Review

Onset Mechanism and Pharmaceutical Management of Dry Skin

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Dry skin is a common symptom of various conditions, and elderly individuals commonly exhibit this physiological symptom. Dry skin develops owing to sebum deficiency; however, the use of moisturizers can typically overcome this issue, particularly in patients in whom there are no other skin problems. If dry skin is left untreated, itching and eczema can occur, resulting in skin damage. Additionally, hemodialysis patients exhibit reduced barrier function and can experience pain associated with repeated needle insertion; the repeated use of lidocaine tape to manage the pain can cause further skin damage. To reduce the occurrence of dry skin, the skin is hydrated using moisturizers. Dry skin is also prominent in patients with varicose veins in the lower extremities, and many biochemical studies have shown that skin immunity is altered in patients with dry skin. Moreover, the incidences of dry skin and pruritus differ in male and female patients. Furthermore, in elderly patients, zinc deficiency is likely to cause dry skin, and zinc supplementation may maintain skin hydration. To date, few reports have described dry skin from a clinical point of view. In this review, research on dry skin is presented, and the findings of basic research studies are integrated.

Key words dry skin; moisturization; varicose vein; zinc

1. INTRODUCTION

The skin is a major organ that is involved in contact with the external environment. Beginning with its surface, the skin is divided into the epidermis, dermis, and subcutaneous tissue. The outermost layer is the stratum corneum, which is covered by the sebum membrane; this tissue is in constant contact with the external environment. The stratum corneum is formed by corneocytes. These cells undergo various changes leading to the disappearance of cellular organelles, resulting in the mixing of ceramide with keratin strands and eventual shedding of corneocytes. During this destructive cycle, the epidermal thickness remains the same. The sebum membrane is formed by a mixture of moisture from sweat excreted by sweat glands and sebum excreted from sebaceous glands. Normal skin shows weak acidity (pH 4.5–6.0); thus, the sebum membrane prevents elevation of transepidermal water loss (TEWL) from the surface of the skin, thereby preventing bacterial invasion.3

Dry skin is a condition in which the capacitance of the skin is reduced owing to a decrease in skin barrier function and an increase in TEWL.2 Dry skin also develops in specific diseases that are affected by aging and environmental factors, such as hemodialysis (HD). HD patients are unable to maintain body fluid homeostasis and must continuously undergo treatment to directly remove the toxic causes of uremia. Moreover, HD patients can develop complications from renal failure and often complain of dry skin. Indeed, HD patients must strictly limit water intake, and water removal by dialysis results in reduced water content in the skin compared with healthy adults, leading to lower skin capacitance.3 Additionally, HD patients commonly wear lidocaine tape to reduce the pain associated with puncturing of the skin. The barrier function of the skin in these patients is often decreased owing to chronic stress under repeated skin insults. Accordingly, these patients commonly use moisturizers, such as heparinoids, for skin care.

In this review, the proper use of lidocaine tape in patients with dry skin is discussed. Dry skin in patients with varicose veins of the lower extremities and related symptoms, such as itching, are also described, as well as research on alleviation of dry skin in elderly individuals.4

2. INFLUENCE OF PREMOISTURIZATION ON THE SKIN BARRIER FUNCTION OF LIDOCAINE TAPE IN HD PATIENTS

HD patients experience much physical and mental pain associated with the insertion of needles prior to dialysis. To alleviate this pain, tape-type lidocaine-containing local anesthetic patches are widely used in Japan.5 This tape is typically applied to the needle insertion site for 30 min; however, some reports have indicated that 30 min is insufficient, and the tape is commonly applied for a longer time.6–8 The absorption of lidocaine is modulated by permeation of the stratum corneum.7–8 Thus, HD patients exhibit a variety of dermatological symptoms, such as pruritus, xerosis, pigmentation, and erythema.9–12 These symptoms may affect transdermal lidocaine absorption, although the extent of this effect is still unclear (Fig. 1).

In research from my laboratory, the current use of lidocaine tape was surveyed, and skin conditions in HD patients were evaluated.3 Additionally, a method to enhance the absorption of lidocaine from the tape was assessed. Importantly, dry skin in HD patients may be caused not only by age but also by other factors specific to these patients.

Many methods have been investigated to enhance the transdermal delivery of lidocaine, including skin pretreatment by tape stripping or benzine, ultrasound, electroporation, and iontophoresis.13–16 In my laboratory, application of absorbent cotton soaked in distilled water at 37°C for 5 min was ex-

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amined as a skin moisturizing method in HD patients (average age: 60.1 ± 13.9 years), and the effects of skin hydration on the anesthetic effects of lidocaine tape were determined. Briefly, the TEWL, electrical capacitance of the skin surface, and skin surface pH were measured (in that order) at the site where lidocaine tape was applied on the forearm. The patients remained in a room maintained at a temperature of 24–26 °C and humidity of 50–55% for 30 min. TEWL, which characterizes the skin water barrier function, was measured using a Tewameter TM 210 (Courage + Khazaka Electronic GmbH, Cologne, Germany). A corneometer CM 825 (Courage + Khazaka Electronic GmbH) was used to assess the electrical capacitance of the skin surface as an indicator of stratum corneum moisture, which is dependent on water content and the high dielectric constant of water relative to other skin components. The electrical capacitance was measured 5 s after removal of the cotton. The skin surface pH was measured with a skin-pH-meter PH905 (Courage + Khazaka Electronic GmbH). This clinical skin hydration method was based on basic research using porcine ear skin, which has major similarities to human skin. Notably, the porcine skin results showed that the electrical capacitance of the skin surface increased significantly with skin hydration. Application of the skin hydration method for 30 min in HD patients was expected in to be at least as effective as longer applications. The lidocaine concentration in skin was found to increase with skin hydration, and a good correlation was observed between capacitance before the application of lidocaine tape and the lidocaine concentration in the skin.

Overall, this skin hydration method, which is simple and easy, only requires water application to the skin and is noninvasive from a clinical perspective, suggesting potential applications in the treatment of pain associated with needle insertion in HD patients. Further investigations are needed to better evaluate the anesthetic effects of lidocaine tape applied using this method.

This method is noninvasive and can be easily performed on patients. Furthermore, the analgesic effect is stable with lidocaine absorption by the skin. In addition, patients complain of skin itching at the time of application. Moisturizers are used because HD patients often present with dry skin. Although cotton has been used in previous studies for skin hydration, there are no studies on the effects of pretreatment with a moisturizer on lidocaine tape application. A previous study examined the effects of skin hydrated with heparinoid lotion on the use of lidocaine tape with HD. In that study, the heparinoid lotion was applied on the skin and then dried rapidly, with any visual residue on the skin surface disappearing within 2 min. On the contrary, a significant increase in capacitance was observed and skin hydration was confirmed even with no visual residue on the skin surface. Skin hydration has been suggested to enhance the absorption of drugs by dry skin. Residual ointment and lotion on the skin would reduce the contact area of lidocaine tape with the skin and reduce adhesiveness. It

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Fig. 1. Skin Condition of Patients Undergoing Hemodialysis

Patients undergoing hemodialysis have reduced skin barrier function. When the barrier function is reduced, the value of the transepidermal water loss (TEWL) increases and the capacitance decreases. Increasing the amount of water in the skin with a moisturizer increases the adhesive force and reduces dermatological issues.
has been confirmed that the application of lidocaine tape to skin pretreated with heparinoid lotion has almost no effect on adhesiveness in both male and female patients with HD. In this study, adhesive strength was evaluated 2 min after the application of lidocaine tape. Lidocaine tape is known to have its lowest adhesive strength initially, which increases over time and eventually reaches its maximum strength. Thus, lidocaine tape is considered to have the highest risk of desquamation in the early stages of its application. Therefore, to evaluate the changes in adhesive strength with maximum sensitivity, we performed an evaluation in the initial stage of application, when the highest risk of tape peeling exists. It was confirmed that the amount of stripped stratum corneum by the tape was significantly reduced by pretreatment with heparinoid lotion. In particular, this phenomenon was significant in women. Thus, the reduction in the amount of stripped stratum corneum by heparinoid lotion lowered the risk of inducing skin irritation and improved the usability of lidocaine tape and cotton.

3. MECHANISM OF ITCH ONSET IN PATIENTS WITH VARICOSE VEINS

Varicose veins of the lower extremities are associated with various symptoms, including pain, swelling, and itching. Among patients with varicose veins, 25.3% of women and 19.0% of men in the Edinburgh varicose vein study complained of pruritus, and the number of women complaining of pruritus increased significantly with age. However, the pathogenic mechanisms through which pruritus is associated with varicose veins of the lower extremities are unclear, and no curative treatment has been reported to date.

In research from my laboratory, the mechanisms of pruritus in patients with varicose veins of the lower extremities were evaluated. Informed consent was obtained from patients who were diagnosed with varicose veins of the lower extremities at the Mie Heart Center and received sclerotherapy, and the amount of water in the stratum corneum, the TEWL, and itching before and after sclerotherapy were assessed. In addition, substance P, histamine, immunoglobulin (Ig) E, matrix metalloproteinase (MMP)-9, tryptase, IgA, adrenocorticotrophic hormone (ACTH), and β-endorphin were measured as inflammatory mediators by collecting blood before and after sclerotherapy. For control patients, the amount of water in the stratum corneum and the TEWL were measured on the day of obtaining informed consent, and substance P, histamine, IgA, and IgE levels were high before sclerotherapy, with higher values in men than in women. In contrast, tryptase levels were clearly elevated in women, but not in men, with varicose veins compared with controls. In addition, ACTH levels were high in men before sclerotherapy and decreased after sclerotherapy, whereas no differences were observed before and after sclerotherapy in women. β-Endorphin levels were increased in both men and women before sclerotherapy, with higher levels in men than in women. Based on these findings, histamine and tryptase levels may play important roles in pruritus in women. In women, the female hormone progesterone induces the activation of immediate-type allergies. Because mast cells are involved in immediate-type allergic responses, these cells may show increased activation and therefore increased tryptase release in women. The results of this study showing significantly higher β-endorphin levels in men than in women may be related to the involvement of elevated β-endorphin in CD4+ T-cell functions. Indeed, levels of CD4+ T cells in the serum were higher in men than in women, suggesting that this increase may have promoted β-endorphin production in men. ACTH has been reported to stimulate keratinocytes and increase histamine secretion. Thus, increased ACTH levels due to varicose veins of the lower extremities may also have caused pruritus in men.

A strong link between skin disorders and zinc deficiency has been suggested. Therefore, the relationship between pruritus in patients with varicose veins of the lower extremities and serum zinc was analyzed. Among patients who were diagnosed with varicose veins of the lower extremities at the Mie Heart Center and received sclerotherapy, the amount of water in the stratum corneum, the TEWL, and serum zinc levels before and after sclerotherapy were measured. For controls, the amount of water in the stratum corneum and the TEWL were measured on the day of obtaining informed consent, and serum zinc was measured by blood sampling. Notably, the water content of the stratum corneum was significantly lower in patients with pruritus than in patients without pruritus. Furthermore, water content in the stratum corneum was significantly lower in both groups than in healthy controls. Moreover, TEWL was significantly higher in patients with pruritus than in patients without pruritus, and the values were signifi-
Significantly higher in both groups than in healthy controls. Serum zinc was significantly lower in patients with pruritus than in healthy controls, but did not differ between patients without pruritus and healthy controls. Finally, there was a correlation between stratum corneum water content and serum zinc and an inverse correlation between TEWL and serum zinc among all patients. Zinc is known to suppress the degranulation of histamine from mast cells, and the decreased zinc results in higher histamine levels in patients with varicose veins than in healthy individuals. Overall, these findings suggest that mast cell-mediated inflammation is also a cause of pruritus in patients with varicose veins of the lower extremities and that the development of pruritus in these patients differs between men and women, with elevated tryptase causing pruritus in women and elevated \( \beta \)-endorphin causing pruritus in men. Furthermore, the findings showed that decreased serum zinc induced the pruritus associated with varicose veins of the lower extremities. In future studies, researchers should evaluate whether zinc supplementation may be an effective treatment for alleviating pruritus in patients with varicose veins of the lower extremities (Fig. 2).

4. CHANGES IN TEWL IN ELDERLY INDIVIDUALS FOLLOWING ADMINISTRATION OF ZINC

Dry skin and chronic itching are common in the elderly. In the clinical setting, clinicians frequently encounter elderly individuals who have not received appropriate treatment, despite complaints of dry skin, itching, and infections as well as decreased QOL, such as sleep disorders and decreased concentration. Therefore, in my laboratory, the relationships between serum zinc concentrations and skin conditions (e.g., skin barrier function and dry skin) were examined in elderly individuals. Furthermore, the beneficial effects of oral zinc supplementation on skin conditions were assessed by administration of a zinc preparation to patients with low serum zinc levels and evaluation of their skin condition. The patients were 65 years of age or older, visited the Jose Clinic (Oda Town, Mie Prefecture, Japan) between October 2018 and February 2019, and had serum zinc concentrations lower than 80 \( \mu \)g/dL (low zinc group) based on the criteria of the Practice Guidelines for Zinc Deficiency. The participants were administered zinc acetate hydrate (Nobelzin \textsuperscript{®} tablets) at 100 mg/d for 12 weeks from the start of the study, and TEWL, stratum corneum moisture content, serum zinc concentrations, and itching were evaluated every 4 weeks. The control patients had serum zinc concentrations greater than or equal to 80 \( \mu \)g/dL and were 65 years of age or older (normal zinc group; Fig. 3). There were nine patients in the study group (three men and six women, age: 78.89 ± 5.75 years) and nine patients in the control group (three men and six women, age: 80.11 ± 3.98 years).

Before taking Nobelzin\textsuperscript{®}, TEWL was significantly higher and the serum zinc concentration was significantly lower in the low zinc group than in the normal zinc group. Additionally, the serum zinc concentration increased significantly 12 weeks after Nobelzin\textsuperscript{®} treatment, and there were significant differences between the values at baseline and those 8 weeks after treatment. TEWL decreased significantly between baseline and 12 weeks after Nobelzin\textsuperscript{®} treatment, and there were significant differences between the values at baseline and 8 weeks after treatment. There were no significant changes in stratum corneum moisture content or itch scores during the observation period. An analysis of 45 samples (nine in the low zinc group with four time points and nine in the normal zinc group) showed a negative correlation between serum zinc concentrations and TEWL. Moreover, significant decreases in TEWL were observed as serum zinc levels increased after treatment in elderly individuals with low serum zinc levels, suggesting an improvement in skin barrier function. However, there were no significant changes in stratum corneum...
moisture content as serum zinc concentrations increased. This parameter is heavily affected by external conditions, such as temperature and humidity. Okada et al. reported that forearm stratum corneum moisture content was lower in winter than in summer.\(^40\) In the study from our laboratory, the study period was October to February, when temperature and humidity are lower. Therefore, although the indoor environment at the time of measurement was temperature and humidity controlled, the stratum corneum moisture content could have decreased. Accordingly, the decrease in TEWL may have contributed to maintenance of the stratum corneum moisture content, despite the environmental conditions. Moreover, oral zinc supplementation in elderly individuals with decreased serum zinc concentrations did not alter the severity of itch, but decreased TEWL and helped to maintain the moisture content of the stratum corneum. Thus, zinc supplementation can improve skin barrier function.\(^41\)

5. CONCLUSION

As the outermost organ, skin serves as a protective mechanism against physicochemical injury and sources of infection. Generally, young, well-moisturized skin is less susceptible to environmental effects, and itching and inflammation associated with the appearance of dry skin are less likely to occur. From research findings from my laboratory, dry skin is often caused by increased TEWL, decreased stratum corneum water content, decreased interkeratinocyte lipids and natural moisturizing factors, and decreased collagen. Moreover, the repair function of the skin tends to be delayed. In Japan, the aging population has increased, resulting in higher rates of skin disorders. In patients with dry skin, the efficacy and safety of transdermal preparations are enhanced by the application of moisturizers. However, the interactions between transdermal preparations and moisturizers are unclear. Further studies are needed to assess the timing of moisturizer application and the proper use of external preparations. The effects of daily diet and drugs on the skin should also be assessed.

The application of lidocaine-containing skin tape/patches is associated with skin damage and breakage. This problem has been evaluated in clinical practice, and researchers have shown that both in vivo and in vitro approaches, such as hydration and zinc supplementation, can prevent such skin disorders. However, the mechanisms cannot be easily verified in humans, and translational studies are still needed. Moreover, because the use of transdermal delivery systems has increased, reports of dermopathy have become more frequent, and greater skin damage is observed with the use of transdermal patches, particularly in patients with dry skin. Heparinoid treatment may alleviate these symptoms. Our experimental studies confirmed that dermopathy was elevated in patients who had transdermal patches applied, suggesting that inflammation should be carefully observed in patients with dry skin, such as elderly individuals. Furthermore, clinical research on the pre-application of moisturizing agents is needed to identify appropriate tape for transdermal delivery systems. Indeed, in studies in hairless mice, the use of moisturizers has been shown to increase blood concentrations of the treatment drug. However, the researchers concluded that skin care should be continued unless clinically problematic levels are observed.\(^42\)

Itching due to dry skin has been observed in patients with varicose veins of the lower extremities, with distinct differences between men and women. However, no reports have investigated the relationships between dry skin and varicose veins of the lower extremities. Most studies of zinc supplementation have been performed in elderly individuals, and some of these reports have shown that zinc alleviates dry skin. Further work is needed to establish novel treatment strategies.

Organ inflammation, such as enteritis and arthritis, causes a decrease in skin barrier function. When applying external preparations to the skin, one should consider the relationship between the drugs and internal organs, and excess or deficiency of various factors inside and outside the body is related to skin barrier function. In future studies, researchers should expand their work to evaluate other conditions related to dry skin in order to further improve outcomes in these patients.

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