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Validation of a novel patient-operated device for measuring skin barrier function in atopic dermatitis

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GPower provided devices for this study.

Abstract

Background: Transepidermal water loss (TEWL) and capacitance are used in atopic dermatitis (AD) trials to provide objective data on clinical change and response to therapy. Many barrier devices are costly, limiting their utility. GPSkin is a novel low-cost, patient-operable device that measures both TEWL and capacitance via smartphone application.

Objective: This validation study investigated the correlation of GPSkin with the AquaFlux and Corneometer, and the reliability of these devices, in patients with AD.

Methods: Fifty AD patients with varying disease severity performed self-measurements with GPSkin, while investigators collected data with all 3 devices, on both nonlesional and lesional skin.

Conclusion: GPSkin and AquaFlux demonstrated strong correlation for TEWL on nonlesional and lesional skin by Spearman's correlation (r_s), independent of device user. For capacitance, GPSkin and the Corneometer showed moderate correlation when obtained by patients, yet a strong correlation when obtained by a clinician. Despite good correlation, GPSkin showed poor agreement with both the AquaFlux and Corneometer in Bland-Altman plots. GPSkin underestimated both TEWL and capacitance. Overall, the devices had good test-retest reliability. None of the devices could discriminate between AD severity states. While GPSkin marks an exciting advancement in barrier technology, further study is needed for validation on AD skin.

KEYWORDS

agreement, atopic dermatitis, barrier, capacitance, correlation, hydration, transepidermal water loss

1 | INTRODUCTION

Skin barrier measurements such as transepidermal water loss (TEWL) and surface capacitance provide objective information to clinicians regarding skin barrier integrity and functionality.[1,2] TEWL is a measure of epidermal permeability,[2] while surface capacitance provides information about stratum corneum (SC) hydration. Both TEWL and capacitance measurements are abnormal in atopic dermatitis (AD), with an increase in TEWL and decrease in capacitance. Previous barrier studies demonstrated elevated TEWL values on both lesional and nonlesional AD skin,[3] with the degree to which TEWL was increased correlating with disease severity.[4] Capacitance (often referred to as hydration or SC hydration) was also decreased on both lesional and nonlesional skin in patients with AD.[5] Clinical

trials often utilize TEWL and capacitance to monitor disease activity and response to interventions.[6-8]

Common devices used to measure TEWL and capacitance are expensive and bulky, with some requiring intricate calibration before use. These features have limited barrier measurement studies to academic centers and tertiary care facilities with properly trained research staff. GPSkin, created by GPower, is a low-cost, non-invasive skin barrier device designed to be patient-operable. The novel, compact device functions via Bluetooth to a smartphone application.

In a previous study, GPSkin was tested on healthy, non-inflammatory skin and was found to have moderate correlation with standard devices for measuring both TEWL and capacitance. The device also demonstrated "good" test-retest reliability, with no statistically significant difference between patient and investigator device use, suggesting that GPSkin may allow for skin barrier monitoring by patients in their home.[9] The objective of this study was to evaluate the validity of the GPSkin device in measuring lesional and nonlesional skin of patients with AD and to determine whether it can discriminate between varying degrees of AD disease severity.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective cross-sectional validation study was conducted at a single institution. Participants were patients 18 years of age and older with atopic dermatitis (n = 50) confirmed by a dermatologist at the Oregon Health & Science University Dermatology Department (Oregon, USA). The Institutional Review Board approved this study and informed consent was obtained for all participants.

The study dermatologist assessed AD severity via the Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD™), which includes clear, almost clear, mild, moderate, and severe options.[10] Patients assessed their own disease severity via a Patient Global Assessment (PtGA) scale in which they were asked, "Thinking of all the ways atopic dermatitis/eczema affects you, how would you rate your atopic dermatitis/eczema today?" and then presented with the following options: clear, almost clear, mild, moderate, and severe.

Transepidermal water loss and capacitance measurements were measured on the volar forearm. The volar forearm was selected as it has been a standard site in previous barrier studies and demonstrates comparable reactivity and baseline measurements to many other body regions.[11] Device probes were held perpendicular to the skin surface.

The GPower GPSkin device was compared against two frequently used devices: the Biox AquaFlux, which measures TEWL, and Courage-Khazaka Corneometer, which measures capacitance (Figure 1). GPSkin measures both TEWL and capacitance simultaneously. Measurements were collected on both nonlesional and lesional skin of patients with AD. For patients with a vIGA of "clear," only nonlesional measurements were collected.

Patients were provided general GPSkin device education and then self-collected measurements with GPSkin during the same visit. Investigators obtained measurements with the AquaFlux and the Corneometer. Two measurements were collected per device-user pair, with subsequent measurement on adjacent, non-overlapping skin immediately following the previous measurement.

2.2 | The devices

2.2.1 | Biox AquaFlux

The Biox AquaFlux AF 200 Evaporimeter is a closed chamber condenser system that measures TEWL. The condenser generates a low humidity region within the chamber relative to the specimen being measured. Moisture from the chamber atmosphere is sequestered onto the condenser and crystallized into ice, leaving an area of relatively lower humidity in the main chamber region. The probe is placed against the skin and water vapor passively diffuses from high to low humidity, from the skin toward the Biox AquaFlux chamber sensor. This process takes 30-90 seconds to generate a TEWL measurement.[12]

2.2.2 | Courage-Khazaka Corneometer

The Courage-Khazaka Corneometer CM 825 provides a high frequency (0.9-1.2 MHz) capacitance measurement of a dielectric skin medium. The Corneometer measures a dielectric constant, which is reported in arbitrary Corneometer units of 0-120. This dielectric constant is sensitive to alterations in moisture content, which is what allows the capacitance measurement to act as a surrogate for SC hydration.[13,14]

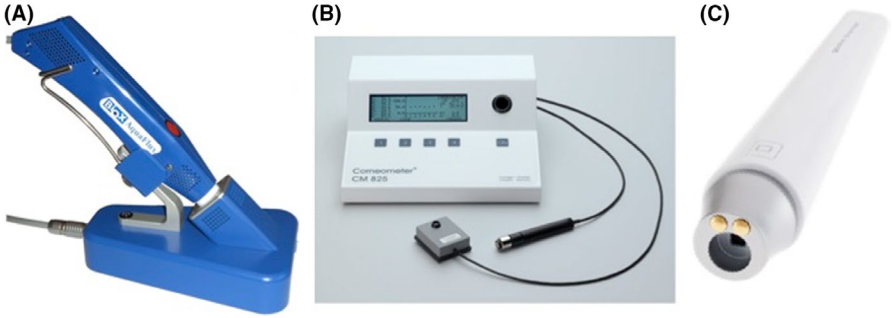

FIGURE 1 Study devices. (A) Biox AquaFlux AF200 measures TEWL, (B) Courage-Khazaka Corneometer CM 825 measures capacitance and (C) GPower GPSkin measures both TEWL and capacitance. TEWL, Transepidermal water loss

2.2.3 | GPower GPSkin

The GPower GPSkin device measures both TEWL and capacitance. GPSkin has a pseudo-closed chamber system for TEWL measurements. Similar to a closed chamber system, the novel pseudo-chamber provides a small degree of chamber ventilation to decrease humidity and pressure. Capacitance is measured by two sensors on the outer edge of the probe and follows the similar technological principles as the Corneometer. Additional details on probe configuration remain proprietary at this time.

Both TEWL and capacitance measurement data are transmitted via Bluetooth to the GPSkin smartphone application where data may be accessed and analyzed.[15] GPSkin is currently being used for investigative purposes only and is not yet FDA approved.

TABLE 1 Patient Demographics

Age in years, mean (standard deviation)	**29.0 (16.6)**
Gender, n	
Male	20
Female	30
PtGA, n	
Clear	2
Almost clear	8
Mild	14
Moderate	16
Severe	10
vIGA-AD™, n	
Clear	2
Almost clear	8
Mild	6
Moderate	24
Severe	12

2.3 | Controlling for variables

Transepidermal water loss and capacitance are sensitive to several external variables including emollients, hygiene habits, and ambient room conditions.[11,16] External variables were controlled for as best as feasibly possible during this study, with room temperature maintained at 20-22°C and a humidity range of 30%-50%. Within these ranges, skin temperature will not greatly impact measurements and perspiration is unlikely.[11] Patients participated in the study after scheduled clinic appointments to allow for maximal acclimation to the study environment (at minimum 10-15 minutes). The microclimate of the skin surface is also sensitive to changes in water vapor, so patients could not use emollients or bathe for 6 hours prior to study participation.

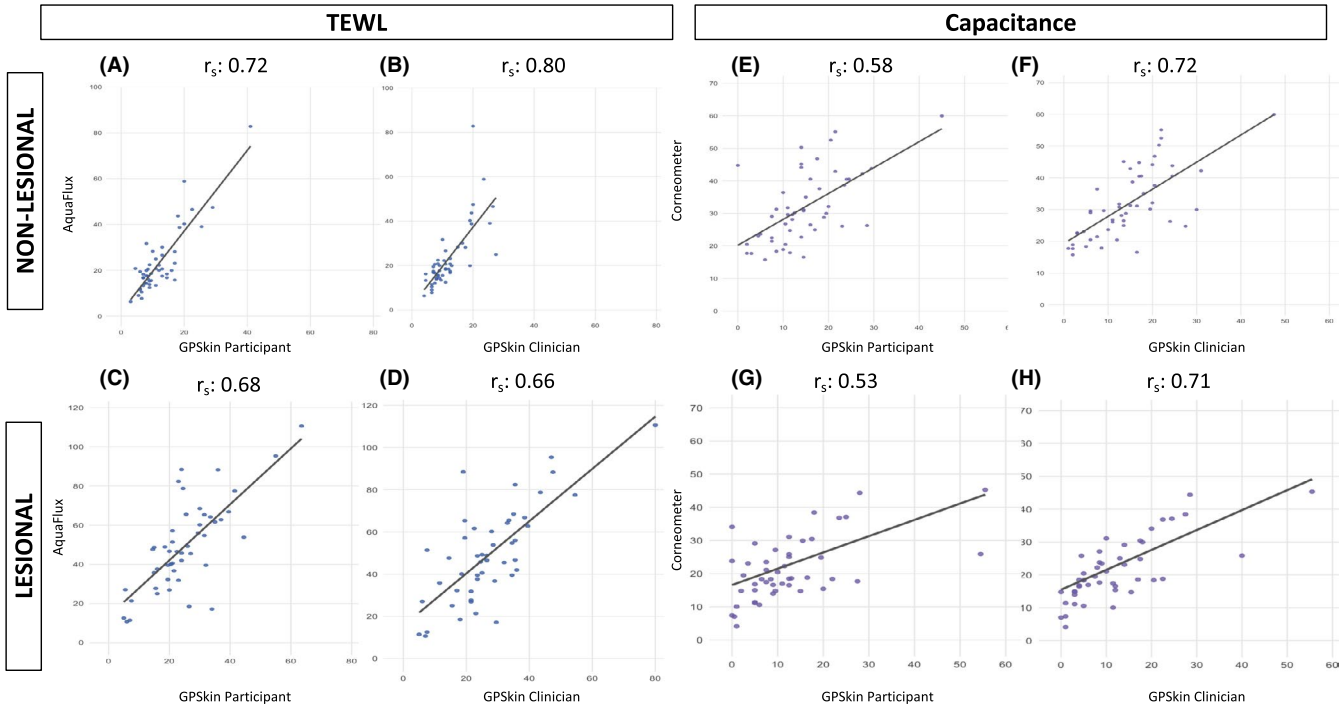

FIGURE 2 Spearman correlation coefficients (r_s) for GPSkin versus standards. GPSkin was tested against the AquaFlux to measure TEWL (A, B, C, D) and the Corneometer to measure capacitance (E, F, G, H) on both nonlesional (top row, A, B, E, F) and lesional (bottom row, C, D, G, H) skin in patients with AD. Both patients (A, C, E, G) and investigators (B, D, F, H) collected measurements with GPSkin. Plot line estimated using linear regression. $P < .001$ for all r_s values. R_s are interpreted as follows: 0.00-0.19 very weak, 0.20-0.39 weak, 0.40-0.59 moderate, 0.60-0.79 strong, and 0.80-1.0 very strong.[18] AD, atopic dermatitis; TEWL, Transepidermal water loss

2.4 | Statistical analysis

Primary outcomes were TEWL and capacitance measurements on atopic skin. Two repeated measurements were collected for each device-user pair. The devices' test-retest reliability was assessed using the repeated measurements and intraclass correlation coefficients (ICCs) calculated via a two-way mixed effect model, with absolute agreement. The ICCs were classified as "poor" (<0.50), "moderate" (0.50-0.75), "good" (0.75-0.90), or "excellent" (>0.90).[17] In all subsequent analyses, the repeated measurements were averaged to create a single value for each device-user pair, and Spearman's rank correlation coefficients (r_s) were used to determine the correlation between measurements from related devices (GPSkin and AquaFlux; GPSkin and Corneometer). R_s were classified as "very weak" (0.00-0.19), "weak" (0.20-0.39), "moderate" (0.40-0.59), "strong" (0.60-0.79), or "very strong" (0.80-1.0).[18] Bland-Altman plots were used to visually assess the agreement and discern any systematic differences between the related devices. One-way ANOVA was used to test differences in mean TEWL and capacitance measures between patients grouped by disease severity. Statistical analysis was performed using R: a language and environment for statistical computing.[19]

3 | RESULTS

3.1 | Correlation and agreement

GPSkin was compared to the AquaFlux for TEWL and the Corneometer for capacitance on both lesional and nonlesional skin in patients with atopic dermatitis (n = 50; Table 1). GPSkin and the AquaFlux demonstrated strong correlation for TEWL values on both nonlesional and lesional skin for both patient ($r_{s\ nonlesional}$: 0.72, $r_{s\ lesional}$: 0.68) and clinician ($r_{s\ nonlesional}$: 0.80, $r_{s\ lesional}$: 0.66) obtained measurements. GPSkin and the Corneometer demonstrated moderate correlation for capacitance measurements when obtained by patients ($r_{s\ nonlesional}$: 0.58, $r_{s\ lesional}$: 0.53), while they had strong correlation when obtained by a clinician ($r_{s\ nonlesional}$: 0.72, $r_{s\ lesional}$: 0.71) (Figure 2).

Despite moderate-to-strong correlation coefficients, GPSkin demonstrated poor agreement with standard devices in Bland-Altman plots (Figure 3). The figures revealed that GPSkin consistently measured lower mean values for both TEWL and capacitance compared to the AquaFlux and the Corneometer, respectively, as indicated by the positive bias line (mean difference between measurements from GPSkin and the standard device) and by the mean values shown in Table 2. This underestimate was independent of device user or skin type. The discrepancy in GPSkin and standard devices was most significant at higher TEWL values (Figure 3A-D). Of note, there are no defined criteria for interpretation of limits of agreement for Bland-Altman plots; however, a greater proportion of values near the solid black bias line is considered good agreement.[20] The devices showed the best agreement for capacitance values on lesional skin (Figure 3G,H).

3.2 | Test-retest reliability

Two measurements were obtained for each device-user pair to allow for assessment of test-retest reliability via intraclass correlation coefficients (Table 3). Multiple ICCs were calculated for GPSkin measurements including analysis of $GPSkin_{patient\text{-}vs\text{-}patient}$, $GPSkin_{patient\text{-}vs\text{-}clinician}$, and $GPSkin_{clinician\text{-}vs\text{-}clinician}$. For TEWL, all GPSkin analyses had had

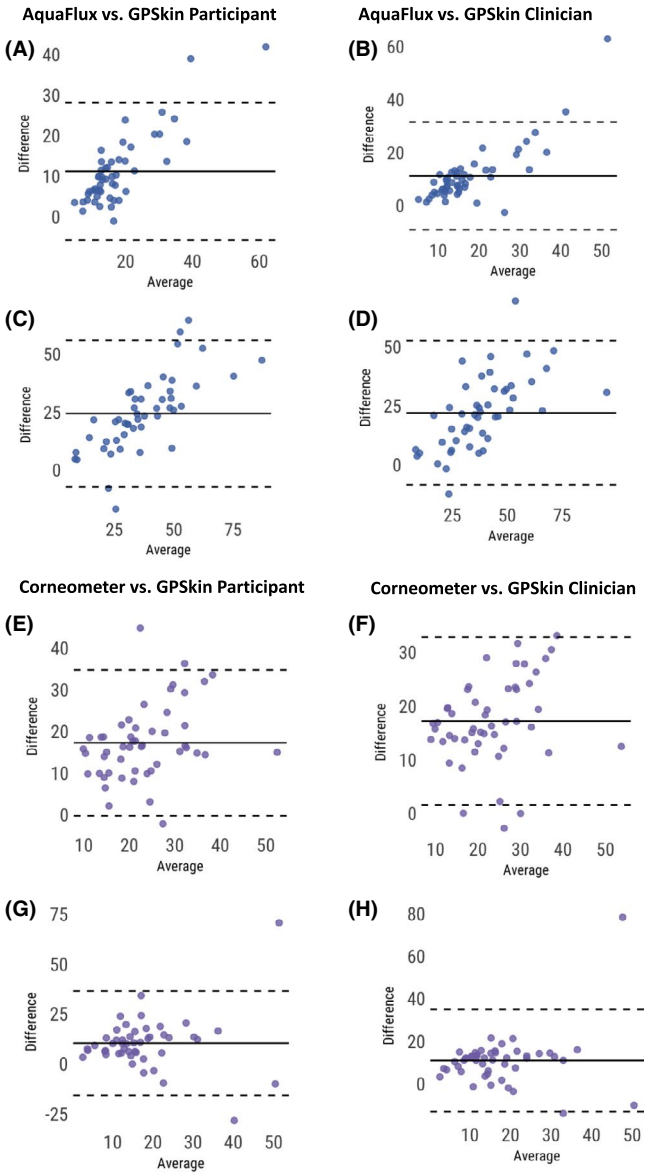

FIGURE 3 Bland-Altman agreement plots. Bland-Altman plots were used to assess mean difference between measurements from GPSkin and the standard device on both nonlesional (top row) and lesional (bottom row) skin. Mean values are plotted on *x*-axis, with difference between device measurements plotted on *y*-axis. The solid line shows bias, or mean difference between device measurements, while dotted lines represent the limits of agreement (ie, confidence interval).[20] Notably, at greater TEWL values, there is a greater difference between AquaFlux and GPSkin measurements, both on nonlesional (A and B) and lesional (C and D) skin. TEWL, Transepidermal water loss

TABLE 2 Mean TEWL and capacitance values

	Mean (± standard deviation)			
	GPSkin			
	Participant	Clinician	AquaFlux	Corneometer
TEWL (g/m^2h)				
Nonlesional	12.0 (7.1)	12.0 (6.3)	23.2 (14.3)	
Lesional	25.0 (13.0)	27.2 (14.4)	49.2 (24.1)	
Capacitance (AU)				
Nonlesional	14.6 (8.8)	14.7 (9.5)		31.8 (12.4)
Lesional	12.5 (12.0)	11.9 (11.5)		22.7 (13.9)

Abbreviation: TEWL, Transepidermal water loss.

TABLE 3 Device test-retest reliability via intraclass correlation coefficients[a]

	Nonlesional		Lesional	
	ICC (95% confidence interval)		ICC (95% confidence interval)	
Device User(s)	TEWL	Capacitance	TEWL	Capacitance
GPSkin Patient vs Patient	0.90 (0.83-0.94)	0.78 (0.64-0.87)	0.67 (0.48-0.80)	0.84 (0.74-0.91)
GPSkin Patient vs Clinician	0.71 (0.54-0.83)	0.77 (0.62-0.86)	0.80 (0.66-0.88)	0.83 (0.71-0.90)
GPSkin Clinician vs Clinician	0.78 (0.65-0.87)	0.77 (0.63-0.86)	0.79 (0.66-0.88)	0.73 (0.56-0.84
AquaFlux	0.90 (0.84-0.94)		0.76 (0.61-0.86)	
Corneometer		0.57 (0.35-0.73)		0.81 (0.68-0.89)

Abbreviation: TEWL, Transepidermal water loss.

[a]ICC interpretation: <0.50 poor, between 0.50-0.75 moderate, between 0.75-0.90 good, >0.90 excellent.[17]

good reliability on both nonlesional and lesional skin, except for $GPSkin_{patient\text{-}vs\text{-}patient}$ on nonlesional skin, which demonstrated excellent reliability (ICC: 0.90, confidence interval (CI): 0.83-0.94), and $GPSkin_{patient\text{-}vs\text{-}patient}$ on lesional skin, which demonstrated moderate reliability (ICC: 0.67, CI 0.48-0.80). The AquaFlux had excellent reliability on nonlesional skin (ICC: 0.90, CI: 0.84-0.94) and good reliability on lesional skin (ICC: 0.76, CI: 0.61-0.86).

For capacitance, analysis of $GPSkin_{patient\text{-}vs\text{-}patient}$, $GPSkin_{patient\text{-}vs\text{-}clinician}$, and $GPSkin_{clinician\text{-}vs\text{-}clinician}$ all demonstrated good reliability on both nonlesional and lesional skin, with the exception of $GPSkin_{clinician\text{-}vs\text{-}clinician}$ on lesional skin which had moderate reliability (ICC: 0.73, CI: 0.56-0.84). The Corneometer had moderate reliability for nonlesional skin (ICC: 0.57, CI: 0.35-0.73) and good reliability for lesional skin (ICC: 0.81, CI: 0.68-0.89).

3.3 | Discriminability by severity

Transepidermal water loss and capacitance measurements were obtained on AD patients with varying disease severity. The majority of patients had moderate AD by vIGA-AD™ (n = 24), followed by severe disease (n = 16), with fewer mild (n = 6), almost clear (n = 8), and clear (n = 2) patients. These numbers were similar to the PtGA scores, with the majority of patients reporting moderate disease (n = 16); however, a greater proportion of patients reported their AD as mild (n = 14) compared to the investigator (Table 1).

Transepidermal water loss and capacitance values were clustered by disease severity (with clear and almost clear grouped), assessed by vIGA-AD™, to assess if any of the devices could discern meaningful differences by severity (Figure 4). None of the 3 devices displayed a statistically significant difference between severities for TEWL or capacitance, or for lesional or nonlesional skin.

4 | DISCUSSION

In this study, we found GPSkin moderate-to-strongly correlated with current industry devices used to measure TEWL and capacitance. Agreement between the measurements from the devices,

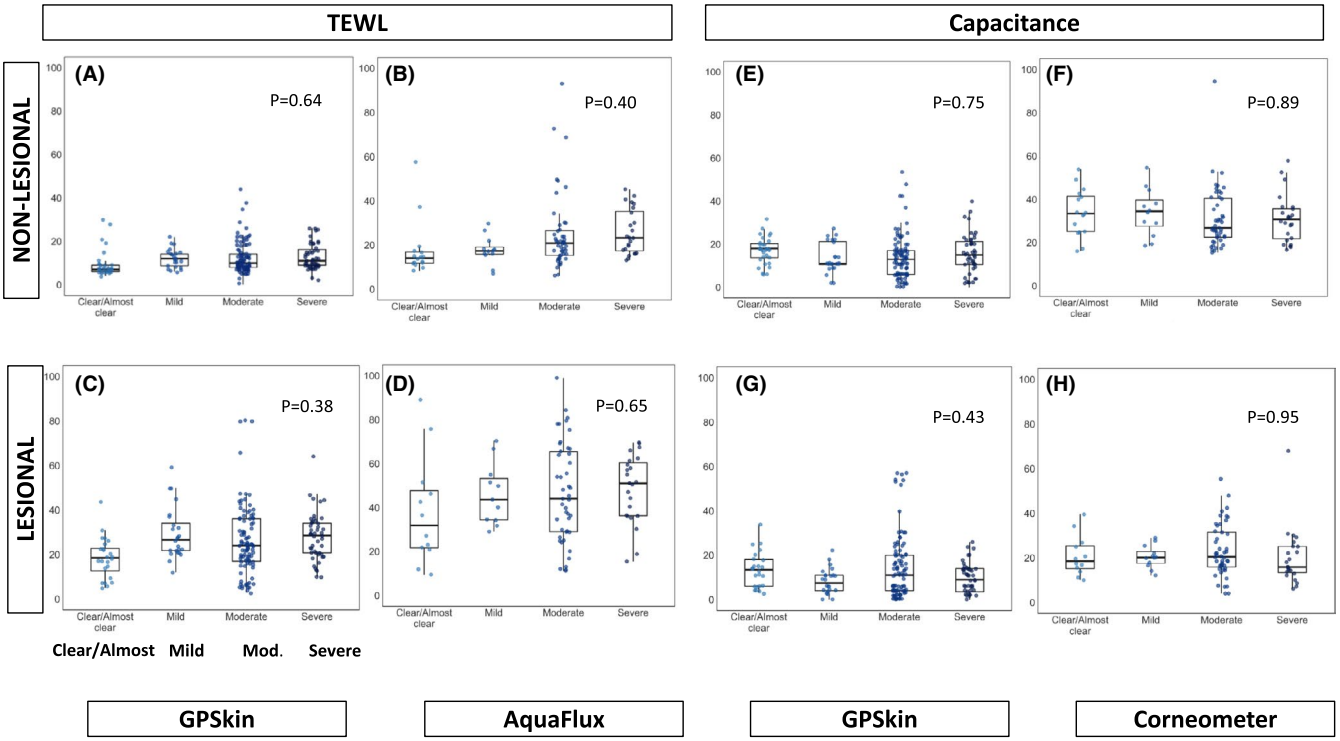

FIGURE 4 Device discriminability between severity groups. GPSkin (A, C, E, G), AquaFlux (B, D), and Corneometer (CM) (F, H) were tested on nonlesional (top row) and lesional (bottom row) skin with varying severities of AD by vIGA-AD™. Clear/almost clear patients were grouped for analysis. Neither GPSkin nor the standard devices were able to discern a statistically meaningful difference between severities on nonlesional or lesional skin. AD, atopic dermatitis

however, appeared poor. This highlights an important statistical concept: Correlation is expected when comparing items of similar measure (ie, two devices that capture the same measurement). Interpretation of correlation should take this into account, either with adjustment of the threshold for what is considered strong, and/or with assessment of agreement.[20] As described by Ranganathan et al, "Two sets of observations, which are highly correlated, may have poor agreement; however, if the two sets of values agree, they will surely be highly correlated." This was true here, with GPSkin well correlated with both the AquaFlux and the Corneometer, yet lacking good agreement with either via Bland-Altman analysis.

Both TEWL and capacitance measurements appeared to be underestimated with GPSkin compared to current devices. The discrepancy was greater, and most notable, at larger TEWL values. A similar phenomenon was observed in the earlier study conducted on healthy, non-inflammatory skin.[9] At that time, the underestimations were consistent and similar in value between TEWL and capacitance, suggesting a possible calibration issue that could be improved with software changes.[9] The underestimations observed here, in the second part of this study, likely require further investigation before GPSkin may be fully validated on atopic skin.

None of the three devices were able to discriminate between AD severities. Previous studies have shown a positive correlation between disease severity and TEWL values, and a negative correlation between disease severity and capacitance values. TEWL and capacitance values have been found to correlate with disease severity via the SCOring Atopic Dermatitis (SCORAD) instrument.[8,21] It is possible our findings were due to insufficient sample size in severity groups, particularly in the clear/almost clear (n = 10) and mild (n = 6) categories, as this study was not powered to examine these subgroups.

This study had several limitations. It was conducted at a single institution; there were single raters for both the Aqua Flux and the Corneometer measurements. Additionally, the AquaFlux and Corneometer were utilized as gold standards for comparison; however, there are no established industry standards for barrier devices.

5 | CONCLUSION

GPSkin marks an exciting advancement in skin barrier technology, with TEWL and capacitance capabilities in one device, and offering patient-operability, affordability, and an easy-to-use smartphone application interface. Additional validation studies are needed on atopic skin, possibly with larger sample size, to further examine agreement and correlation with disease severity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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