ALTERATIONS IN EPIDERMAL FUNCTION IN TYPE 2 DIABETES: IMPLICATIONS FOR THE MANAGEMENT OF THIS DISEASE

Mao-Qiang Man1,2 | Joan S. Wakefield2 | Theodora M. Mauro2 | Peter M. Elias2

1Dermatology Hospital of Southern Medical University, Guangzhou, China
2Dermatology Services, Veterans Affairs Medical Center and University of California San Francisco, San Francisco, California, USA

Correspondence
Mao-Qiang Man, Dermatology Service (190), 4150 Clement Street, San Francisco, CA 94121, USA.
Email: mqman@hotmail.com

Funding information
National Institute of Arthritis and Musculoskeletal and Skin Diseases, Grant/Award Number: AR061106

Abstract
Epidermal function is regulated by numerous exogenous and endogenous factors, including age, psychological stress, certain skin disorders, ultraviolet irradiation and pollution, and epidermal function itself can regulate cutaneous and extracutaneous functions. The biophysical properties of the stratum corneum reflect the status of both epidermal function and systemic conditions. Type 2 diabetes in both murine models and humans displays alterations in epidermal functions, including reduced levels of stratum corneum hydration and increased epidermal permeability as well as delayed permeability barrier recovery, which can all provoke and exacerbate cutaneous inflammation. Because inflammation plays a pathogenic role in type 2 diabetes, a therapy that improves epidermal functions could be an alternative approach to mitigating type 2 diabetes and its associated cutaneous disorders.

KEYWORDS
aging, cytokines, diabetes, keratinocytes, permeability barrier, stratum corneum hydration

Highlights
- Individuals with type 2 diabetes display epidermal dysfunction.
- Epidermal dysfunction can provoke cutaneous and extracutaneous inflammation.
- Because of the pathogenic role of inflammation in type 2 diabetes, improvements in epidermal functions could benefit type 2 diabetes.

1 | INTRODUCTION

Diabetes is a common disorder with a worldwide prevalence of 9.3%, 90% of which are cases of type 2 diabetes.1 The prevalence of type 2 diabetes is higher in males than in females,2 and older individuals (aged >60 years) have a higher prevalence than young people.3 Over 20% of individuals aged ≥65 years are diagnosed with type 2 diabetes.4 The estimated occurrence of type 2 diabetes was 0.67 per 1000 subjects aged 10 to 19 years in the United States in 2017,5 and living in rural areas and/or having a higher education level lowers the risk for type 2 diabetes.3,6 In addition to its frequency, type 2 diabetes is further complicated by a number of comorbidities such as cardiovascular disorders, obesity, neuropathy, and nephropathy.7–10 Moreover, cutaneous comorbidities are also common in patients with diabetes. About 79% of patients with either type 1 or 2 diabetes have at least one
| Models                        | Epidermal permeability barrier function | SC hydration | Skin surface pH | References |
|------------------------------|----------------------------------------|--------------|-----------------|------------|
| Animal models                |                                        |              |                 |            |
| Otsuka Long-Evans Tokushima Fatty Rats | No changes in baseline TEWL. Barrier recovery was normal in 20-week-old rats; Delayed recovery at 3 and 6 h in 30- and 45-week-old rats; Slower barrier recovery in rats with higher levels of HbA1c (>6.5%) than those with lower HbA1c (≤6.5%) at 3 h; Decreased SC integrity at age of 45 weeks. | Decreased at age of 45 weeks. | ND | 14 |
| C57BLKS/J-db/db mice         | No changes in baseline TEWL.           | No changes   | Increased       | 15         |
| KK-A/ +/TaJcl mice           | No changes in baseline TEWL.           | Low hydration | ND              | 37,42      |
| STZ-induced T2D mice         | No changes in baseline TEWL in T2D; Increased TEWL in T1D | Low hydration; No changes in T1D | ND | 37 |
| C57BLKS/J-db/db mice         | Low baseline TEWL                     | Low hydration | ND              | 31         |
| Humans                       |                                        |              |                 |            |
| Patients with T2D            | Decreased baseline TEWL; Delayed recovery at 3 h. | Decreased; SC hydration levels correlated negatively with HbA1c levels. | ND | 14 |
| 38 patients with T2D and 11 patients with T1D | TEWL was significantly lower in high HbA1c (>5.8%) than in low HbA1c (<5.8%). TEWL was higher in young (<45 years old) than in old patients (>45 years old). | Similar hydration between high HbA1c (>5.8%) and low HbA1c (<5.8%). But hydration conversely correlated with FPG levels | ND | 17 |
| 35 patients with T2D and 7 patients with T1D | Lower TEWL in diabetic patients than in the controls. Patients with peripheral autonomic neuropathy had lower TEWL than those without peripheral autonomic neuropathy. TEWL negatively correlated with age in controls, not in diabetic patients. | ND | ND | 19 |
| 34 patients with T2D and 4 patients with T1D | No changes in baseline TEWL. | No differences | ND | 20 |

(Continues)
kind of skin disorders, including cutaneous infections (48%), xerosis (26%), and inflammation (21%).\(^{11}\) Acanthosis nigricans, skin tags, and chronic ulcers are also common cutaneous manifestations in type 2 diabetic patients.\(^{12,13}\) Additionally, changes in epidermal functions, reflected by variations in biophysical properties, have been demonstrated in both animal models and humans with type 1 and 2 diabetes. This review summarizes these epidermal functional alterations in type 2 diabetes and discusses some implications for the management of this disease.

## 2 ALTERATIONS IN EPIDERMAL FUNCTIONS

### 2.1 Epidermal permeability barrier

Epidermal permeability barrier function is regulated by a number of exogenous and endogenous factors such as age, gender, some skin disorders, ultraviolet irradiation, and air pollution. An altered epidermal permeability barrier is observed in both human diabetic patients and murine models of type 2 diabetes (Table 1). For example, epidermal permeability barrier recovery is delayed in Otsuka Long-Evans Tokushima Fatty rats, a model of type 2 diabetes, at 30 weeks of age, although no changes in either baseline transepidermal water loss or barrier recovery rate were observed in rats younger than 30 weeks old.\(^{14}\) Similar results were observed in db/db mice, another murine model of type 2 diabetes.\(^{15}\) More prominent delays in barrier recovery were observed in diabetic rats with higher circulating levels of hemoglobin A1c (HbA1c) (>6.5%) than in those with low HbA1c (<6.5%). Ibuki et al\(^{16}\) reported that baseline transepidermal water loss (TEWL) rates, an indicator of epidermal permeability barrier function, were significantly higher in obese diabetic patients than in the normal controls (14.27 vs. 11.30 g/m\(^2\)/hr), suggesting a link between type 2 diabetes and epidermal permeability barrier dysfunction. In contrast, another study showed lower baseline TEWL rates on the forearm of diabetic patients (mix of type 2 diabetes and type 1 diabetes) with high HbA1c (>5.8%) than those with low HbA1c (<5.8%) (\(p < 0.05\)).\(^{17}\) Likewise, another study showed that baseline TEWL rates were lower in diabetic patients with high HbA1c (>6.5%), and insulin injections increased TEWL rates.\(^{18}\) Other studies showed that baseline TEWL rates were either unchanged or significantly lower in both humans and murine models of Type 2 diabetes.\(^{15,17,19,20}\) The variation of results among these studies could be the result of the differences in the individual health conditions of each patient, including HbA1c levels, duration of diabetes, and whether patients had any peripheral neuropathy.
For example, TEWL rates were lower in patients with either higher HbA1c levels or neuropathy. High HbA1c levels indicate a higher level of glucose over a prior 2–3-month period. In keratinocyte cultures, a high concentration of glucose (20 mM) enhances calcium-induced keratinocyte differentiation, whereas topical glucose increases filaggrin and claudin-1 expression in NC/Nga mice. Stimulation of keratinocyte differentiation benefits epidermal permeability barrier function. Thus, a diabetic patient’s lower TEWL rate may be owing to their higher plasma glucose levels, but a correlation of TEWL rates with plasma glucose levels has not been completely assessed. Because the data on TEWL in diabetic patients are limited, additional studies are needed to determine the changes in epidermal permeability barrier in individuals with diabetes.

Although the precise underlying mechanisms contributing to the altered epidermal permeability barrier function in type 2 diabetes are not clear, evidence points to several potential processes. Our previous studies demonstrated that both vascular endothelial growth factor and antimicrobial peptides (β-defensin and cathelicidin-related antimicrobial peptides) are required for epidermal permeability barrier homeostasis, whereas high glucose inhibits the expression levels of transglutaminase 1 and loricrin in keratinocyte cultures. Thus, decreased expression levels of differentiation-related marker proteins can contribute to delayed permeability barrier recovery. The delayed permeability barrier recovery in mice and humans with type 2 diabetes can be attributed to elevated skin surface pH (discussed later) and reduced hyaluronic acid, which is required for epidermal lipid production, keratinocyte differentiation, and proliferation. Finally, psychological stress can downregulate antimicrobial peptide expression levels and epidermal lipid synthesis, leading to delayed permeability barrier recovery. Thus, the compromised epidermal permeability barrier function in patients with type 2 diabetes can be attributed to reductions in expression levels of antimicrobial peptides, connexin 43, and vascular endothelial growth factor, differentiation-related proteins and increases in skin surface pH and fatty acid content, as well as to increased psychological stress.

### 2.2 Stratum corneum hydration

Stratum corneum hydration levels are reduced in both murine models and humans with type 2 diabetes (Table 1). For example, significantly low levels of stratum corneum hydration were observed in several murine models of type 2 diabetes (streptozotocin-induced nonobesity and obesity diabetes [KK-Ay/TaJcl] mice and C57BLKS/J-db/db mice). Similarly, patients with type 2 diabetes exhibit low levels of stratum corneum hydration in comparison to subjects without diabetes. However, some studies did not show changes in stratum corneum hydration levels in diabetes vs. controls in either humans or mice. These varying results could be because of differences in experimental methodology and other health conditions of the subjects. For example, in Otsuka Long-Evans Tokushima Fatty rats, reduced stratum corneum hydration was observed only in older rats (45-week-old), not in younger...
ruth. Thus, stratum corneum hydration can be normal in young db/db mice, but a significant reduction develops later. In humans with type 2 diabetes, only patients with fasting blood glucose level of >7 mM/L display reduced levels of stratum corneum hydration. Likewise, another study showed that high-frequency conductance, an indicator of stratum corneum hydration, is lower in patients with fasting blood glucose levels of >110 mg/dL than in those patients with levels <110 mg/dL. But high-frequency conductance did not differ significantly in patients with high (>5.8%) versus low (<5.8%) HbA1c levels. Hence, a diabetic patient can exhibit normal levels of stratum corneum hydration if his/her fasting blood glucose levels are in (or close to) a normal range.

Different metabolic changes can contribute to reduced stratum corneum hydration in type 2 diabetes. First, our previous studies demonstrated that skin surface lipids (sebum from sebaceous glands) are a key determinant for hydration. Skin surface lipid content is markedly lower in type 2 diabetic patients with low stratum corneum hydration and higher fasting blood glucose levels (>110 mg/L). (Note: the different measurement standards shown here are due to different methodologies used in studies featured here.) Second, aquaporin 3 deficiency can cause a reduction in stratum corneum hydration. Expression levels of cutaneous aquaporin 3 are decreased in db/db mice, suggesting a pathogenic role for reduced aquaporin 3 in type 2 diabetes-associated dry skin. Third, during epidermal maturation, proteins are degraded to amino acids, which serve as natural moisturizers in the stratum corneum, and stratum corneum hydration levels correlate positively with amino acid content in the stratum corneum. Both mice and humans with type 2 diabetes display higher blood glucose levels, and high concentrations of glucose (12 mM) inhibit keratinocyte proliferation and protein synthesis compared to low concentrations of glucose (6 mM). Hence, the decreased keratinocyte proliferation and protein synthesis can be attributed to the reduced stratum corneum hydration in type 2 diabetic patients. Fourth, topical or oral administrations of hyaluronic acid both improve stratum corneum hydration, whereas hyaluronic acid levels in the plasma of diabetic mice are 25–70% lower than that of their respective controls, possibly because of increased hyaluronidase activity. Finally, stratum corneum lipid content is decreased by over 60% in patients with type 2 diabetes vs. normal controls, whereas stratum corneum lipids (originating from keratinocytes), particularly ceramides, are one of the major natural moisturizers in the skin. Collectively, multiple endogenous factors can contribute to the reduction in stratum corneum hydration levels in type 2 diabetes.

2.3 Skin surface pH

Although diabetes-associated changes in skin surface pH have not been thoroughly researched, all recent studies that measured skin surface pH demonstrated a higher skin surface pH in both mice and humans with type 2 diabetes. The underlying mechanisms are not clear. However, low sebum content in patients with type 2 diabetes can explain, in part, the elevated skin surface pH because of the known negative correlation of sebum content with skin surface pH. In conclusion, the bulk of evidence mentioned previously indicates that alterations in epidermal functions commonly occur in type 2 diabetes (Table 1).

Another noticeable change is the decreased epidermal thickness in diabetic rats (61.62 ± 13.48 μm vs. 71.71 ± 19.50 μm, p < 0.0001), possibly owing to inhibition of keratinocyte proliferation by high glucose. For example, culture of human keratinocytes with 12 mM glucose increased mean cell population time from 3.65 days (cultured in medium with 6 mM glucose) to 5.43 days. Chao et al reported that reduced epidermal thickness was observed only in patients with diabetic complications such as ulcer and neuropathy, not in those without complications, in humans. Thus, type 2 diabetes-associated changes in epidermal thickness remain to be explored.

3 CONSEQUENCES OF ALTERED EPIDERMAL FUNCTIONS

3.1 Epidermal dysfunction provokes cutaneous inflammation

Previous studies have shown that epidermal functional abnormalities can provoke and exacerbate cutaneous inflammation, potentially leading to systemic inflammation. For instance, reduced stratum corneum hydration leads to increased levels of cytokines and histamine, accompanied by inflammatory infiltration in the skin. A lower level of stratum corneum hydration occurs with type 2 diabetes, provoking an increased density of mast cells (a sign of inflammation) in the skin. Moreover, either increased histamine and/or cytokines can induce pruritus. Correspondingly, 90% of patients with type 2 diabetes experience chronic itch, the intensity of which correlates with fasting plasma glucose levels. Pruritus-caused scratching can further damage the stratum corneum, the critical structure for effective epidermal permeability and antimicrobial barrier function. Although a disrupted epidermal permeability barrier can be rapidly repaired in normal skin, its recovery is delayed
in the skin of patients with type 2 diabetes, as noted earlier. Disruption of the epidermal permeability barrier increases cutaneous cytokine releases and inflammatory infiltration.\(^{63-65}\) Prolonged dry skin and repeated scratching make the skin constantly release cytokines. Sustained release of cytokines from the skin can eventually increase cytokine levels in the circulation, leading to systemic inflammation (a vicious circle).\(^{65}\)

Furthermore, elevated skin surface pH alone can delay epidermal permeability barrier recovery and worsen cutaneous inflammation.\(^{66,67}\) Diabetes is featured by high glucose levels, which alone can increase secretion of cytokines by keratinocytes,\(^{68}\) and contribute, in part, to epidermal dysfunction,\(^{14,15,17,50,57}\) whereas epidermal dysfunction can result in cutaneous and systemic inflammation.\(^{63-67}\) Because of the pathogenic role of inflammation in type 2 diabetes,\(^{69,70}\) the feedback loop of high glucose-epidermal dysfunction-inflammation can worsen underlying disease (Figure 1).

### 3.2 Link between cutaneous inflammation and type 2 diabetes

Type 2 diabetes has been considered as an inflammation-driven disorder,\(^{69,70}\) and serum levels of proinflammatory cytokines are increased in patients with inflammatory dermatoses such as atopic dermatitis and psoriasis.\(^{71-73}\) Clinical evidence has linked cutaneous inflammation to the development of type 2 diabetes. Epidemiological studies show that the risk of type 2 diabetes in subjects with psoriasis is higher than those without psoriasis (age-adjusted relative risk 1.21, 95% confidence interval [CI] 1.01–1.44; body mass adjusted relative risk 1.64, 95% CI 1.23–2.18).\(^{74,75}\) Prurigo nodularis, another inflammatory dermatosis, is also associated with type 2 diabetes (adjusted odds ratio 1.37; 95% CI 1.22–1.54).\(^{76}\) A link between atopic dermatitis and type 2 diabetes has also been demonstrated, with an odds ratio of 1.52 (95% CI 1.16–1.99) although some studies showed reduced odds of type 2 diabetes in patients with atopic dermatitis (odds ratio 0.78; 95% CI 0.71–0.84).\(^{77,78}\) The reduced odds ratio in some patients with atopic dermatitis could be because those patients had already received anti-inflammatory treatment. In comparison to psoriasis, patients with atopic dermatitis experience more severe pruritus,\(^{79,80}\) promoting them to seek medical care, including administration of anti-inflammatory agents such as glucocorticoids. Anti-inflammatory therapies can mitigate type 2 diabetes, which could explain the lack of a significant association of atopic dermatitis with type 2 diabetes observed in some studies.\(^{81,82}\)

### 3.3 Association of inflammation with diabetes

Inflammation, originating partly from adipose tissue, has been considered a trigger of inflammaging, resulting in insulin resistance and the development of type 2 diabetes.\(^{69}\) Accordingly, anti-inflammation regimens have been deployed to effectively treat type 2 diabetes. For example, blood HbA1c levels were markedly reduced in patients with poorly controlled type 2 diabetes (95% CI −1.09–0.13, \(p < 0.05\) vs. placebo), following orally administered diacerein, an inhibitor of proinflammatory cytokines, at a dosage of 100 mg once-daily for 24 weeks.\(^{83}\) And following anti-inflammation treatment, 7 out of 43 patients in the treated group were able to reduce their insulin dosage, whereas 10 out of 41 patients in the placebo group increased insulin dosage. Similarly, Tres et al.\(^{84}\) showed that oral administration of 50 mg diacerein twice-daily for 12 weeks decreased HbA1c levels with an adjusted difference (age, gender, and duration of disease) of −0.98% (95% CI −2.02–0.05) in comparison to a
placebo-treated group. More profound reductions in HbA1c levels were observed in patients with a disease duration of <14 years (−1.3%, 95% CI −2.3 to −0.4, p < 0.01 vs. placebo). More subjects in the diacerein-treated group exhibited lower plasma tumor necrosis factor alpha (TNFα) levels (1.46 pg/mL) than those in the placebo-treated group (66% vs. 34%, relative risk 95% CI 1.04–2.1, p < 0.05). Several clinical trials demonstrated diacerein-induced reductions in fasting blood glucose levels in patients with type 2 diabetes. Other anti-inflammatory agents such as interleukin (IL)-1 receptor blockers, IL-1β, and TNF antagonists have also been shown to lower fasting blood glucose levels, while increasing insulin sensitivity and insulin secretion, although these are debated findings. Collectively, accumulating data supports a pathogenic role for inflammaging in type 2 diabetes.

4 | PERSPECTIVE

It is now widely accepted that aging-associated chronic low-grade inflammation, also termed “inflammaging,” contributes to the development of various aging-associated disorders, including type 2 diabetes. Inflammaging can derive from a number of sources, including senescent macrophages in the adipose tissue, responses of immune cells to accumulation of damaged macromolecules, and microbial constituents, as well as secretion of proinflammatory cytokines by senescent cells. Although inflammation from these sources can increase circulating levels of proinflammatory cytokines in the elderly, the contribution of the skin (surface area-wise, the largest organ of the body) to inflammaging has been underestimated to date. Because of its vast size (≈2 m² surface area and 15% of body weight), with only mild inflammation, the skin alone can potentially provoke a low-grade systemic inflammation. Indeed, all aged humans display some signs and symptoms of inflammation in their skin. For example, over 45% of individuals aged >60 years exhibit xerosis, which can increase cutaneous inflammatory infiltration and cytokine production, and 25% of the aged population has chronic pruritus, an indicator of cutaneous inflammation. As noted previously, sustained cutaneous inflammation can eventually increase circulating levels of proinflammatory cytokines. Thus, the cutaneous origin of inflammation in aged individuals can be a source of inflammaging. In line with this assumption, we demonstrated that expression levels of cytokines are increased in both the skin and the circulation of aged mice compared to young mice, while improving epidermal function with either topical glycerol or petrolatum lowers cytokine levels in both the skin and circulation. Likewise, improvements in epidermal function with a topical emollient (Atopalm® MLE cream) lower the levels of cytokines in the circulation of aged humans. Dysfunction of cutaneous macrophages can also contribute to inflammaging and age-associated disorders. Although whether epidermal dysfunction is linked to altered macrophage function in the skin is unknown, these lines of evidence suggest the skin’s contribution to both inflammaging and type 2 diabetes.

As mentioned, the skin of people with type 2 diabetes displays epidermal dysfunction, which can provoke and exacerbate cutaneous inflammation, leading to elevation in circulating cytokine levels. Therefore, correction of epidermal dysfunction and alleviation of pruritus are pivotal in the management of type 2 diabetes and possibly other inflammaging-associated disorders.

In summary, individuals with type 2 diabetes display epidermal dysfunction, including delayed permeability barrier recovery, increased skin surface pH and reduced stratum corneum hydration, which can all induce and worsen cutaneous inflammation. Although it is not clear whether type 2 diabetes causes epidermal dysfunction, or vice versa, prolonged, constant cutaneous inflammation can eventually result in systemic inflammation, potentially leading to exacerbation of inflammaging-associated disorders such as type 2 diabetes. Coupled with the evidence that topical emollients lower cytokine levels in both the skin and the circulation, improvements in epidermal functions could be a valuable approach to mitigating inflammaging and its associated disorders, including type 2 diabetes, in the elderly. However, proper clinical trials are required to validate this hypothesis.

AUTHOR CONTRIBUTIONS
MMQ, conceptualization, literature search and draft; PME and JSW, critical review and draft; TMM, critical review.

ACKNOWLEDGEMENTS
This work was supported, in part, by the National Institutes of Health grant AR061106, administered by the Northern California Institute for Research and Education, with resources from the Research Service, Department of Veterans Medical Health Care System, San Francisco. This content is solely the responsibility of the authors and does not necessarily represent the official views of the funder.

CONFLICT OF INTEREST
MQ Man serves as a consultant to Neopharm Co., Ltd and Dr. Raymond Laboratories, Inc. Peter Elias is a co-
inventor of EpiCeram®, licensed from the University of California to Primus Pharmaceuticals, LLC, Scottsdale, AZ and a consultant to Dr. Raymond Laboratories, Inc.

**ORCID**

Mao-Qiang Man https://orcid.org/0000-0002-0957-4903

**REFERENCES**

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843.

2. Sengoku T, Ishizaki T, Goto Y, et al. Prevalence of type 2 diabetes by age, sex and geographical area among two million public assistance recipients in Japan: a cross-sectional study using a nationally representative claims database. *J Epidemiol Community Health*. 2022;76(4):391-397.

3. Magriplis E, Panagiotakos D, Papakonstantinou E, et al. Prevalence of type 2 diabetes mellitus in a representative sample of Greek adults and its association with modifiable risk factors: results from the Hellenic National Nutrition and health survey. *Public Health*. 2021;197:75-82.

4. Cowie CC, Casagrande SS, Geiss LS. Prevalence and incidence of type 2 diabetes and prediabetes. In: Cowie CC, Casagrande SS, Menke A, et al., eds. *Diabetes in America*. 3rd ed. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018Aug CHAPTER 3. https://www.ncbi.nlm.nih.gov/books/NBK568004/

5. Xia M, Liu K, Feng J, Zheng Z, Xie X. Prevalence and risk factors of type 2 diabetes and prediabetes among 53,288 middle-aged and elderly adults in China: a cross-sectional study. *Diabetes Metab Syndr Obes*. 2021;14:1975-1985.

6. Lawrence JM, Divers J, Isom S, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001–2017. *JAMA*. 2021;326(8):717-727.

7. Jelinké HF, Osman WM, Khandoker AH, et al. Clinical profiles, comorbidities and complications of type 2 diabetes mellitus in patients from United Arab Emirates. *BMJ Open Diabetes Res Care*. 2017;5(1):e000427.

8. Einarson TR, Aci A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. 2018;17(1):83.

9. Amelia R, Wahyuni AS, Yunanda Y. Diabetic neuropathy among type 2 diabetes mellitus patients at Amplus primary health Care in Medan City. *Open Access Mced J Med Sci*. 2019;7(20):3400-3403.

10. Lim AK. Diabetic nephropathy – complications and treatment. *Int J Nephrol Renovasc Dis*. 2014;7:361-381.

11. Demirseren DD, Emre S, Akoglu G, et al. Relationship between skin diseases and extracutaneous complications of diabetes mellitus: clinical analysis of 750 patients. *Am J Clin Dermatol*. 2014;15(1):65-70.

12. Levy L, Zeichner JA. Dermatologic manifestation of diabetes. *J Diabetes*. 2012;4(1):68-76.

13. Sanches MM, Roda A, Pimenta R, Filipe PL, Freitas JP. Cutaneous manifestations of diabetes mellitus and prediabetes. *Acta Med Port*. 2019;32(6):459-465.

14. Park HY, Kim JH, Jung M, et al. A long-standing hyperglycaemic condition impairs skin barrier by accelerating skin ageing process. *Exp Dermatol*. 2011;20(12):969-974.

15. Kim JH, Yoon NY, Kim DH, et al. Impaired permeability and antimicrobial barriers in type 2 diabetes skin are linked to increased serum levels of advanced glycation end-product. *Exp Dermatol*. 2018;27(8):815-823.

16. Ibuki A, Kuriyama S, Toyosaki Y, et al. Aging-like physiological changes in the skin of Japanese obese diabetic patients. *SAGE Open Med*. 2018;6: 2050311218756662.

17. Sakai S, Kikuchi K, Satoh J, Tagami H, Inoue S. Functional properties of the stratum corneum in patients with diabetes mellitus: similarities to senile xerosis. *Br J Dermatol*. 2005;152(3):319-323.

18. Lai CCK, Md Nor N, Kamaruddin NA, Jamil A, Safian N. Comparison of transepidermal water loss and skin hydration in diabetics and nondiabetics. *Clin Exp Dermatol*. 2021;46(1):58-64.

19. Han SH, Park JW. Diabetic and sympathetic influences on the water permeability barrier function of human skin as measured using transepidermal water loss: a case-control study. *Medicine (Baltimore)*. 2017;96(45):e8611.

20. Selrafi H, Farsinnejad K, Firooz A, et al. Biophysical characteristics of skin in diabetes: a controlled study. *J Eur Acad Dermatol Venereol*. 2009;23(2):146-149.

21. Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. Glucose effects on skin keratinocytes: implications for diabetes skin complications. *Diabetes*. 2001;50(7):1627-1635.

22. Yamada K, Matsushita K, Wang J, Kanekura T. Topical glucose induces Claudin-1 and Filaggrin expression in a mouse model of atopic dermatitis and in keratinocyte culture, exerting anti-inflammatory effects by repairing skin barrier function. *Acta Derm Venereol*. 2018;98(1):19-25.

23. Elias PM, Arbiser J, Brown BE, et al. Epidermal vascular endothelial growth factor production is required for permeability barrier homeostasis, dermal angiogenesis, and the development of epidermal hyperplasia: implications for the pathogenesis of psoriasis. *Am J Pathol*. 2008;173(3):689-699.

24. Aberg KM, Man MQ, Gallo RL, et al. Co-regulation and interdependence of the mammalian epidermal permeability and antimicrobial barriers. *J Invest Dermatol*. 2008;128(4):917-925.

25. Hu SC, Lan CE. High-glucose environment disturbs the physiological functions of keratinocytes: focusing on diabetic wound healing. *J Dermatol Sci*. 2016;84(2):121-127.

26. Martin PE, Easton JA, Hodgins MB, Wright CS. Connexins: sensors of epidermal integrity that are therapeutic targets. *FEBS Lett*. 2014;588(8):1304-1314.

27. Maass K, Ghanem A, Kim JS, et al. Defective epidermal barrier and antimicrobial barriers in neonatal mice lacking the C-terminal region of connexin43. *Mol Biol Cell*. 2004;15(10):4597-4608.

28. Bäsler K, Bergmann S, Heisig M, Naegel A, Zorn-Kruppa M, Brandner JM. The role of tight junctions in skin barrier function and dermal absorption. *J Control Release*. 2016;242:105-118.

29. Ahern WP, Lynch SA. The gut microbiome in IBD and other disorders. *SAGE Open Med*. 2018;6: 2050311218756662.
30. Yu H, Yang J, Zhou X, Xiao Q, Lü Y, Xia L. High glucose induces dysfunction of airway epithelial barrier through down-regulation of connexin 43. Exp Cell Res. 2016;342(1):11-19.

31. Kim M, Jeong H, Lee B, et al. Enrichment of short-chain ceramides and free fatty acids in the skin epidermis, liver, and kidneys of db/db mice, a type 2 diabetes mellitus model. Biomol Ther (Seoul). 2019;27(5):457-465.

32. Man MQ, Feingold KR, Elias PM. Exogenous lipids influence permeability barrier recovery in acetonate-treated murine skin. Arch Dermatol. 1993;129(6):728-738.

33. Feingold KR, Elias PM. Role of lipids in the formation and maintenance of the cutaneous permeability barrier. Biochim Biophys Acta. 2014;1841(3):280-294.

34. Takayanagi T, Hirai H, Asada Y, et al. Terminal differentiation of keratinocytes was damaged in type 2 diabetic mice. Biophys Acta. 2019;2007;49:5875-5882. doi:10.1007/s11033-022-07367-4. Epub ahead of print PMID: 35347543.

35. Zhang J, Yang P, Liu D, et al. C-Myc upregulated by high glucose inhibits HaCaT differentiation by S100A6 transcriptional activation. Front Endocrinol (Lausanne). 2021;12:676403.

36. Yosipovitch G, Tur E, Cohen O, Rusecki Y. Skin surface pH in intertriginous areas in NIDDM patients. Possible correlation to candidal intertrigo. Diabetes Care. 1993;16(4):560-563.

37. Horikawa T, Hiramoto K, Goto K, Sekijima H, Ooi K. Differences in the mechanism of type 1 and type 2 diabetes-induced skin dryness by using model mice. Int J Med Sci. 2021;18(2):474-481.

38. Bourguignon LY, Ramez M, Gilad E, et al. Hyaluronan-CD44 interaction stimulates keratinocyte differentiation, lamellar body formation/secration, and permeability barrier homeostasis. J Invest Dermatol. 2006;126(6):1356-1365.

39. Aberg KM, Radek KA, Choi EH, et al. Psychological stress downregulates epidermal antimicrobial peptide expression and increases severity of cutaneous infections in mice. J Clin Invest. 2007;117(11):3339-3349.

40. Choi EH, Brown BE, Crumrine D, et al. Mechanisms by which psychologic stress alters cutaneous permeability barrier homeostasis and stratum corneum integrity. J Invest Dermatol. 2005;124(3):587-595.

41. Garg A, Chren MM, Sands LP, et al. Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. Arch Dermatol. 2001;137(1):53-59.

42. Sekijima H, Goto K, Hiramoto K, Komori R, Ooi K. Characterization of dry skin associating with type 2 diabetes mellitus using a KK-ay/TaJcl mouse model. Cutan Ocul Toxicol. 2018;37(4):391-395.

43. Craciun A-E, Moldovan M, Nita C, et al. Predictors of changes in physical properties of skin in patients with diabetes mellitus. RJDNMD. 2012;19(1):33-40.

44. Choi EH, Man MQ, Wang F, et al. Is endogenous glycerol a determinant of stratum corneum hydration in humans? J Invest Dermatol. 2005;125(2):288-293.

45. Fluhr JW, Mao-Qiang M, Brown BE, et al. Glycerol regulates stratum corneum hydration in sebaceous gland deficient (asebia) mice. J Invest Dermatol. 2003;120(5):728-737.

46. Ma T, Hara M, Sougrat R, Verbavatz JM, Verkman AS. Impaired stratum corneum hydration in mice lacking epidermal water channel aquaporin-3. J Biol Chem. 2002;277(19):17147-17153.

47. Ikarashi N, Mizukami N, Pei C, et al. Role of cutaneous Aquaporins in the development of Xeroderma in type 2 diabetes. Biomedicine. 2021;9(2):104.

48. Fowler J. Understanding the role of natural moisturizing factor in skin hydration. Practical Dermatol. 2012;July;36-40.

49. Horii I, Nakayama Y, Obata M, Tagami H. Stratum corneum hydration and amino acid content in xerotic skin. Br J Dermatol. 1989;121(5):587-592.

50. Terashi H, Izumi K, Deveci M, Rhodes LM, Marcelo CL. High glucose inhibits human epidermal keratinocyte proliferation for cellular studies on diabetes mellitus. Int Wound J. 2005;2(4):298-304.

51. Lubart R, Yariv I, Fixler D, Lipovsky A. Topical hyaluronic acid facial cream with new micronized molecule technology effectively penetrates and improves facial skin quality: results from in-vitro, ex-vivo, and in-vivo (open-label) studies. J Clin Aesthet Dermatol. 2019;12(10):39-44.

52. Draelos ZD, Diaz I, Namkoong J, Wu J, Boyd T. Efficacy evaluation of a topical hyaluronic acid serum in facial Photaging. Dermatol Ther (Heidelb). 2021;11(4):1385-1394.

53. Hsu TF, Su ZR, Hsieh YH, et al. Oral Hyaluronan relieves wrinkles and improves dry skin: a 12-week double-blinded, placebo-controlled study. Nutrients. 2021;13(7):2220.

54. Rawlings AV, Mats P. Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle. J Invest Dermatol. 2005;124(6):1099-1110.

55. Kim MK, Choi SY, Byun HJ, et al. Comparison of sebum secretion, skin type, pH in humans with and without acne. Arch Dermatol Res. 2006;298(3):113-119.

56. Danielsen PL, Jorgensen LN, Jorgensen B, Karlmark T, Ågren M. Erythema persists longer than one year in split-thickness skin graft donor sites. Acta Derm Venereol. 2013;93(3):281-285.

57. Craciun A-E, Moldovan M, Nita C, et al. Changes in physical properties of skin in patients with insufficient therapeutic controlled diabetes mellitus. RJDNMD. 2011;18(4):341-346.

58. Choi EH. Aging of the skin barrier. Clin Dermatol. 2019;37(4):336-345.

59. Boric M, Skopljanac I, Ferhatovic L, Jelicic Kadic A, Banozic A, Puljak L. Reduced epidermal thickness, nerve degeneration and increased pain-related behavior in rats with diabetes type 1 and 2. J Chem Neuroanat. 2013;53:33-40.

60. Chao CY, Zheng YP, Cheing GL. Epidermal thickness and biochemical properties of plantar tissues in diabetic foot. Ultrasound Med Biol. 2011;37(7):1029-1038.

61. Wang Z, Man MQ, Li T, Elias PM, Mauro TM. Aging-associated alterations in epidermal function and their clinical significance. Aging (Albany NY). 2020;12(6):5551-5565.

62. Stefaniak AA, Krajewski PK, Bednarska-Chabowska D, Bolanski M, Mazur G, Szepietowski JC. Itch in adult population with type 2 diabetes mellitus: clinical profile, pathogenesis and disease-related burden in a cross-sectional study. Biol (Basel). 2021;10(12):1332.

63. Elias PM, Wood LC, Feingold KR. Epidermal pathogenesis of inflammatory dermatoses. Am J Contact Dermat. 1999;10(3):119-126.

64. Proksch E, Brusch J. Abnormal epidermal barrier in the pathogenesis of contact dermatitis. Clin Dermatol. 2012;30(3):335-344.

65. Hu L, Mauro TM, Dang E, et al. Epidermal dysfunction leads to an age-associated increase in levels of serum inflammatory cytokines. J Invest Dermatol. 2017;137(6):1277-1285.
66. Mauro T, Holleran WM, Grayson S, et al. Barrier recovery is impaired at neutral pH, independent of ionic effects: implications for extracellular lipid processing. Arch Dermatol Res. 1998;290(4):215-222.

67. Jang H, Matsuda A, Jung K, et al. Skin pH is the master switch of Kallikrein 5-mediated skin barrier destruction in a murine atopic dermatitis model. J Invest Dermatol. 2016;136(1):127-135.

68. Lan CC, Wu CS, Huang SM, et al. High-glucose environment enhanced oxidative stress and increased interleukin-8 secretion from keratinocytes: new insights into impaired diabetic wound healing. Diabetes. 2013;62(7):2530-2538.

69. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol. 2019;14(1):50-59.

70. Cruz NG, Sousa LP, Sousa MO, Pietrani NT, Fernandes AP, Gomes KB. The linkage between inflammation and type 2 diabetes mellitus. Diabetes Res Clin Pract. 2013;99(2):85-92.

71. Brunner PM, Suárez-Fariñas M, He H, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. Sci Rep. 2017;7(1):8707.

72. Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. Exp Dermatol. 2018;27(4):409-417.

73. Bai F, Zheng W, Dong Y, et al. Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. Oncotarget. 2017;9(1):1266-1278.

74. Wan MT, Shin DB, Hubbard RA, Noe MH, Mehta NN, Gelfand JM. Psoriasis and the risk of diabetes: a prospective population-based cohort study. J Am Acad Dermatol. 2018;78(2):315-322.e1.

75. Holm JG, Thomsen SF. Type 2 diabetes and psoriasis: links and risks. Psoriasis (Auckl). 2019;9(1):1-6.

76. Woo YR, Wang S, Sohn KA, Kim HS. Epidemiology, comorbidities, and prescription patterns of Korean Prurigo Nodularis patients: a multi-institution study. J Clin Med. 2021;11(1):95.

77. Silverberg JI, Gelfand JM, Margolis DJ, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol. 2018;121(5):604-612.e3.

78. Drucker AM, Qureshi AA, Dummer TJB, Parker L, Li WQ. Atopic dermatitis and risk of hypertension, type 2 diabetes, myocardial infarction and stroke in a cross-sectional analysis from the Canadian Partnership for Tomorrow Project. Br J Dermatol. 2017;177(4):1043-1051.

79. Kaaz K, Szeptewoski JC, Matusiak L. Influence of itch and pain on sleep quality in atopic dermatitis and psoriasis. Acta Derm Venereol. 2019;99(2):175-180.

80. O’Neill JL, Chan YH, Rapp SR, Yosipovitch G. Differences in itch characteristics between psoriasis and atopic dermatitis patients: results of a web-based questionnaire. Acta Derm Venereol. 2011;91(5):537-540.

81. Andersen YMF, Egeberg A, Gislason GH, Skov L, Knop FK, Thyssen JP. Adult atopic dermatitis and the risk of type 2 diabetes. J Allergy Clin Immunol. 2017;139(3):1057-1059.

82. Richard MA, Sei JF, Philippe C, Taieb C, Joly P, Ezzedine K. Prevalence of comorbidities in atopic dermatitis and psoriasis in the French population. Ann Dermatol Venereol. 2021;148(1):28-33.

83. Cardoso CRL, Leite NC, Carlos FO, Loureiro AA, Viegas BB, Salles GF. Efficacy and safety of Diacerein in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Care. 2017;40(10):1356-1363.

84. Tres GS, Fuchs SC, Piovesan F, et al. Effect of Diacerein on metabolic control and inflammatory markers in patients with type 2 diabetes using antiobiotic agents: a randomized controlled trial. J Diabetes Res. 2018;2018:4246521-4246528.

85. Guo S, Guo X, Zhang H, Zhang X, Li Z. The effect of Diacerein on type 2 diabetic mellitus: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. J Diabetes Res. 2020;2020:2593792-2593799.

86. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. Nat Rev Drug Discov. 2014;13(6):465-476.

87. Prattichizzo F, De Nigris V, Spiga R, et al. Inflammageing and metaflammination: the Yin and Yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

88. Matacchione G, Perugini J, Di Mercurio E, et al. Senescent macrophages in the human adipose tissue as a source of inflamming. Gerosocience. 2022. doi:10.1007/s11357-022-00536-0.

89. Franceschi C, Campisi J. Chronic inflammation (inflamma-ging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69(Suppl 1):S4-S9.

90. Dąbrowska AK, Sapan F, Derler S, Adlhart C, Spencer ND, Rossi RM. The relationship between skin function, barrier properties, and body-dependent factors. Skin Res Technol. 2018;24(2):165-174.

91. Kumar D, Das A, Bandyopadhyay D, et al. Dermatoses in the elderly: Clinico-demographic profile of patients attending a tertiary care Centre. Indian J Dermatol. 2021;66(1):74-80.

92. Man MQ, Elias PM. Stratum corneum hydration regulates key epidermal function and serves as an indicator and contributor to other conditions. J Eur Acad Dermatol Venereol. 2019;33(1):15-16.

93. Valdes-Rodriguez R, Mollanazar NK, González-Muro J, et al. Itch prevalence and characteristics in a Hispanic geriatric population: a comprehensive study using a standardized itch questionnaire. Acta Derm Venereol. 2015;95(4):417-421.

94. Ye L, Mauro TM, Dang E, et al. Topical applications of an emollient reduce circulating pro-inflammatory cytokine levels in chronically aged humans: a pilot clinical study. J Eur Acad Dermatol Venereol. 2019;33(11):2197-2201.

95. Guimarães GR, Almeida PP, de Oliveira SL, et al. Hallmarks of aging in macrophages: consequences to skin Inflammaging. Cell. 2021;10(6):1323.

96. Yue Z, Nie L, Zhang P, Chen Q, Lv Q, Wang Q. Tissue-resident macrophage inflamming aggravates homeostasis dysregulation in age-related diseases. Cell Immunol. 2021;361:104278.