Title: Raster-scanning optoacoustic mesoscopy (RSOM) imaging as an objective disease severity tool in atopic dermatitis patients.

Short title: Optoacoustic imaging in atopic dermatitis.

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Funding Support

Authors would like to thank National Medical Research Council (NMRC) project, OFIRG 18 Nov-0101, for this study's funding support and Biomedical Research Council (BMRC), A*STAR, Singapore for the intramural funding support for some aspects of this study.

Conflict of Interest

Vasilis Ntziachristos: Equity ownership and advisory board member of iThera medical GmbH. The rest of the authors have no conflict of interest to declare.

Institutional Review Board Approval

This study was sanctioned by the Domain Specific Review Board (DSRB) of National Health Group, Singapore (Ref No. 2017/00932)

Manuscript Details

Word count: 498

References: 4

Figures: 2

Tables: 0

Keywords

atopic dermatitis; eczema; optoacoustic imaging, morphology, vasculature, objective scoring

Abbreviations

AD, atopic dermatitis; EVSI, Eczema vascular and structural index; ET, epidermal thickness; LHFR, the ratio of low and high frequency acoustic signal; OCT, optical coherence tomography; RSOM, raster scanning optoacoustic mesoscopy; SCORAD, Scoring AD; TBV, total blood volume; VD, vessel diameter in the dermis.

To the Editor:

Accurate assessment of disease severity in atopic dermatitis (AD) is important in monitoring response to treatment and guiding subsequent management. Current disease severity markers have limitations. Eczema Area Severity Index and Scoring AD (SCORAD) are observer-dependent[1], while skin biopsies are invasive. Recent studies have described the role of imaging in assessing AD severity, including optical coherence tomography (OCT).[2] This study evaluates the feasibility of raster-scanning optoacoustic mesoscopy (RSOM) imaging as an objective disease severity tool for atopic dermatitis. RSOM involves the detection of ultrasound waves generated in response to pulsed light illumination. Light absorbed by melanin results in thermo-elastic expansion, producing ultrasound waves which are then detected by transducers and reconstructed to form a three-dimensional image.[3]

This prospective study included 69 AD patients and 22 healthy volunteers. All AD patients were assessed by a dermatologist and all participants had RSOM imaging using RSOM Explorer C50 system (iThera Medical GmbH, Germany). From the RSOM images generated, epidermis thickness (ET), total blood volume (TBV), vessel diameter in the dermis and the ratio of low and high frequency signals (LHFR) in the dermis were computed (Supplementary File, Figure 1). We trained a linear kernel-based support vector machine model for eczema classification using ET, TBV and LHFR. A novel Eczema Vascular and Structural Index (EVSI) was formulated to assess eczema severity (Supplementary File, Methods).

This study cohort consisted of 24 females (26.4%) and majority (95.2%) were of Fitzpatrick skin types III – IV (Supplementary File, Table 1). 69 AD patients had SCORAD measured: 26 had mild AD, 33 had moderate AD and 10 had severe AD.

RSOM cross-sectional images of healthy and AD subjects (mild, moderate, severe) showed significant differences (Figure 1). The resultant EVSI could accurately differentiate between healthy and eczematous skin (Supplementary File, Figure 2) and also between the different severities, with at least $p < 0.05$. The Pearson's correlation coefficient between EVSI and SCORAD was 0.768 (Figure 2). Receiver operating characteristic curve of EVSI-based classification showed a solid evaluation of the trained model with area under the curve of 0.921, accuracy of 0.872, and high sensitivity and specificity values of 0.853 and 0.838 respectively (Supplementary File, Figure 3).

The strengths of RSOM-derived EVSI are that it is objective, has a short turn-around time and allows for repeated non-invasive measurements. Compared to OCT which has poor lateral resolution due to light scattering, RSOM detects ultrasound waves allowing for clearer distinction of vascular structures and the epidermal-dermal junction.[3,4]

One limitation of this study is that all subjects were of Asian descent and RSOM images are affected by the melanin content present. However, our previous study showed that melanin signal intensity derived from RSOM exhibited an excellent correlation with that obtained from a clinical colorimeter for subjects of varying skin phenotypes and hence specific imaging metrics could be derived.[3] Moreover, direct histopathological and RSOM imaging correlation has been previously demonstrated.[4]

RSOM provides a direct and objective assessment of the skin ultra-structures in a non-invasive manner and could be valuable in assessing AD severity.

Acknowledgements

Authors would like to thank National Medical Research Council (NMRC) project, OFIRG 18 Nov-0101, for this study's funding support and Biomedical Research Council (BMRC), A*STAR, Singapore for the intramural funding support for some aspects of this study. Acknowledgement also goes to Dr. Wong Chi Lok, Miss Lim Hann Qian and colleagues at Singapore Bioimaging Consortium (SBIC), A*STAR for their help in this study. Authors would also like to thank Dr. Yi Qiu and Dr. Katja Haedicke (iThera Medical GmbH) for their help in analyzing the RSOM images.

Figures

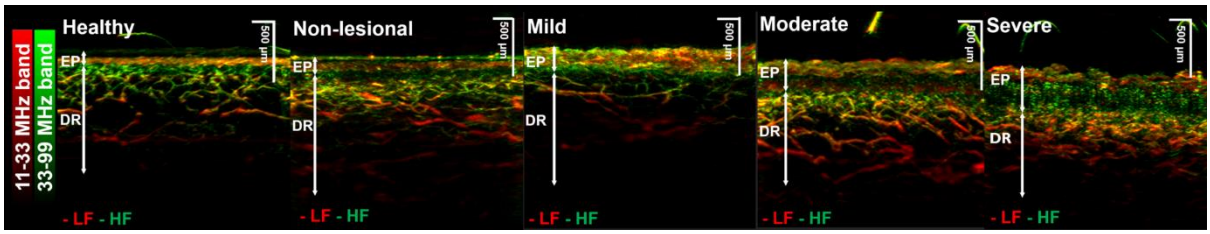

Figure 1. RSOM images of healthy and eczematous skin and quantitative analysis of specific metrics for varying AD severity. Representative cross-sectional RSOM images of varying eczema severities with the vertical white lines indicating the epidermal (EP) and dermal (DR) skin regions with low-frequency (LF) band in red and high-frequency (HF) band in green. The capillary loops extend from the epidermis and can be seen as the 'dot'-like structures in the moderate and severe images. All scale bars; 500 μm. In total 91 subjects with healthy controls (n = 22), non-lesional patch of eczema patients (n = 69), mild (n = 26), moderate (n = 33), and severe (n = 10) subjects.

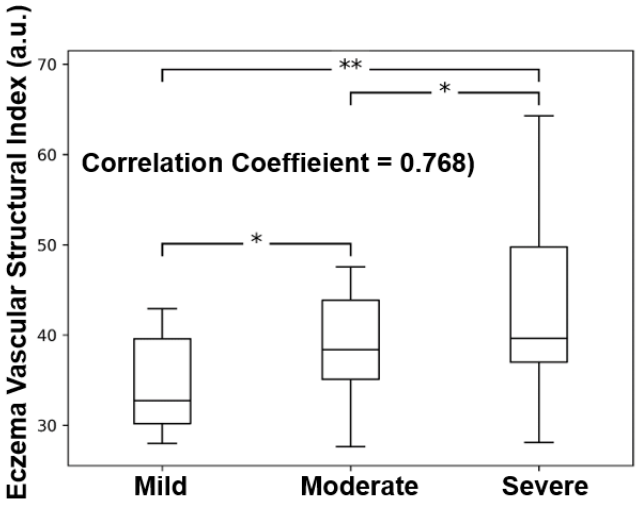

Figure 2. Eczema severity classified by EVSI corresponded with patients' clinical SCORAD scores (< 25 = mild, 25 ~ 50 = moderate and > 50 = severe), with Pearson's correlation coefficient of 0.768. The median value of EVSI in the moderate group was ~ 17% higher than

the mild group with $p < 0.05$, the severe group was ~ 5% higher than the moderate group with $p < 0.05$ and severe group was ~ 24% higher than the mild group with $p < 0.01$.

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