Atopic dermatitis and psoriasis are the most common chronic inflammatory skin disorders. Both disorders are associated with a skin barrier deficit that varies in intensity with the severity of the lesions, but they differ in terms of immune cell participation and gene expression patterns (Segre, 2006). Atopic dermatitis is distinguished by an immunological imbalance where T helper type 2 (Th2) cells predominate in acute skin lesions, instead T helper type 1 (Th1) and T helper type 17 (Th17) lymphocyte subpopulations prevail in psoriatic plaques. Atopic dermatits predominantly begins in childhood, with only a very discrete incidence peak in adulthood. Patients with psoriasis are generally more overweight, obese and physically inactive, and have a positive smoking history, compared with the general population. Patients with both diseases experienced more frequent flares with increasing disease severity. With the advent of new therapies to treat atopic dermatitis and psoriasis, the two diseases are increasingly being discussed and presented together in publications and scientific symposia. The sparing effect of emollient on topical corticosteroid application observed in this review could be explained by the fact that by improving the skin barrier function, it limits the penetration of environmental irritants and allergens that trigger cutaneous inflammatory mechanisms. Besides, emollients contains specific active extracts that could display potential anti-inflammatory properties in skin inflammatory disorders such as atopic dermatitis and psoriasis. Even in the absence of lesions, persons with atopic dermatitis and psoriasis should use emollients on a regular, frequent, and liberal basis to preserve skin barrier function. Long-term management focuses on avoiding triggers and adhering to appropriate moisturizing regimes in order to minimize possible exacerbations. Patients may be tempted to stop using emollients once their symptoms have subsided; however, this is not recommended. Given the potential for local and systemic adverse effects to occur with long-term topical corticosteroid therapy it is considered desirable to minimize topical corticosteroid exposure as much as possible. Emollients are a safe and effective choice for treating patients who have atopic dermatitis and psoriasis owing to the advantages they offer in restoring barrier function and hydration, in addition to potential steroid-sparing effects.

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