

Diabetic Skin Changes Can Benefit from Moisturizer and Cleanser Use: A Review

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ABSTRACT

Introduction: Diabetes mellitus (DM) associated skin changes, which may be the first sign of DM in undiagnosed patients. Frequently these patients present with dry skin, which may benefit from the use of gentle cleansers and moisturizers. A review paper was developed to explore DM-associated skin changes and possible benefits of cleanser and moisturizer use.

Methods: For this purpose, an expert panel of physicians involved in the care of patients with DM selected information from literature searches coupled with expert opinions and experience of the panel.

Results: A defective skin barrier predisposes the skin to water loss leading to dryness, hyperkeratosis and inflammation. Skin changes that may benefit from the use of gentle cleansers and moisturizers are, amongst others, diabetic foot syndrome, ichthyosiform skin changes, xerosis, and keratosis pilaris. Adherence to treatment is a considerable challenge making education essential, especially about the need to keep skin clean and what skin care to use. Specifically designed diabetic skin care that contains anti-aging ingredients, urea, and essential ceramides, has demonstrated benefits for dry/itchy skin.

Conclusions: Skin disorders are common complications among either diabetic patients with patients with DM and may lead to serious adverse events. Evidence suggests that daily application of optimal skin care using gentle cleansers and moisturizers is one of the measures that may help improve skin barrier dysfunction, preventing complications by providing early-stage treatment of patients with diabetes.

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INTRODUCTION

Diabetes mellitus (DM) is a common and debilitating disease that also affects the skin. Thirty percent (30%) to 70% of patients with DM have associated skin diseases. The severity of skin disease may vary, ranging from benign to deforming to life-threatening.¹ These diabetic skin changes may allow insight into patients' glycemic control and may be the first signs of DM in undiagnosed patients.² Recog-

niton and management of DM-related skin conditions are important in maximizing patients' quality of life and in avoiding serious complications.²

Maintaining an intact skin barrier by preventing and treating skin dryness may improve skin conditions in patients with diabetes.³ Currently gentle cleansers and moisturizers are un-

der-utilized. Skin care is frequently lacking or overlooked as part of patients' DM skin treatment.³

To address these unmet needs, a review paper was developed to explore DM skin changes and possible benefits of appropriate cleanser and moisturizer use in DM skin treatment.

METHODS

An expert panel of physicians involved in the care of patients with DM convened in Miami, FL, in March 2019, to deliberate about diabetic skin changes and the impact of cleanser and moisturizer use on skin health. For this purpose, selected information from literature searches coupled with expert opinions and experience of the panel were used. The literature review was conducted prior to the meeting; the results were presented and discussed during the meeting. The selected literature was deemed clinically relevant to DM skin changes and challenges in treating diabetic skin. Skin conditions that differ from DM skin changes, or those that would not necessarily benefit from cleanser and moisturizer use, are outside the scope of this review.

Diabetes Mellitus and Related Skin Changes

DM-related skin changes are a common complication seen in both type 1 and type 2 DM.² Dermatologic conditions linked with DM vary in severity and while usually benign can in certain circumstances lead to major complications, including amputations.^{4,5}

Cutaneous manifestations in DM may be classified into four categories: 1) Skin associated with DM (from strongest to weakest association include necrobiosis lipoidica, diabetic dermopathy, diabetic bullae, yellow skin, eruptive xanthomas, perforating disorders, acanthosis nigricans, oral leucoplakia, lichen planus); 2) Infections (bacterial, fungal); 3) Cutaneous manifestations of diabetic complications (microangiopathy, macroangiopathy, neuropathy); and 4) Skin reactions to diabetes treatment (ie, sulphonylurea rash or insulin lipohypertrophy).² Additionally, hyperglycemia may lead to skin changes (Table 1), the mechanism of action is unclear and other factors are likely involved.^{2,6}

In patients with DM, functional properties of the stratum corneum (SC) may be altered, impacting skin barrier function.⁴ A defective skin barrier predisposes the skin to water loss and to invasion by pathogens, which in turn may lead to dryness, hyperkeratosis and redness from inflammation.⁷ The status of the permeability and antimicrobial barrier of the skin in DM remains unknown.² In-vivo impairment of the skin barrier was observed in type 2 DM mice models, which results from impairment of skin barrier homeostasis and decreases in epidermal proliferation and epidermal lipid synthesis.⁸

In vivo and in vitro, pre-clinical studies show that, diabetes alters epidermis histology and suppresses proliferation of keratinocytes.⁹ Impaired keratinocyte homeostasis and epidermal barrier function, results in higher risk of chronic wounds and infection.^{10,11,13-15}

TABLE 1.

Altered Functional Properties of the Skin Barrier in Diabetes. Diabetes mellitus (DM); Stratum corneum (SC); Advanced glycation end-product (AGE); lamellar body (LB); epidermal antimicrobial peptides (AMPs).

Reference	Impact on Skin Barrier Function
Campos de Macedo GM, et al ²	DM caused skin changes are common complications of both type 1 and type 2 DM and are usually neglected and frequently underdiagnosed.
Spravchikov N. ⁶	Hyperglycemia and impaired insulin signaling might be directly involved in the development of chronic complications of diabetes by impairing glucose utilization of skin keratinocytes as well as skin proliferation and differentiation.
Kim JH, et al ⁸	The status of the permeability and antimicrobial barrier of the skin in DM remains unknown. In-vivo (mice) impairment of the skin barrier was observed in type 2 DM, which results from impairment of skin barrier homeostasis, decreases in epidermal proliferation and epidermal lipid synthesis, and decreases in LB and AMPs.
Okano J, et al ⁹	In-vivo and in-vitro diabetes alters epidermis histology, suppresses proliferation of keratinocytes and reduces proliferation in epidermal cells.
Quondamatteo F. ¹⁰	Impaired keratinocyte homeostasis and epidermal barrier function through direct and indirect mechanisms results in susceptibility to skin complications, chronic wounds and infection.
Eaglstein WH, et al ¹¹	Dermatologic comorbidities of DM and related issues.
Sakai S, et al ¹²	Patients with DM showed a reduced hydration state of the SC together with decreased sebaceous gland activity.
Piérard GE, et al ¹³	The most common skin changes of DM are "dry skin," xerosis, and acquired ichthyosis, occurring predominately on the shins and feet. Moisturizers improve the feeling of well-being for diabetes patients.
Muller LM, et al ¹⁴	Patients with type 1 and type 2 DM are at increased risk for skin and mucous membrane infection. Studies are warranted into management of such infections.
Park HY, et al ²⁴	A long-standing hyperglycaemic condition impairs the skin barrier and accelerates the skin aging process.

Diabetic skin also ages faster due to inflammation triggered by both intrinsic and extrinsic factors. In diabetic skin in vitro studies showed elevated levels of MMP-1 and MMP-2, increased lysyl oxidase (LOX) expression, higher cross-linked collagens and fragmented collagen fibrils compared to healthy skin. It is thought that deterioration of dermal collagen structural integrity and mechanical properties occurs at an earlier age in those with diabetes.¹² Mechanisms that alter skin surface integrity have been identified for various skin conditions that present with dry skin.^{6,7,13-15} The formation of the SC barrier, specifically generation of its lipophilic components, involves several pH-dependent enzymes.⁷ Two key lipid-processing enzymes, β -glucocerebrosidase and acid sphingomyelinase, have pH optima of 5.6 and 4.5, respectively, as part of the skin's acid mantle. They are involved in the synthesis of ceramides—critical components of the permeability barrier.⁷ Activity of β -glucocerebrosidase is 10 times lower in situ at pH 7.4 than at pH 5.5. The processing of lipids secreted by lamellar bodies and the formation of lamellar structures require an acidic environment.⁷

Skin Conditions That May Benefit from Skin Cleanser and Moisturizer Use

Examples of common skin changes in DM that may benefit from gentle skin cleansers and moisturizers are, diabetic foot syndrome (DFS), ichthyosiform skin changes, and xerosis due to diabetes, and keratosis pilaris.

Acanthosis nigricans is mentioned as an example of a condition that may benefit from gentle skin cleansers and moisturizer use as an adjunctive measure together with treatment of the underlying condition, for example, insulin resistance.

Acanthosis Nigricans

Acanthosis nigricans (AN) presents with multiple poorly demarcated plaques with grey to dark-brown hyperpigmentation and a thickened velvety to verrucous texture. In insulin resistant states the proposed mechanism is stimulation of IGF-1 receptors in the skin by cross-reaction with insulin.^{16,17} Common locations for AN are posterior neck, axilla, elbows, palms, inframammary creases, umbilicus, and groin; it is typically asymptomatic.^{16,17}

Management of AN includes lifestyle changes such as dietary modifications, increased physical activity, and weight reduction. While AN can occur in other settings, in patients with DM, medication such as metformin may be recommended to improve glycemic control and reduce insulin resistance, although conclusive evidence to support this is lacking.^{16,17} Topical therapies are usually ineffective in patients with generalized involvement of the condition. In those with thickened or macerated areas of skin, topical keratolytics such as ammonium lactate, retinoic acid, or salicylic acid can improve appearance of AN.^{16,17}

Diabetic Foot Syndrome

Diabetic foot syndrome (DFS) is a broad term denoting anatomic and physiologic changes in the feet resulting from DM.^{1,4,5} The incidence and prevalence of DFS is reported at 1% to 4%, and 4% to 10%, respectively.¹ DFS is slightly more prevalent in type 1 DM compared with type 2 DM.¹

Diabetic foot ulcer (DFU), the end stage of DFS, is a global pandemic of diabetes, developing countries are especially on the frontline (Figure 1).⁴ Persons with DM have a 15–25% lifetime risk of DFU, and have a 50–70% recurrence rate within 5 years.^{4,5} Depending on size, duration and depth, healing can be difficult and take, on average, 11–14 weeks to heal. They precede amputation in 85% of cases, with a 1-year amputation rate estimated at 15%.^{4,5} DFS and DFUs profoundly impact costs to the health system.^{4,5}

DFS presents initially with callosities and dry skin related to diabetic neuropathy.^{4,5} In later stages, chronic ulcers and a variety of other malformations of the feet may develop.^{4,5} DFUs frequently present with secondary infection, diabetic neuro-osteopathy and clawing deformity (Figure 2).^{4,5} Neuropathic, but mostly painless, ulceration results from peripheral neuropathy, and is the most common type of complication. However, ulceration may be due to either ischemic changes or due to both peripheral neuropathic and ischemic disease.^{4,5} Dry skin of the diabetic foot is mostly due to the autonomic component of the peripheral neuropathy that may be present.^{4,5}

The interdisciplinary, team-based approach to DFU should in-

FIGURE 1. Diabetic foot ulcer (DFU). DFS presents initially with callosities and dry skin related to diabetic neuropathy. In later stages, chronic ulcers and a variety of other malformations of the feet develop.^{18,19}



FIGURE 2. Deformation and callus formation in the diabetic foot syndrome patient. Callus formation is the body's natural response to excessive friction and pressure. Biomechanical factors may play a role in callus formation as well as an abnormal gait.²⁰ Photograph courtesy of Dr. Sherkin.



TABLE 2.

Interdisciplinary Team-Based Approach for Patients With Diabetic Foot Ulcers. Adapted from Botros M, et al.¹⁹

Treat the Cause	Vascular – infection – pressure <ul style="list-style-type: none"> • Manage comorbidities • Assess risk based on health status
Address Patient-Centered Concerns	<ul style="list-style-type: none"> • Provide individualized patient education • Engage patient and family in care planning • Explore potential barriers to adherence
Local Wound and Skin Care	<ul style="list-style-type: none"> • <i>Debridement</i>: Remove necrotic tissue and remove callus • <i>Infection/inflammation control</i>: Rule out or treat localized/spreading infection • Wound moisture balance: Provide a moist, interactive wound environment • Remove dry scales • Daily use of gentle cleansers and moisturizers on dry skin areas

volve lifestyle changes such as dietary modifications, daily foot surveillance, appropriate foot hygiene, footwear and skin care (Table 2).^{4,5,18,19} Treatment of a patient with DFU can follow an algorithm called "VIPS,"¹⁸ to treat the cause of the ulceration. The abbreviation stands for: V = Vascular supply, which can be assessed by detecting a palpable foot pulse of ≥ 80 mmHg, an ankle-brachial pressure index (ABPI) of >0.5 and <1.3 , a transcutaneous oxygen tension of >30 mmHg, and toe pressure of >55 mmHg. If the ABPI is >1.3 , calcifications could be present indicating peripheral ischemic disease. The ABPI is to be followed by a full Doppler examination of the affected extremity, which may include the abdomen, to detect the extent of the disease and to define the healing ability of the ulcer.¹⁸

I = Inflammation and/or Infection treatment, in case there are clinical signs of an infection, such as erythema, edema, enhanced exudate production, pus, deterioration of the ulcer, and increased pain.¹⁸ However, in those patients with neuropathy, pain sensation may not be present and erythema and warmth may likewise not be as evident due reduced sympathetic arteriolar tone due to the autonomic component of the neuropathy.¹⁸ Abnormal blood glucose values in patients that were previously well controlled may also indicate the presence of an infection.¹⁸

P = Plantar pressure redistribution and **S = Sharp Surgical serial debridement**.¹⁸

Early stages of DFS include dry skin, callus formation, hyperkeratosis. While they are relatively benign compared to DFU, these skin conditions can progress into skin infections or DFU if not treated appropriately. For instance, A defective skin barrier exposes the skin to water loss and to invasion of pathogens and may lead to dry/hyperkeratotic skin and inflammation.^{3-5,18,19}

Callus formation is the body's natural response to excessive friction and pressure; biomechanical factors may play a role in callus formation as does an abnormal gait.¹⁸⁻²⁰

Hyperkeratosis in the patients with DFS can be prevented and managed by offloading and by suitable footwear, as well as by callus removal and pressure prevention (Figure 3).¹⁸⁻²⁰

It is important to debride crusts, callouses, scabs, and scales, and to restore moisture balance of the skin, by using a gentle cleanser and moisturizer on a consistent basis. Appropriate care of the skin using gentle cleansers and moisturizers and early-stage treatment of skin-barrier dysfunction may help prevent complications in the patients with DFS.^{3-5,18-20} Utilization of routine gentle cleanser and moisturizer may also help establish a durable barrier against further drying and irritation of the skin, preventing skin cracks, and infection.^{3-5,18-20}

FIGURE 3. Pressure areas at risk in the diabetic foot syndrome patient.

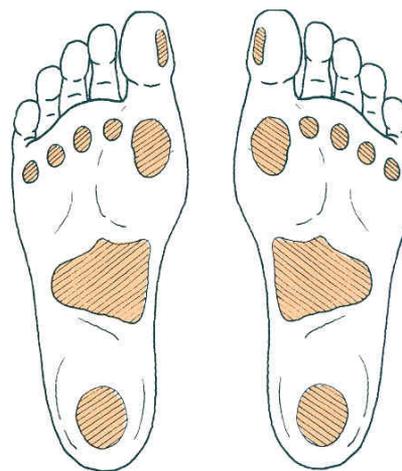


FIGURE 4. Ichthyosiform skin changes related to diabetes.



Ichthyosiform Skin Changes

These ichthyosiform skin changes present as large bilateral areas of dryness and scaling, and may be described as “fish scale” skin (Figure 4).^{21,22} Development of ichthyosiform skin changes is related to production of advanced glycosylation end products and to microangiopathic changes.^{21,22} Treatment of these skin changes is limited; however, topical moisturizers containing keratolytic agents may be beneficial.^{21,22}

Xerosis Due to DM

Xerosis presents as abnormally dry skin that may also show scaling or fissures, and appears most commonly on the feet in patients with DM (Figure 5).^{3-5,18-20} Dry skin conditions result from an abnormal, persistent cohesion between corneocytes, with secondary thickening of the SC, impaired moisturization of the uppermost SC layers, increased transit time of corneocytes in the SC, and altered skin barrier function.^{12,23,24} The decreased sebaceous gland activity in patients with DM further contributes to a reduced hydration state of the SC. The physical characteristic of the SC depends on its moisture content and water holding capacity.¹²

Patients with dry skin may have a feeling of skin tightness, especially after showering, bathing or swimming.³ The skin may feel shrunken or dehydrated and looks rough rather than smooth.³ Itching and pain may be intense and there may be slight to severe scaling or peeling, fine lines, cracks and/or fissures, erythema, and inflammation.^{3-5,18-20} Deep fissures that may bleed are frequently present in the more severe cases and pose a risk for infection (Figure 6).^{3-5,18-20} Skin barrier dysfunction may be compounded by excessive keratin formation resulting in hyperkeratosis.²⁰ Xerosis and hyperkeratosis can be triggered by shoes constructed of materials, that do not allow for sufficient moisture evaporation, by improperly fitting shoes, socks and stockings, by excessive perspiration, and by heating or air conditioning that reduces humidity and dries the skin.²⁰ Other factors leading to cracked skin on heels are prolonged standing, especially on hard floors, and being overweight, which increases the pressure on the normal fat pad under the heel.²⁰ If the skin is not supple and flexible, the pressure to crack is high. This may be the case in open backs on shoes, which allow the fat pad under the heel to expand sideways, thereby increasing the pressure and causing the skin to crack.²⁰

In dry skin, the risk for infection is enhanced. The protective acid mantle is less functional while the warm moist environment in poor footwear may predispose to the development of skin infection.^{3-5,18-20}

Xerosis in DM is often associated with pruritus, mostly localized, such as on the scalp, ankles, feet, trunk, or genitalia. Pruritus is more likely in those patients with DM who have dry skin and/or neuropathy.^{15,25} Involvement of the genitalia or intertriginous

FIGURE 5. Diabetes-related dry skin on the foot.



FIGURE 6. Cracked heels in a diabetes patient.



FIGURE 7. Diabetes-related keratosis pilaris.



areas may occur in those who have an infection (eg, candidiasis).^{15,25}

Keratosis Pilaris

Keratosis pilaris presents on the extensor surfaces of the upper arms (Figure 7) and less frequently on the thighs, face and buttocks.²¹ Compared to the general population, keratosis pilaris occurs more frequently and with more extensive involvement in those patients with DM. Keratosis pilaris can be treated with various topical therapies, including salicylic acid-containing moisturizers, combined with gentle exfoliation.²¹

Skin Care for Diabetic Skin Changes

Adherence to treatment is a considerable challenge in people with DM,¹⁻⁵ making education essential, especially about the need to keep the skin clean and with regard to what cleansers to use.³ Using cleansers with a high pH (9.0–10.0) increases skin pH, thereby causing irritation and leading to lower lipid production. However, conclusive evidence is lacking that shows lowered skin pH, using near-physiologic skin surface pH (4.0–6.0) products, improves diabetic skin.¹⁻⁵

TABLE 3.

Skin Care for Xerosis. Lactic acid (LA); glycolic acid (GA); hyaluronic acid (HA); topical corticosteroids (TCS); topical calcineurin inhibitors (TCI).
Adapted from Guenther L, Lynde CW, Andriessen A, et al.³

Products	Function	Ingredients
Cleansing	Removing pollutants and bacteria	Synthetically produced detergent cleansers
'Classic' Moisturizers	Close fissures by filling spaces and seal moisture into the skin	Mineral oils (eg. liquid paraffin, petrolatum), waxes (eg. lanolin, bees-wax, carnauba), long-chain esters, fatty acids, and mono-, di-, and triglycerides
Moisturizers With Humectants	Moisturizers act as humectants, hydrate the stratum corneum through a hygroscopic effect, increasing its elasticity	Combine humectants with ingredients of classic moisturizers, eg, alpha-hydroxy acids (LA, GA, HA), urea, glycerine, propylene glycol and ceramides
TCS	Anti-inflammatory effects	Combine TCS with a moisturizer, such as a ceramide containing cream
TCI	Anti-inflammatory effects	Combine TCI with a moisturizer such as ceramide containing cream

Moisturizer use decreases trans-epidermal water loss (TEWL) through occlusive agents, which can be combined with humectants to attract water to the skin.²⁶

Gentle cleansers and moisturizers are recommended for daily use to restore and preserve skin barrier integrity in dry skin conditions.²⁷ This type of skin care was shown to improve the clinical signs and symptoms of AD, including pruritus, erythema, fissuring, and lichenification.²⁷

Products composed of ceramides, cholesterol and fatty acids aim to mimic natural lipids,⁷ and may reduce the need for other medications.²⁷⁻²⁹ These moisturizers help to close fissures by filling spaces, sealing moisture into the skin through the production of an occlusive barrier, thereby softening the skin (Table 3).^{3,20}

A cream with skin-identical ceramides has been shown to ameliorate dry skin conditions, which in turn improves skin barrier function, thus reducing skin irritation.^{28,29} A cohort study by Vender et al²⁸ demonstrated that daily use of a ceramides-containing cleanser and moisturizer regimen over a four-week period significantly improved dry skin conditions and subject-reported quality of life.

Specifically designed diabetic skin care might contain anti-aging ingredients, urea, and essential ceramides, and MVE (layered delivery of ingredients) technology may be of benefit to treat some of the common skin conditions seen in DM or as adjunct skin maintenance regimen. A moisturizer acts as a humectant, hydrating the SC through a hygroscopic effect, thereby increasing its elasticity.^{27,28} Moreover, a physiological pH moisturizer has keratolytic and anti-pruritic action, providing soothing and nourishing relief for dry/itchy skin.^{27,28} An unpublished clinical study using products with these components demonstrated that improvement in skin hydration following product application lasted up to 48 hours.

Diabetic skin changes may benefit from the use of the products

included in the diabetic skin care line, enabling easy and effective skin care.

DISCUSSION

Metabolic changes associated with DM exert a major impact on the skin, leading to skin lesions, infections, angiopathy and neuropathy.^{2,5,18} The prevalence of DM-associated skin infections is greater when compared to the normal population.²

Although there is evidence from in-vitro and in-vivo studies supporting that hyperglycemia and impaired insulin signaling might be directly involved in the development of chronic complications of diabetes, the mechanisms behind DM-related skin changes are not yet elucidated and clinical data are lacking.^{1,2} There are limited clinical data regarding early-stage skin disorders in DM patients, which consequently impede efforts to include skin care as part of prevention and treatment of diabetic skin changes.^{2,3}

As patients encounter a broad spectrum of disorders in DM, skin conditions are usually neglected and frequently underdiagnosed.^{1,2,11} Moreover, adherence to treatment is a considerable challenge in patients with diabetes^{1-5,18-20} For this reason, it is important to educate patients on DM skin care, as well as physicians, ancillary health care professionals such as diabetes educators and nurses, who may have more extensive contact with and influence on patients with DM.¹⁸⁻²⁰ For educational purposes, the authors of the current review propose the term "diabetic skin syndrome" a broad term denoting anatomic and physiologic changes in the skin of those with DM. The use of this term may support education on the various issues related to this condition, with a structured approach to its prevention, treatment and maintenance as part of the multidisciplinary total care package of these patients.

Updating knowledge on skin care is required, since classical physician training used to include the message that "one can't add moisture to the skin." As such, many physicians practicing today may still hold this view. Evidence supporting the use of gentle cleansers and moisturizers^{3,27-30} should be included in

educational programs together with information about products that should not be used on the skin (eg, harsh soaps or alcohol).³⁰ Repeated washing with alkaline soap and the use of high pH moisturizers reduce buffer capacity by washing away inherent buffering components in the skin.³⁰ Skin surface pH influences skin barrier homeostasis, SC integrity and cohesion, and antimicrobial defense mechanisms.³⁰ Moreover, soaps with a high pH can aggravate or predispose patients to candidal intertrigo that is more common in diabetics.³⁰

Cleansing and moisturizer use may be an important measure to sustain skin pH at physiological levels in DM-affected skin, thus improving barrier function and skin condition. Consistent routine is also important in maintaining skin hydration and potentially reducing the risk for progression or complications of DFS.

CONCLUSION

- Skin disorders are common complications among diabetes patients, yet frequently underdiagnosed and usually neglected.
- Recognition and management of diabetes-related skin conditions are important in maximizing the patients' quality of life and in avoiding bothersome symptoms and serious adverse effects.
- There is evidence suggesting that daily application of a ceramides-containing moisturizing skin care regime, particularly on compromised lower extremities, may control both pruritus and dry skin conditions.
- Optimal skin care using moisturizers is one of the measures that may help improve skin barrier dysfunction, preventing complications by providing early-stage treatment of patients with diabetes.

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