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ORIGINAL ARTICLE

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Can a handheld device accurately measure barrier function in ichthyoses?

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Abstract

Background: Transepidermal water loss (TEWL) is a surrogate measure of skin barrier dysfunction. Historically, devices that measure TEWL are expensive, complex, and require connection to a computer and energy source. Consequently, measurement of skin's TEWL has been limited to the research setting.

Objectives: Evaluate the accuracy of the handheld device gpskin Barrier Light® in comparison with a standardly used device, AquaFlux AF200®, for measuring TEWL.

Methods: Transepidermal water loss measurements by gpskin Barrier Light® and AquaFlux AF200® in ichthyotic and healthy skin were compared.

Results: AquaFlux AF200® TEWL readings were consistently higher than those from gpskin Barrier Light®. In the pooled cohort, TEWL values were strongly correlated and both devices had excellent reliability. When subjects and controls were examined separately, there was moderate correlation between devices, with stronger agreement at higher TEWL values.

Limitations: Transepidermal water loss was determined at one time point. There is no formally established industry standard TEWL-assessing device.

Conclusion: Although gpskin Barrier Light® and AquaFlux AF200® devices cannot be used interchangeably, correlation in measuring TEWL was strong in patients with skin disease. This finding suggests that the low-cost, handheld device can accurately capture change in TEWL to track disease improvement.

KEYWORDS

epidermis, ichthyosis, measurement, skin barrier, transepidermal water loss

1 | INTRODUCTION

Transepidermal water loss (TEWL) is a noninvasive biomarker for epidermal barrier integrity. TEWL has been a useful measurement in clinical trials for potential new therapies.[1,2] However, its incorporation into objective assessments in the clinic setting has been limited by the size and cost of most currently available devices, including the AquaFlux AF200® ("AquaFlux") unit (Biox Systems, LTD), which is most often used by researchers to measure TEWL. A pocket-sized, lightweight device has recently become available, the gpskin Barrier Light® ("gpskin") (gpower, Inc), which transmits data using Bluetooth, costs much less than traditional devices, and does not require an equilibration period before use.

The ichthyoses are a group of genetic disorders characterized by scaling, skin thickening, and cutaneous inflammation, which are thought to represent responses to the epidermal barrier abnormality.[3]

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As such, measurement of barrier function would be a desirable objective marker of severity that could be tracked serially during treatment with over-the-counter and prescription products. In this study, we compared TEWL measurements using the AquaFlux and gpskin devices in the subjects with ichthyosis and healthy controls.

2 | METHODS

In this prospective cross-sectional study, all ichthyosis subjects were enrolled at the Foundation for Ichthyosis and Related Skin Types family conference on June 30, 2018. Subjects >18 years of age and parents (if a pediatric subject) provided written informed consent, while children >12 years provided written assent, approved by Institutional Review Board of the Ann and Robert H. Lurie Children's Hospital of Chicago. Inclusion criteria included: (a) diagnosis of ichthyosis other than ichthyosis vulgaris, verified clinically (by Dr Paller) or, for sex- and age-matched healthy controls, lack of inflammatory skin or systemic disease; (b) 1-70 years of age; and (c) volar forearm skin that was representative of overall skin. Exclusion criteria were as follows: (a) personal history of atopic dermatitis or any other skin disorder that could affect barrier function; (b) exposure to systemic immunosuppressants in the month prior to the study; and (c) exposure to topical immunosuppressant therapy in the week before the study. Given the need for recurrent emollient use in this population and the study's focus on comparison of two devices at the same site, emollient use within 24 hours was not considered an exclusion criterion; however, data about duration since last use were collected.

Demographic information was collected, and patients (or parent if under 8 years of age) were asked to rate the severity, based separately on erythema and scaling, each with a 5-point Likert scale (0-4). A single trained investigator (Dr Murphrey) with assistance (Dr Paller) serially obtained TEWL readings on two successive days using the AquaFlux and gpskin devices.[4] Three serial TEWL readings were taken at non-overlapping locations on the volar arm to allow for calculation of means and to assess test-retest reliability for each device. The order of device use was alternated in each successive subject (ie, AquaFlux assessment performed first in every other subject) to avoid the potential influence of order of assessment. Ambient temperature was 20-22°C, and ambient humidity was 23%-26%.

Statistical analysis utilized SPSS version 25 (SPSS Inc) (2-sided type I error rate of 5%). Ichthyosis and control characteristics were compared using Kruskal-Wallis and chi-square analyses. Spearman's correlation coefficients (r_s) were used for correlation analyses, and results were classified as very poor (<0.20), poor (0.20-<0.40), moderate (0.40-<0.60), strong (0.60-<0.80), and very strong (0.80-1.0). Intraclass correlation coefficients (ICCs) were calculated using a mean-rating (k = 3), 2-way mixed effect model with absolute agreement. ICCs were considered as: poor (<0.50), moderate (0.5-<0.75), good (0.75-<0.90), and excellent (>0.90). Bland-Altman analyses were performed to assess for device agreement.

3 | RESULTS

3.1 | AquaFlux and gpskin have strongly correlated TEWL readings and excellent reliability in pooled analyses

Thirty subjects with ichthyosis and 25 age- and sex-matched controls were enrolled (Table 1). Age matching was achieved in groups of children and every 20 years of age in adults. The mean age for subjects with ichthyosis (29.6 years) and controls (33.2 years) was not significantly different ($P = .472$).

Overall, mean TEWL values were significantly higher with AquaFlux than gpskin. Readings from the two instruments were strongly positively correlated for the entire cohort (r_s = 0.743, $P < .001$) and moderately well correlated when analyzed separately for ichthyosis ($r_s = 0.518$, $P = .003$) and controls ($r_s = 0.536$, $P = .006$) (Figure 1). Bland-Altman analysis was performed to assess agreement between AquaFlux and gpskin (Figure 2), which was worse at higher TEWL values for gpskin. However, when the entire population was divided at the median of gpskin measurements, the correlation between gpskin and AquaFlux was better at the higher range (above the median, 9.7 $g/m^2/hr$; $r_s = 0.675$, $P < .001$) than below the median (r_s = 0.499, P = .008), although correlation was still moderate to strong with both devices. There were significant but moderate correlations between self-assessed severity and TEWL with both instruments (Aquaflux: $r_s = 0.401$, $P = .028$; gpskin: $r_s = 0.442$, $P = .015$).

In our combined cohort, both devices showed excellent test-retest reliability, with ICC = 0.984 [95% CI, 0.973-0.991] for

TABLE 1 Subject demographics

	Ichthyosis (N = 30)	Control (N = 25)	*P*-value
Age (years)			
Mean (SD)	29.6 (18.5)	33.2 (18.1)	.472
Median (range)	26 (3-70)	37 (4-62)	
≤18 yo (%)	10 (33)	8 (32)	
>18 yo (%)	20 (67)	17 (68)	
Sex, N (%)			
Male	12 (40)	10 (40)	>.999
Female	18 (60)	15 (60)	
Subtype, N (adults)/N (children)			
LI	5/ 1	N/A	
EI	5/ 6		
CIE	4/ 1		
NS	5/ 1		
EKV	0/ 1		
TTD	1/ 0		

Note: Abbreviations: CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; EKV, erythrokeratodermia variabilis; LI, lamellar ichthyosis; NS, Netherton syndrome; SD, standard deviation; TTD, trichothiodystrophy.

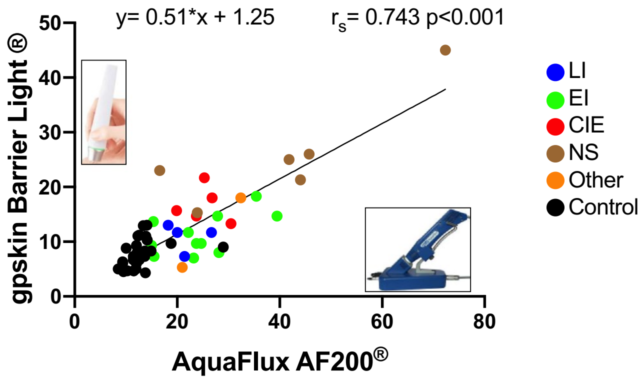

FIGURE 1 Spearman Correlation Coefficient Measurements Taken Using gpskin Barrier® vs AquaFlux AF200® in Subjects with Ichthyosis and Healthy Skin. Raw TEWL values are plotted for each instrument, with black dots control skin and colored dots ichthyosis skin subtypes (see Key). The associated linear regression equation is shown. R_s denotes the Spearman correlation coefficient, calculated using the rank order of measurements for each device, and shows strong correlation between the devices for the entire set. LI, lamellar ichthyosis; EI, epidermolytic ichthyosis; CIE, congenital ichthyosiform erythroderma; NS, Netherton syndrome. Others included ichthyosis with confetti, erythrokeratodermas, and trichthiodystrophy

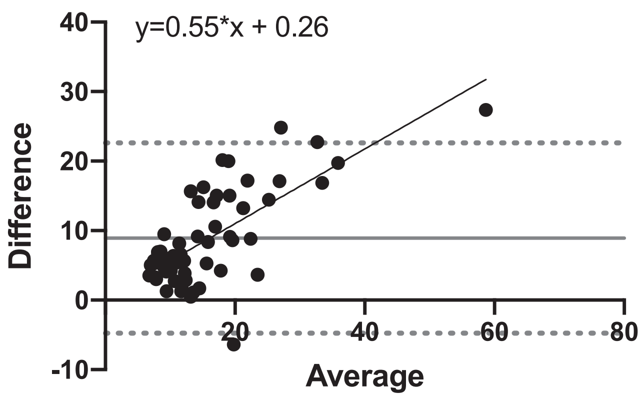

FIGURE 2 Bland-Altman Agreement Analysis for gpskin Barrier Light® vs AquaFlux AF200® for Subjects with Ichthyosis and Healthy Skin. The average TEWL measurements for gpskin Barrier Light® and AquaFlux AF200® were plotted against the difference of the mean gpskin Barrier LIght® measurement subtracted from the same subject's mean AquaFlux AF200® value. Linear regression equation is shown. At higher TEWL values (subjects with ichthyosis), the difference between gpskin Barrier Light® and AquaFlux AF200® is greater

AquaFlux and ICC = 0.974 [95% CI, 0.959-0.984] for gpskin. When the population was analyzed after sub-dividing into ichthyosis and controls, the ICC's remained excellent for subjects with ichthyosis (AquaFlux ICC = 0.976 [95% CI, 0.954-0.988], gpskin ICC = 0.974 [95% CI, 0.953-0.987]), and was good for controls (AquaFlux ICC = 0.816 [95% CI, 0.646-0.912], gpskin ICC = 0.868 [95% CI, 0.745-0.937]).

4 | DISCUSSION

Given the central importance of poor barrier function as the shared feature among ichthyoses,[5] the paucity of available tools to objectively measure barrier improvement in ichthyosis, and the opportunity to measure TEWL in the same room at the same time in ichthyosis patients and controls at a family conference, we chose to compare TEWL values in orphan forms of the ichthyoses. These results are particularly relevant to pediatric dermatologists, who frequently manage both adults and children with these orphan forms of ichthyosis.

Three types of devices have traditionally been used to evaluate TEWL: open-chamber, closed-chamber, and condenser-chamber devices. Open-chamber devices, such as the Tewameter TM300®, heavily depend on ambient conditions. Closed-chamber devices, such as VapoMeter SWL-2®, are independent of the environment but do not allow for continuous measurement. Condenser-chamber devices, including AquaFlux AF200®, depend on environmental conditions and thus require equilibration (although less than open-chamber devices), but allow for continuous measurement.[1] In a study by Farahmand et al[6], AquaFlux AF200® was more sensitive than Tewameter TM300® and VapoMeter®, including the effect of applied moisturizer and reduced barrier function after skin tape stripping. The gpskin Barrier Light® has a different structure as a pseudo-closed-chamber device. It incorporates a small hole in the closed-chamber, allowing for water evaporation that is independent of air pressure. This allows for continuous measurement and eliminates the need for equilibration. It costs approximately 1%-2% of AquaFlux AF200® and transmits readings to a smartphone via Bluetooth. Because equilibration is unnecessary, readings can quickly be performed in the clinic setting. Measurements require approximately 15 seconds, although 90 seconds, is required between readings (ie, 3.75 minutes for triplicate readings in a clinic room). In contrast, the AquaFlux AF200® consists of a handheld probe and a base unit requiring connection to a computer and outlet. Equilibration takes 20-30 minutes and each triplicate reading requires 60-75 seconds, although readings can be done serially without a pause.

Our study found TEWL measurements were strongly correlated between the handheld gpskin device and the Aquaflux in the pooled control and ichthyosis population. The gpskin TEWL measurements were consistently lower than those from AquaFlux, as shown by Bland-Altman analyses. These findings are consistent with the only previously published comparative reports of gpskin TEWL measurements, which compared gpskin vs AquaFlux[4] and gpskin Barrier Light® vs Tewameter dTM300®,[7] both in healthy adult skin. Our Bland-Altman data suggest that the agreement between AquaFlux AF200® and gpskin Barrier Light® readings is less at higher TEWL values, which parallels the greater differences found by Grinich et al[4] in lesional vs nonlesional atopic dermatitis skin. However, at higher vs lower values of the overall cohort, the Spearman correlation was similar between the two instruments. This finding supports the utility of these devices in individuals with skin disease and higher TEWL levels.

Collecting TEWL measurements serially at the same location in the same individual on the same day carefully controlled environmental conditions; however, the previous use of emollients was a factor that could not be controlled. This potential limitation was likely negated by testing TEWL in parallel with both devices on skin treated identically with emollient. However, data on emollient use prior to the readings were collected. Few controls (5/25 or 20%), but most ichthyosis subjects (24/30 or 80%), had applied emollient during the previous 12 hours, consistent with the need for frequent and recurrent emollient use within the ichthyosis population. The mean time since last emollient use for ichthyosis was 8 hours (median time, 5 hours; range: 20 minutes to >24 hours). Although not relevant to our comparisons, the question of the impact of emollient use on TEWL remains. Of note, another limitation is the lack of formally established industry standards for barrier devices, including the AquaFlux AF200®.

The gpskin device's low cost, ability to evaluate TEWL independent of environment, and easy-to-use functionality highlight the potential utility of this device in the clinic. TEWL instruments have typically not been used in daily clinical practice, given the expense and difficulty of the devices, and have been reserved for research settings. TEWL measurements at clinic visits would provide an objective measure of treatment impact on the skin's barrier function to complement visual clinical changes, not only for ichthyosis but also for other skin disorders with inherent barrier abnormalities. Additionally, the commercial availability of an environment-independent handheld device enables TEWL readings at home between office visits.

In summary, the availability of an affordable, pocket-sized device that correlates well with the frequently used AquaFlux AF200® allows the capture of objective data for patients with skin disease, adding to the objective skin severity measurements and patient-reported outcomes for ichthyoses and other skin disorders with impaired barrier function. Future studies should address the value of gpskin Barrier Light® measurements in longitudinal interventional studies, the impact of emollient use at different times before measurement on TEWL, and serial measurements of TEWL in studies with serial tape stripping (TEWL area under the curve/AUC measurements).

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REFERENCES

1. Alexander H, Brown S, Danby S, Flohr C. Research techniques made simple: transepidermal water loss measurement as a research tool. *J Invest Dermatol*. 2018;138(11): 2295-2300.e1.
2. Akdeniz M, Gabriel S, Lichterfeld-Kottner A, Blume-Peytavi U, Kottner J. Transepidermal water loss in healthy adults: a systematic review and meta-analysis update. *Br J Dermatol*. 2018;179(5):1049-1055.
3. Elias PM, Williams ML, Holleran WM, Jiang YJ, Schmuth M. Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism. *J Lipid Res*. 2008;49(4):697-714.
4. Grinich EE, Shah AV, Simpson EL. Validation of a novel smartphone application-enabled, patient-operated skin barrier device. *Skin Res Technol*. 2019;25(5):612-617.
5. Elias PM, Williams ML, Feingold KR. Abnormal barrier function in the pathogenesis of ichthyosis: therapeutic implications for lipid metabolic disorders. *Clin Dermatol*. 2012;30(3):311-322.
6. Farahmand S, Tien L, Hui X, Maibach HI. Measuring transepidermal water loss: a comparative in vivo study of condenser-chamber, unventilated-chamber and open-chamber systems. *Skin Res Technol*. 2009;15(4):392-398.
7. Ye L, Wang Z, Li Z, Lv C, Man MQ. Validation of GPSkin Barrier® for assessing epidermal permeability barrier function and stratum corneum hydration in humans. *Skin Res Technol*. 2019;25(1):25-29.

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