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Diabetic and sympathetic influences on the water permeability barrier function of human skin as measured using transepidermal water loss

A case-control study

Seung Hoon Han, MD, PhD[b], Ji Woong Park, MD, PhD[a,*]

Abstract

The presence of long-standing hyperglycemic conditions has been suggested to lead to many skin problems associated with an impaired skin barrier function. However, the relationship between impaired skin barrier status and altered peripheral nervous system function has not yet been determined. The purpose of this study was to investigate the water evaporation rate as a measure of the permeability barrier function of diabetic skin and its relationship to diabetic sensorimotor polyneuropathy (DSPN) and peripheral autonomic neuropathy (PAN) using well-controlled confounding variables.

This case-control study included 42 participants with chronic diabetes and 43 matched healthy controls. The diabetic group underwent a nerve conduction study and sympathetic skin response (SSR) test to confirm the presence of DSPN and PAN, respectively. Different skin regions were analyzed using the noninvasive Tewameter instrument (Courage+Khazaka Electronic GmbH, Cologne, Germany). The impacts of PAN, DSPN, age, and diabetes duration on the values of transepidermal water loss (TEWL) were each analyzed and compared between the groups.

Regardless of the presence of DSPN or PAN, the TEWL values as measured on the distal extremities were significantly lower in the diabetic group than in the control group. In the diabetic group, participants with abnormal SSR test results showed decreased TEWL values in the finger, sole, and first toe, as compared with participants with normal SSR test results. In the control group, age showed a negative correlation with the TEWL values with respect to some measured regions. However, in the diabetic group, there was no significant correlation between either patient age or diabetes duration and TEWL values.

The presence of a long-term hyperglycemic state can reduce the permeability barrier function of the skin, a phenomenon that might be related to the presence of an impaired peripheral sympathetic nervous system, rather than peripheral sensorimotor denervation.

Abbreviations: BMI = body mass index, DAN = diabetic autonomic neuropathy, DM = diabetes mellitus, DPN = diabetic polyneuropathy, DSPN = diabetic sensorimotor polyneuropathy, NCS = nerve conduction study, PAN = peripheral autonomic neuropathy, SC = stratum corneum, SSR = sympathetic skin response, TEWL = transepidermal water loss.

Keywords: diabetes mellitus, diabetic polyneuropathy, diabetic sensorimotor polyneuropathy, peripheral autonomic neuropathy, skin, sympathetic skin response, transepidermal water loss

1. Introduction

The presence of diabetes mellitus (DM) causes many skin changes and complications. DM is a systemic disease that can affect the metabolic, immune, vascular, and nervous systems. Long-standing hyperglycemic conditions can induce diabetic polyneuropathies (DPNs), which have a prevalence of 30% to 70%.[1–3] The generalized family of DPNs can be classified into typical and atypical subgroups.[4–6] Typical DPN is usually referred to as diabetic sensorimotor polyneuropathy (DSPN) and is considered to be the most common variant of DPNs. DSPN is known to be a length-dependent, symmetrical polyneuropathy that mainly affects the large nerve fibers within the body.[5,7] Atypical DPNs are small-fiber polyneuropathies involving intercurrent pain and autonomic symptoms.[5] Diabetic autonomic neuropathy (DAN) represents a disorder of the autonomic nervous system that may affect the cardiovascular, gastrointestinal, and urogenital systems, as well as the sudomotor function. Among the DAN family of conditions, peripheral autonomic neuropathy (PAN) can induce many pathological skin conditions such as dryness, fissure, and ulceration due to atrophy of the

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sweat glands and an abnormal sudomotor response that degrades the sweating function.[8,9] The sudomotor function can be assessed through a sympathetic skin response (SSR) test, which is a simple, noninvasive method for evaluating small-fiber sudomotor function.[3,10] A transepidermal water loss (TEWL) test can evaluate the water barrier function of the stratum corneum (SC) and can measure the gradient of water evaporation in an open chamber.[11,12] It had been reported that TEWL values, which reflect the water barrier function, remain generally preserved in patients with diabetes,[12–14] although the hydration state of their skin was mostly decreased.[12,13] However, the subjects of those previous studies had relatively short durations of DM, and did not undergo TEWL measurements according to the presence of peripheral autonomic or sensorimotor polyneuropathy.[12–14]

The aims of this study were to compare the TEWL values recorded at various sites of the limbs of participants with chronic DM and age- and sex-matched controls, and to investigate the relationship between the TEWL value and the PAN or DSPN status in a diabetic cohort.

2. Materials and methods

2.1. Study design

This study employed a case-control design and was performed at Soonchunhyang University Hospital (SCHUH), Seoul, South Korea, from March 2010 to February 2011. The study was approved by the Institutional Review Board (SCHUH 2009–011) of SCHUH. Written informed consent was obtained from all participants before their participation in the study. Forty-two participants with chronic diabetes were selected for consideration, and 43 age- and sex-matched normal controls were recruited (Fig. 1). Because age and sex may affect the function of the human skin barrier, the control group was selected at a ratio of 1:1 with the diabetic group to match the sex and age characteristics of the patients with diabetes within a 10-year interval. All participants in the diabetic group underwent a nerve conduction study (NCS) and SSR test for a subgroup analysis conducted depending on their DSPN and PAN status.

2.2. Participants

The diabetic group included participants aged 19 years or older who had had DM for >1 year to date. From these patients, we recorded information on the type of diabetes; fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) levels; smoking history; and anthropometric data including weight, height, and body mass index (BMI). The same information was also collected from the participants of the control group. We excluded participants with skin lesions at the site of measurement (eg, burn, scar, and keloid); history of skin disorders capable of influencing the properties of the skin barrier (eg, atopic dermatitis, eczema, psoriasis, and pruritus); systemic disorders capable of influencing the hydration of the skin (eg, syndrome of inappropriate antidiuretic hormone secretion and diabetes insipidus); presence of focal neuropathies on both limbs (eg, radiculopathy and carpal tunnel syndrome); central nervous system lesions; and/or inability to assume or hold a neutral supine postural position owing to skeletal deformities.

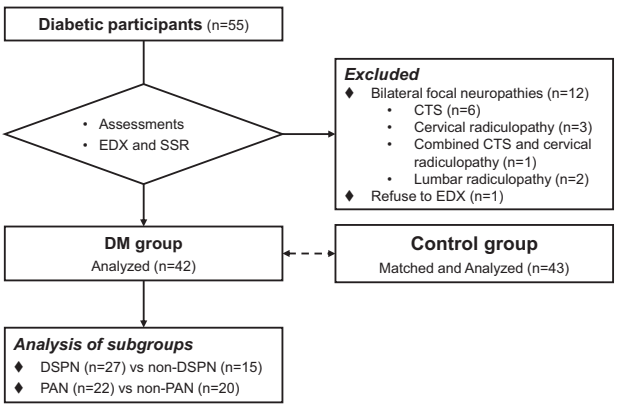

Figure 1. Flowchart of the study design. CTS = carpal tunnel syndrome, DSPN = diabetic sensorimotor polyneuropathy, EDX = electrodiagnostic study, PAN = peripheral autonomic neuropathy, SSR = sympathetic skin response.

2.3. Electrodiagnostic study

A physiatrist with an electrodiagnostic experience of >10 years performed the electrodiagnostic studies including the SSR test with a Medelec Synergy Mobile 5-channel device (Oxford Instruments, Abingdon, UK). NCS was performed in both upper and lower limbs to diagnose DSPN, and to screen for focal entrapment neuropathies and radiculopathies. The diagnostic criteria for DSPN were defined as a sural sensory action potential of <7.3 μV, and a peroneal motor conduction velocity of <43.9 m/s observed at the same time during the NCS.[15] When the patients were suspected to have focal entrapment neuropathies, the presence of which were determined on the basis of the observation of the known symptoms and the results of the NCS tests, we performed additional needle electromyograms to confirm the diagnosis. The SSR test results indicate the changes in the electrical potential recorded from the skin and reflect the sudomotor function. The SSR method used in this study has been previously described.[16] Active electrodes were attached to both palms and both soles, which are areas that include the highest density of eccrine sweat glands in the human body. Reference electrodes were also placed on the dorsum of the patients' hands and feet. The median and tibial nerves were then stimulated with an intensity of 20 mA and pulse duration of 0.2 ms, and the potentials were recorded via the ipsilateral and contralateral electrodes by using a 4-channel recording system. When the potentials generated after the electrical stimulations were simultaneously recorded at the 4 extremities, it was considered to be an "abnormal SSR" test, representing a situation in which there were no responses in at least 2 limbs.[16]

2.4. TEWL measurements

All outcomes were measured on one visit, whereas the body composition was measured and the details of adverse events were recorded throughout the study period. Upon receiving informed consent information, instructions were provided to the participants according to previous guidelines,[17] including directions on skin hygiene practices (shower, washing),[18] use of topical products (cosmetics, lotions, barrier creams, etc.),[19,20] and consumption of caffeine-containing drinks[21,22] or smoking before the measurements.[23] The primary outcome was the TEWL value, which was measured 3 times at the selected sites with >30 s lag time. The mean value was then calculated.[17] The TEWL reflects the water permeability barrier function of the SC by measuring the water evaporation rate through evaporimetry with a Tewameter TM 300 probe (Courage + Khazaka Electronic

GmbH, Cologne, Germany).[17] The TEWL value (g/h·m^2) can be obtained by calculating the difference in water evaporation rates measured at 2 different points, using Fick law of diffusion. During the study, the participants were examined comfortably in the supine position. The air flow and room temperature were maintained using an air conditioner set at 20°C to 25°C, whereas the relative humidity was preserved at 40% to 50%.[17] The TEWL values were measured in several body regions that were selected for the purpose of evaluating the regional variations between the proximal and distal parts of the upper and lower limbs. The detailed measurements of body regions are presented in Figure 2.

2.5. Statistical analysis

To estimate the sample size, we referred to a previous study that compared TEWL values in accordance with the level of HbA_{1C}.[12] To detect this difference in a case-control study using Student *t* test, assuming a 2-tailed significance level of $\alpha = 0.01$ and a power of 90%, the suggested sample size was 42 participants per group. The normality of distribution was assessed with the Shapiro-Wilk test. All demographic data are presented as the mean and standard deviation (SD). Student *t* test was used to compare the most continuous variables, and the chi-square test was utilized to compare the categorical variables, such as sex and smoking ratio, between the 2 groups. Pearson correlation coefficient test was used to evaluate the relationship between the TEWL variables and the participants' age and diabetes duration. All variables with a value of $P < .05$ were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) 14.0 software for Windows (SPSS Inc, Chicago, IL) was used to conduct data analysis.

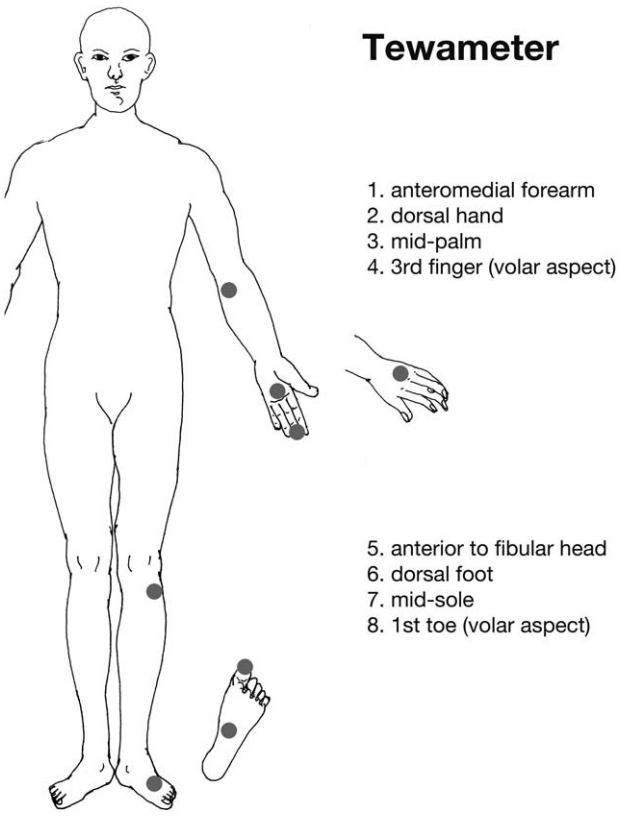

Figure 2. Body regions of the skin measurements. Different skin regions were measured using a Tewameter (round; Courage+Khazaka Electronic GmbH, Cologne, Germany) probe.

Table 1

Baseline characteristics of participants.

Variables	Group		*P*
	DM, N = 42	Control, N = 43	
Age, y	61.1 (9.7)	59.8 (7.8)	.480†
Sex: Female, n, %	21 (50.0)	21 (48.8)	.915*
Height, cm	161.8 (6.8)	162.4 (5.7)	.668†
Weight, kg	63.4 (8.4)	61.6 (7.5)	.296†
BMI, kg/m^2	24.3 (3.6)	23.3 (2.2)	.125†
Smoker, n, %	6 (14.3)	7 (16.3)	.799*
Diabetic duration, y	15.7 (8.6)	NA	
FPG, mg/dL	143.9 (32.8)	NA	
HbA_{1C}, %	6.1 (1.2)	NA	
Types of DM			
Type 1	7 (16.7)	NA	
Type 2	35 (83.3)	NA	
Incidence of DPNs			
DSPN, n, %	27 (64.3)	NA	
PAN, n, %	22 (52.4)	NA	

Data are expressed as mean (standard deviation) or number (percentage). *P* values were calculated with *chi-square test for qualitative data and †Student *t* test for quantitative data. BMI = body mass index, DM = diabetes mellitus, DPNs = diabetic polyneuropathies, DSPN = diabetic sensorimotor polyneuropathy, FPG = fasting plasma glucose, HbA_{1C} = hemoglobin A_{1C}, NA = not applicable, PAN = peripheral autonomic neuropathy.

3. Results

A total of 55 participants with diabetes were initially screened and enrolled in the study (Fig. 1). Of these 55 participants, 12 did not meet the study inclusion criteria and 1 refused to undergo the electrodiagnostic study. Therefore, 42 eligible participants were finally placed in the diabetic group. Then, 43 age- and sex-matched controls were recruited. The 42 participants in the diabetic group were divided into subgroups according to the results of their electrodiagnostic studies and SSR tests. The participants' characteristics are summarized in Table 1. There were no significant differences in terms of age, sex, smoking, weight, height, and BMI between the 2 groups. The mean (SD) age was 61.1 (9.7) years in the diabetic group and 59.8 (7.8) years in the control group. In the diabetic group, the mean duration of DM was 15.7 (8.6) years. Of the 42 participants in the diabetic group, 7 (16.7%) had type 1 DM and 35 (83.3%) had type 2 DM. In the diabetic group, DSPN and PAN were diagnosed in 27 (64.3%) and 22 (52.4%) participants, respectively. The FPG level was 143.9 (32.8) mg/dL and the HbA_{1C} level was 6.1% (1.2%). Additionally, there were no differences in the values between the 2 subgroups of DSPN and PAN. To investigate the influence of long-standing hyperglycemia on the permeability barrier function of the skin, we compared the mean values of TEWL for the measurement sites between the 2 groups. The diabetic group (n = 42) demonstrated significantly lower TEWL values on the distal portion of the upper and lower limbs than did participants in the control group: specifically, these values were recorded on the mid-palm ($P < .001$), volar side of the third finger ($P < .001$), dorsal foot ($P < .001$), mid-sole ($P < .001$), and volar side of the first toe ($P < .001$) (Table 2 and Fig. 3A). In the diabetic group participants (n = 43), the PAN subgroup (n = 22) showed significantly lower TEWL values than the non-PAN subgroup

Table 2

Comparison of TEWL values between groups.

Variable	Group: DM, N = 42	Group: Control, N = 43	Differences of means (95% CI)	*P*
TEWL, g/h/m^2				
Forearm	28.9 (8.8)	30.8 (4.9)	1.8 (−1.2, 4.9)	.235
Dorsal hand	33.7 (11.8)	35.2 (8.2)	1.5 (−2.9, 5.9)	.499
Mid-palm	58.0 (10.8)	76.5 (13.1)	18.5 (13.3, 23.7)	<.001*
Third finger	67.7 (17.6)	88.6 (15.1)	20.9 (13.9, 28.0)	<.001*
Fibular head	31.6 (10.6)	35.4 (10.2)	3.8 (−0.7, 8.3)	.093
Dorsal foot	31.8 (10.6)	41.6 (11.3)	9.7 (5.0, 14.4)	<.001*
Mid-sole	45.5 (9.5)	61.7 (10.0)	16.2 (12.0, 20.4)	<.001*
First toe	55.6 (15.0)	77.3 (15.8)	21.8 (15.1, 28.4)	<.001*

Data are expressed as mean (standard deviation) unless otherwise indicated. *P* values were calculated using Student *t* test. CI = confidence interval, DM = diabetes mellitus, TEWL = transepidermal water loss.

* $P < .05$.

(n = 20) on the distal part of the limbs, specifically as recorded on the third finger ($P = .029$), mid-sole ($P = .049$), and first toe ($P = .030$) (Table 3 and Fig. 3B). However, there was no difference in TEWL values between the DSPN subgroup (n = 27) and the non-DSPN subgroup (n = 15) within the diabetic group (Table 4). The Pearson correlation coefficients between the TEWL values and the participants' age or diabetes duration were analyzed (Table 5). In the control group, age had a negative correlation with TEWL values as measured in the forearm ($r = -0.415$; $P = .006$), dorsal hand ($r = -0.335$; $P = .028$), and fibular head ($r = -0.378$; $P = .012$). However, in the diabetic group, there was no significant correlation between either patient age or disease duration and the TEWL value.

4. Discussion

The results of this study first confirmed that the presence of a long-term hyperglycemic state could reduce the water barrier function of the skin on the peripheral limbs, a phenomenon that is closely related to peripheral sympathetic denervation rather than somatosensory denervation.

The epidermis of the skin is composed of glycolytic tissue, and it is known that insulin plays an important role in maintaining the homeostasis of the epidermis.[24,25] It has been reported that patients with diabetes have decreased water content in the SC.[12,13] Furthermore, impaired hydration of the skin might be more severely present in aged patients with diabetes than in those who are younger.[12] However, it has also been reported that TEWL values, reflecting water barrier function, were generally preserved in patients with diabetes.[12–14] In contrast with the results of previous reports, we found that the diabetic group had significantly lower TEWL values on the distal parts of the upper and lower limbs than did the control group. This could be explained by the fact that the participants in our study were predominantly older (mean age, 61.1 ± 9.7 years) and had a chronic diabetic condition (mean duration of DM, 15.7 ± 8.6 years). Moreover, more than half (52.4%) of the participants in the diabetic group had a confirmed PAN status. In the diabetic group, participants with PAN showed significantly lower values of TEWL in the distal limbs than did those without PAN. However, we did not find any significant differences between the 2 groups when comparing TEWL values according to the presence or absence of DSPN in the diabetic group. This suggests that the sympathetic sudomotor dysfunction might be related to the permeability barrier function of the SC of the skin. One of the most common long-term complications known to occur in >50% of patients with diabetes is neuropathy, mainly in the distal segmental demyelination of nerve fibers, and is usually a mixture of peripheral sensorimotor and autonomic polyneuropathies.[26,27] DSPN typically involves sensorimotor disturbances incorporating large nerve fibers; however, PAN as an atypical DPN usually involves small nerve fibers to express autonomic dysfunctions that can lead to painful diabetic neuropathy, anhidrosis, fissure, and cracking of the skin.[5,26,27] Our results showed that peripheral sympathetic denervation as confirmed with SSR testing in patients with diabetes can be assessed quantitatively by determining the TEWL value, which represents the permeability barrier function. Additionally, the eccrine sweat glands test can evaluate the distribution and extent of deficits in the sympathetic cholinergic function. In addition to the SSR test, other useful examinations include the quantitative sudomotor axon reflex test (QSART), sweat imprint test, and thermoregulatory sweat test. The SSR test can be easily performed by connecting the lines of surface electrodes attached to the body to a standard electromyogram instrument to evaluate gland function.[26,28] In this study, we used the SSR test to detect PAN

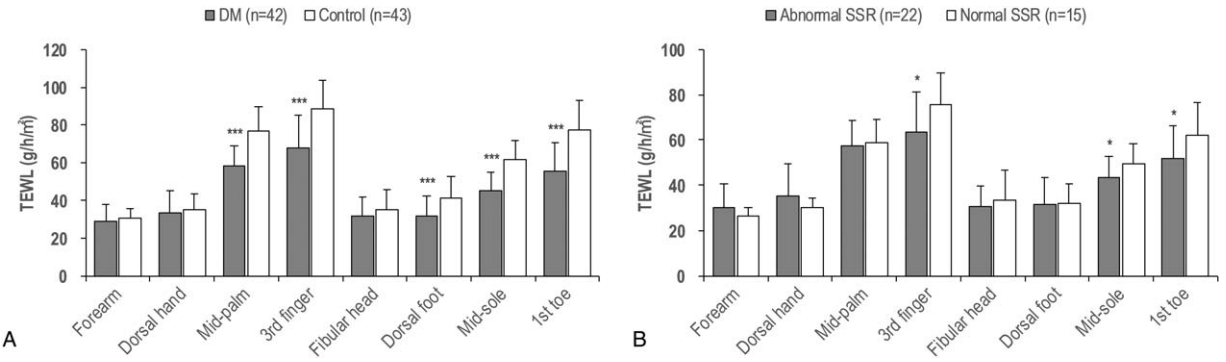

Figure 3. Comparisons of TEWL between the DM and control groups (A), and between patients with diabetes with abnormal and normal SSR test results (B). The diabetic group showed significantly lower TEWL values as measured at the distal regions of the limbs than did the control group (A). Patients with diabetes with abnormal SSR test results showed significant lower TEWL values in the distal limbs (B). The TEWL values are presented as the mean and standard deviation. Student *t* test was used for comparing the mean between the DM and control groups. * $P < .05$, ** $P < .01$, *** $P < .001$. DM = diabetes mellitus, SD = standard deviation, SSR = sympathetic skin response, TEWL = transepidermal water loss.

Table 3

A comparison of TEWL values according to the results of SSR test in the diabetic group.

Variables	DM group, N = 42			
	PAN, N = 22	Non-PAN, N = 20	Differences of means (95% CI)	P
TEWL, g/h/m^2				
Forearm	30.2 (10.5)	26.6 (3.7)	3.6 (−1.0, 8.2)	.117
Dorsal hand	35.6 (14.1)	30.2 (4.4)	5.4 (−0.6, 11.4)	.076
Mid-palm	57.4 (11.4)	59.0 (10.0)	−1.6 (−8.8, 5.5)	.643
Third finger	63.3 (18.0)	75.6 (14.2)	−12.2 (−23.1, −1.3)	.029*
Fibular head	30.6 (8.9)	33.3 (13.3)	−2.7 (−9.6, 4.2)	.436
Dorsal foot	31.8 (11.6)	31.9 (8.8)	−0.2 (−7.1, 6.8)	.964
Mid-sole	43.4 (9.1)	49.3 (9.1)	−5.9 (−11.8, 0.1)	.049*
First toe	51.9 (14.4)	62.3 (14.1)	−10.4 (−19.7, −1.1)	.030*

Data are expressed as mean (standard deviation) unless otherwise indicated. *P* values were calculated using Student *t* test. CI = confidence interval, DM = diabetes mellitus, PAN = peripheral autonomic neuropathy, TEWL = transepidermal water loss.

* $P < .05$.

Table 5

Correlations of age and diabetic duration with the TEWL variables.

Variable	Correlation coefficient, r		
	DM group, N = 42		Control group, N = 43
	Age	Diabetic duration	Age
TEWL, g/h/m^2			
Forearm	0.001	0.067	−0.415**
Dorsal hand	−0.041	−0.088	−0.335*
Mid-palm	0.021	−0.244	−0.185
Third finger	0.018	−0.145	−0.242
Fibular head	−0.143	0.028	−0.378*
Dorsal foot	−0.145	−0.130	−0.278
Mid-sole	−0.145	−0.136	−0.084
First toe	−0.024	−0.039	−0.252

Data are expressed as coefficient (*r*) by Pearson correlation test. DM = diabetes mellitus, TEWL = transepidermal water loss.

* $P < .05$.

** $P < .01$.

because it has been reported that PAN symptoms are significantly associated with abnormal SSR findings in the limbs of patients with DPN.[3,8] Moreover, a previous study reported that the TEWL values are mutually connected with cutaneous microcirculatory function and various autonomic nervous activities in healthy adults.[29] However, there have been no clinical or laboratory trials conducted to date investigating the pathophysiologic mechanisms of and the relationship between skin barrier function and sudomotor dysfunction. In line with results from previous studies,[30,31] we found that the TEWL values measured in most of the body regions we considered showed negative correlations with age in the control group. However, we could not find any relationship between the TEWL value and the duration of diabetes. This lack of a connection may be because the duration of DM was not evenly distributed and was mostly chronic in our study population.

This study has several limitations. First, we relied on the patients' SSR test results without recording additional clinical symptoms when identifying participants to include in the PAN subgroup. Although abnormal SSR test results have been reported to be associated with major PAN symptoms, it may be difficult to generalize the diagnosis of PAN only according to the results of SSR testing. Second, we did not distinguish the severity of DSPN in the different included participants when we established the DSPN subgroup after the completion of the NCS. Third, there was no attempt to quantify the duration of sunlight exposure, amount of water intake, other diabetic complications, or medication use (insulin, diuretics, etc.) before the skin measurements, although it is known that these factors may affect skin barrier function. Moreover, it is recommended that the TEWL should be measured on 3 to 5 visits (ie, at different time points), with the average taken, to reduce bias. However, in this study, TEWL measurement was carried out only at the time of 1 visit, although 3 measurements at the same site were conducted. Finally, each participant's skin health was recorded only based on medical history without direct examination by experienced dermatologists. There could be a bias if the participants' dermatoses were not yet diagnosed or if the skin had a normal external appearance. For example, TEWL values measured on the uninvolved skin of patients with atopic dermatitis are generally higher than those of normal subjects.[32]

For the TEWL test to be a useful indicator for assessing the complications associated with sudomotor dysfunction, further research that utilizes QSART and considers major PAN symptoms is required to clarify the relationship between the skin permeability barrier function and PAN. Moreover, molecular biological work should be completed to investigate the process of biomechanical transduction in determining the presence and scope of alterations of cutaneous sudomotor functions.

Table 4

Comparison of TEWL values according to the presence of DSPN in the diabetic group.

Variables	DM Group, N = 42			
	DSPN, N = 27	Non-DSPN, N = 15	Differences of means (95% CI)	P
TEWL, g/h/m^2				
Forearm	30.4 (11.4)	27.3 (4.5)	3.1 (−2.3, 8.5)	.245
Dorsal hand	34.7 (14.4)	32.6 (8.4)	2.1 (−5.3, 9.5)	.574
Mid-palm	57.5 (11.9)	58.4 (9.7)	−0.9 (−7.7, 5.9)	.789
Third finger	64.3 (19.2)	71.4 (15.2)	−7.1 (−18.0, 3.8)	.195
Fibular head	30.8 (9.7)	32.5 (11.6)	−1.6 (−8.3, 5.0)	.625
Dorsal foot	32.0 (12.7)	31.7 (8.0)	0.3 (−6.4, 7.0)	.925
Mid-sole	43.7 (9.5)	47.5 (9.3)	−3.8 (−9.6, 2.1)	.197
First toe	51.9 (13.2)	59.6 (16.1)	−7.7 (−16.9, 1.4)	.096

Data are expressed as mean (standard deviation) unless otherwise indicated. *P* values were calculated with Student *t* test. CI = confidence interval, DM = diabetes mellitus, DSPN = diabetic sensorimotor polyneuropathy, TEWL = transepidermal water loss.

* $P < .05$.

5. Conclusion

As a noninvasive bioengineering method, TEWL measurement is useful for the quantitative evaluation of the water evaporation rate of the skin of patients with diabetes. The findings of this study suggest that the predisposition of patients with diabetes to skin complications may be the result of the impaired water permeability barrier function of their skin at baseline and is due, in part, to impairment in the peripheral sympathetic nervous system rather than peripheral sensorimotor denervation.

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