proach for Quantifying Atopic Dermatitis Severity Across Fitzpatrick Skin Types

Keywords: Atopic dermatitis (AD), Effective Corneocyte Topographical Index (ECTI), atomic force microscopy (AFM), Deep learning

1. Introduction

Skin barrier integrity is significantly dependent on the stratum corneum (SC). This outermost skin layer consisting of keratinocytes (also known as corneocytes) serves as the body's primary defense against environmental threats [1]. Disruptions to this barrier are key contributors to a wide range of dermatological conditions, including atopic dermatitis (AD) [2,3]. This chronic inflammatory skin condition, characterized by scaly, itchy, and erythematous skin lesions, affects approximately 101.27 million adults and 102.78 million children worldwide [4]. Early diagnosis and treatment may prevent significant morbidity resulting from symptoms manifestation and reduce the risk of secondary skin infections caused by Staphylococcus and Streptococcus species, which is an increasing concern due to rising antibiotic resistance [5-8].

Unfortunately, effective diagnosis and clinical assessment of AD are still lacking. Current diagnostic tools, such as SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index), evaluate visible sequelae of the disease but fail to capture microscopic changes in skin morphology that indicate early disease progression [9-11]. Moreover, EASI's reliance on visual indicators, particularly erythema, indicated imitations in diagnostic consistency across the Fitzpatrick skin spectrum (type I-VI, depending on the amount of melanin pigmentation in the skin) [12,13], especially in patients with higher Fitzpatrick skin types, thereby affecting the assessment's accuracy and reproducibility [14-17].

Building on these limitations, a major challenge in dermatological diagnostics remains the lack of objective and quantifiable methods for evaluating disease severity. [18-20]. Recently identified circular nano-size objects (CNOs) on corneocyte surfaces have emerged as groundbreaking morphological biomarkers. Unlike standard clinical diagnostic methods such as EASI or SCORAD, CNO-based AD assessments have been proposed to evaluate skin barrier function independently of Fitzpatrick scale variations [21,22].

The recently proposed Effective Corneocyte Topographical Index (ECTI) leverages state-of-the-art deep convolutional neural networks and spatial analysis algorithms to enhance the accuracy and robustness of CNOs density calculations for assessing AD severity. This approach provides a non-invasive and reproducible method delivering accurate and quantifiable analysis. [23,24]

This study aims to evaluate the performance of ECTI in quantifying AD severity across a diverse cohort of Taiwanese and Danish subjects with Fitzpatrick skin types II–V using high-speed dermal atomic force microscopy (HS-DAFM) to ensure scalable diagnostics for barrier-related skin disorders (see Figure 1).

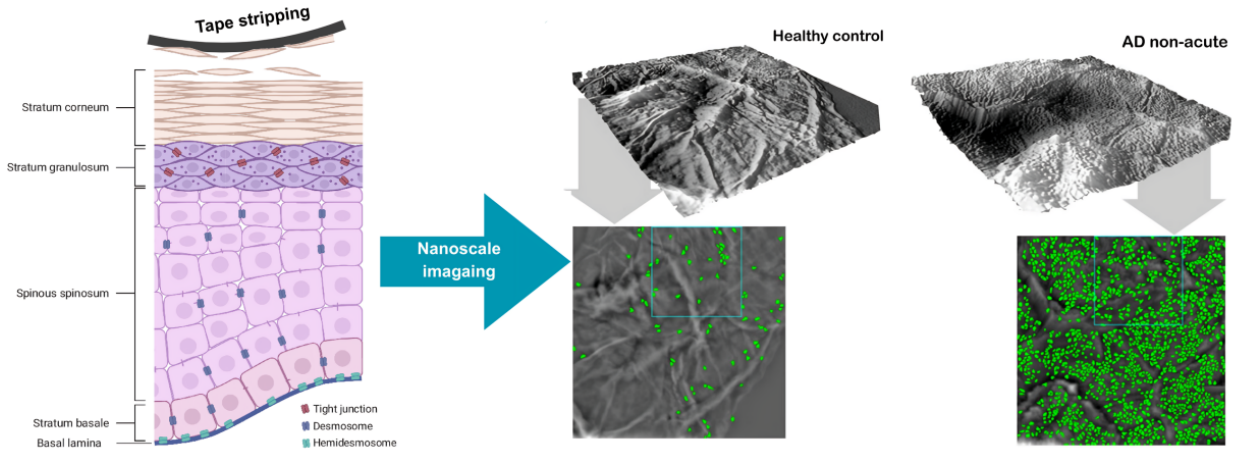


Figure 1. Schematic of tape stripping and nanoscale corneocyte imaging showing differences between healthy and AD skin.

2. Materials and Methods

Participant Recruitment and Sample Collection

This study included 45 AD patients and 15 healthy participants of Taiwanese origin, along with an equal number of participants of Danish origin. Samples in severely defective condition were excluded from the measurement. To ensure a comprehensive assessment of AD severity, SC samples were systematically collected from both lesional and non-lesional skin areas of each patient. Thus, a total of 105 SC samples were collected and analyzed from each country group.

All research subjects were adults (aged 18 years and above), spanned different ages and covered a broad spectrum of AD severities across Fitzpatrick scale (see Table 1). Participants were categorized by Fitzpatrick skin type and AD severity based on dermatologists' assessment. The SC sample was collected from the volar forearm area using a standardized tape-stripping procedure (D101, D-Squame; 1.54 cm²) [25], as shown in Figure 1. Each strip was applied for 10 seconds under a constant pressure of 225 g/cm² using a pressure device (D500, D-Squame; Clinical & Derm). Subsequently, each tape strip was carefully removed by tweezers and was then stored separately in sampling vials. The initial 2 strips were excluded to prevent potential contamination and skin surface impurities. The SC tapes designated for topography measurement with HS-DAFM were stored at room temperature.

Participants of the study were informed about its purpose and their data use and processing. Ethical standards were ensured by relevant institutional review board and required written informed consent to process with participation.

Table 1. Distribution of study participants according to Fitzpatrick skin type and AD severity. For each country, the collected samples were divided into four groups (G1–G4) based on AD severity, with 15 samples assigned to each group. AD severity was determined according to EASI scores: G1 (AD mild, EASI= 0.1–7.0), G2 (AD moderate, EASI = 7.1–21.0), G3 (AD severe, EASI > 21.0), and G4 (no AD history, healthy control group). The asterisk (*) denotes the defective samples that were excluded from the study.

Parti-cipants Group	Fitzpatrick Scale					AD Severity
	Type I	Type II	Type III	Type IV	Type V	
Denmark	-	6	7	2	-	Mild (G1)
	-	7	5	3	-	Moderate (G2)
	1*	3	4	6	1	Severe (G3)
	1	5	5	4	-	Control (G4)
Taiwan	-	2	4	5	4	Mild (G1)
	-	-	3	5	7	Moderate (G2)
	-	-	5	5	5	Severe (G3)
	-	2	4	9	-	Control (G4)
Total	**2***	**25**	**37**	**39**	**17**	-

High-Speed Dermal Atomic Force Microscopy and Dataset Generation

We used HS-DAFM in contact mode with an aluminium-coated silicon-nitride probe (CSC38/Al, 0.03 N/m, 8 nm tip radius; MikroMasch) to capture corneocyte nanotexture. The contact force was kept below 10 nN to ensure uniform conditions for image acquisition. Scanner calibration was performed using a 1 × 1 cm² DVD track layer [26] (740 nm period, 160 nm depth). For each SC sample, 10 randomly selected regions measuring 20 × 20 µm² were imaged at a resolution of 512 × 512 pixels resulting in over 2,000 corneocyte nanotexture images across both Danish and Taiwanese samples. The scan area was chosen to correspond with the typical dimensions of CNOs (273 nm in height, 305 nm in width) [21].

Corneocyte Nanotexture Analysis

To enhance visualization of subtle features and reduce environmental noise, AFM-acquired corneocyte images were preprocessed using Gaussian smoothing and row-wise mean subtraction to remove striping artifacts [27–31]. The images were normalized to a 0.0–1.0 range, and local contrast was enhanced using disk-shaped percentile filters (9 and 15 pixels), improving CNO visibility and facilitating the annotation process [32–34].

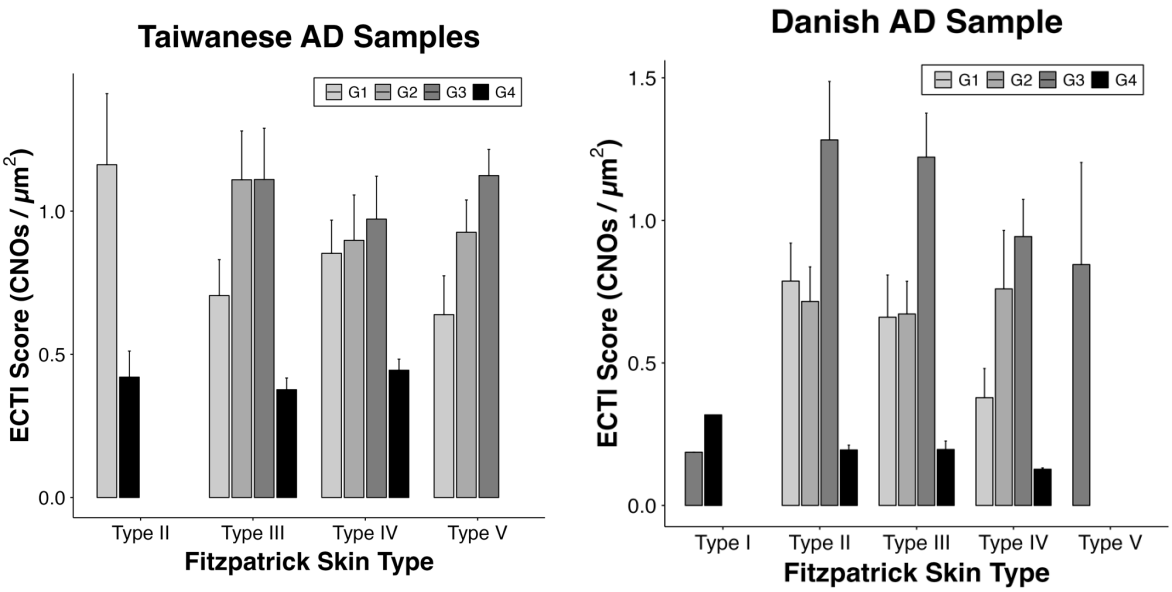
For automated detection, a YOLOv10-based [35] deep learning model was trained on a manually annotated dataset of 300 images (averaging ~250 CNOs per image; over 74,000 total annotations). Kernel density estimation (KDE) was subsequently applied to generate spatial density maps, revealing heterogeneous CNO distributions due to surface features like ridges and occlusions [23,35,36]. From these maps, the ECTI was computed as the mean CNO density derived from the central KDE layers, capturing the core distribution of surface nanotexture. The corneocyte nanotexture analysis was thoroughly described in the study by Wang et al. (2024) published in GigaScience [23].

3. Results

ECTI Scores Across Fitzpatrick Skin Types and AD Severity

A total of 210 SC tape samples, 105 from Taiwanese participants and 105 from Danish participants, were measured using HS-DAFM and analyzed by deep learning models to compute the ECTI. The ECTI scores were calculated to assess the relationship between corneocyte nanotexture and AD severity across various Fitzpatrick skin types (II–V).

As shown in Table 1, the data visualizes the distribution of Taiwanese and Danish participants across various Fitzpatrick skin types and their corresponding AD severity levels. The data highlights the number of participants within each group classified according to the severity of their AD, ranging from mild (G1) to severe (G3), along with a healthy control group (G4). The data shows an overall balance of severity levels within each skin type category, allowing for an evaluation of the ECTI scores across different Fitzpatrick skin types.



(a) **(b)**

Figure 2. (a) Correlation of ECTI with AD severity across Fitzpatrick skin type with Taiwan participants; **(b)** Correlation of ECTI with AD severity across Fitzpatrick skin type with Danish participants

Figure 2 (a) and (b) illustrate the trend of ECTI scores across various Fitzpatrick skin types for both Taiwanese and Danish participants. These graphs demonstrate a clear trend, as AD severity increases, the ECTI scores also increase. This indicates a correlation between the severity of AD and corneocyte nanotexture. It also revealed that the healthy control group (G4) consistently shows the lowest ECTI scores across all skin types, while the most severe AD groups (G3) show elevated scores.

4. Discussion

The results from both the Taiwanese and Danish cohorts show that individuals in the healthy control group (G4) were consistently associated with the lowest ECTI scores, while those in higher AD severity groups (G3) had the highest scores. Importantly, even within each Fitzpatrick skin type, the G4 group could still be clearly separated from the other severity groups. A steady increase in ECTI scores was also observed as AD severity increased within each skin type, showing a clear trend. These patterns are consistent across both Taiwanese and Danish cohorts which supports the usefulness of ECTI in assessing AD severity while remaining independent of Fitzpatrick skin type, validating the generalizability of ECTI as a reliable biomarker for AD severity across various skin pigmentation levels.

Unlike traditional diagnostic methods, such as SCORAD and EASI, which rely on the qualitative observation of symptoms, like erythema, ECTI provides non-invasive, quantitative measurements which are not affected by melanin content. This feature is particularly important for improving diagnostic accuracy across populations with diverse skin tones. The ability of ECTI to remain consistent across Fitzpatrick skin types highlights its potential as a universal diagnostic tool for dermatologists and clinicians managing AD. High-resolution AFM imaging of the corneocyte topography can deepen our understanding of microstructural skin changes associated with inflammatory conditions like AD. The HS-DAFM system enables detailed exploration of corneocyte nanotexture, providing a valuable tool for characterizing barrier function at the nanoscale.

Investigating skin nanotexture can provide valuable insights into the pathophysiology of AD, aiding in the early detection of barrier dysfunction and inflammatory changes, which then improves dermatological diagnostics and patient care. Future investigations could explore how such nanotextural features may contribute to broader diagnostic or treatment-monitoring applications across dermatology in clinical settings.

Although this study revealed valuable findings, some limitations should be considered when interpreting the results. The sample size across Fitzpatrick Types I and V in the Danish cohort were relatively small, which may affect the generalizability of the findings for these specific skin types. Furthermore, the Taiwanese cohort had no Type V healthy control group (G4) and had no participants with a Fitzpatrick skin Type I. These gaps in patient data restrict our ability to fully validate the consistency of ECTI scores at both ends of the skin tone spectrum, which remains a key area for future investigation. Expanding datasets to include more balanced representation of Fitzpatrick types from various countries will be critical for generalizing findings and developing standardized clinical applications.

5. Conclusion

This study reinforces the validity of the ECTI as a reliable biomarker for assessing AD severity across a wide range of Fitzpatricks skin types. By demonstrating consistent ECTI performance across both Taiwanese and Danish populations, this study demonstrates that ECTI provides consistent results regardless of Fitzpatrick skin type. These findings address a key limitation in current diagnostic tools, which often vary in effectiveness depending on skin tone. The ability of ECTI to provide objective and skin type-agnostic measurements support its integration into more inclusive dermatological assessments, contributing to improved care for individuals across diverse populations worldwide.

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