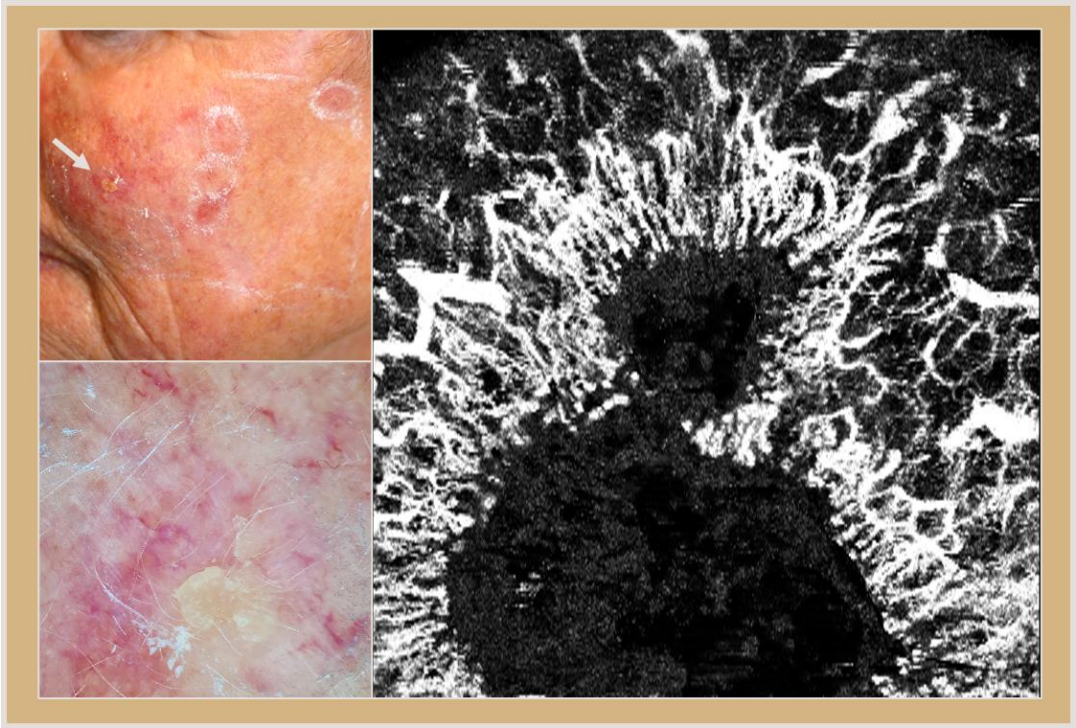
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

DEPARTMENT OF DERMATOLOGY
COPENHAGEN UNIVERSITY HOSPITAL, BISPEBJERG



PhD Thesis

Gabriella Fredman, MD

In-vivo assessments of actinic keratosis microvasculature with dynamic optical coherence tomography

Supervisor: Merete Haedersdal, Prof., MD, PhD, DMSc

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 30.06.2024.

SUMMARY

Actinic keratosis (AK) is a pre-malignant condition that often appears in sun-exposed areas with widespread preneoplastic changes known as field-cancerization. While most untreated AK remains chronic in immunocompetent patients, individual lesions have a low risk of developing into squamous cell carcinoma. In immunocompromised patients, the risk of malignant transformation is significantly higher. Guidelines recommend treatment of all lesions, as well as field-cancerized areas, for both patient groups. Since AK frequently requires repeated retreatment due to recurrent lesions, improved identification of treatment-resistant AK (trAK) is crucial for enhancing treatment decision-making.

The clinical evaluation of AK is challenging due to the absence of an objective assessment tool to guide treatment strategies. Lesions are typically classified from grade I to III based on clinically evaluated features. This method is subjective and shows low reproducibility in clinical studies. Recently, there has been a development of non-invasive diagnostic methods that adds the possibility to examine subsurface structures of trAK. Specifically, dynamic optical coherence tomography (D-OCT) has proven useful for assessment of the skin´s microvascularization. Based on vascular subsurface differences, D-OCT has enabled distinction between different types of skin cancer and their precursor lesions, including AK.

The aim of this thesis was to use D-OCT to identify blood vessel morphology in AK and quantify specific changes associated with the different clinical grades of AK I-III, comparing these findings to photodamaged skin (PD). Additionally, we investigated vascular differences between treatment-resistant and treatment-responsive AK after field-directed treatment with daylight photodynamic therapy (dPDT).

The qualitative assessments of D-OCT scans from AK I-III and PD skin (Study I), revealed that vascularization in all AK grades was more intense and disorganized compared to PD skin. These qualitative analyses revealed differences in vascular patterns and the direction of vessel growth, with vessels tending to configure towards the center of lesions and around follicle openings. Compared to dermatoscopy, D-OCT was particularly useful for differentiating between thin AK I and thick AK III based on qualitatively assessed vascular differences.

Combination of D-OCT with automated vascular quantification (Study II) provided similar results. The quantification of parameters related to total vessel length and density, as well as the number and structural characteristics of vessel branches, revealed an increased vascularization and disorganization of the vascular network in all AK grades compared to PD skin. These automated assessments overcame the challenge of visualizing the microvascular network in thick AK III by enabling subregional vessel analysis. These subregional analyses also demonstrated a correlation between AK thickness and increased and disorganized vascularization.

In Study III, D-OCT with automated vascular analysis was employed to investigate vascular differences between treatment-resistant and treatment-responsive AK undergoing dPDT treatment. These analyses unveiled the presence of an increased vascularization and disorganization of the vascular network in trAK at baseline compared to AK that responded well to treatment.

Overall, this thesis demonstrated that D-OCT can link clinical characteristics with underlying vascular changes in AK. Automated vascular assessments provide standardized analyses, making them a valuable supplement to AK evaluation in both clinical and research settings. Additionally, D-OCT demonstrates potential in identification of AK lesions that require additional treatment, which may enhance treatment stratification long-term outcomes.

DANISH SUMMARY

Aktinisk keratose (AK) er en præmalign tilstand, der ofte optræder i soludsatte områder med udbredte dysplastiske forandringer, kendt som field-cancerization. Selvom de fleste ubehandlede AK forbliver kroniske hos immunokompetente patienter, har individuelle læsioner en lav risiko for at udvikle sig til pladecellecarcinom. Hos immunsupprimerede patienter, er risikoen for malign transformation betydeligt højere. Retningslinjer anbefaler behandling af alle læsioner, samt områder med field-cancerization, for begge patientgrupper. Da AK ofte kræver gentagne behandlinger på grund af tilbagevendende læsioner, er forbedret identifikation af behandlingsresistente AK afgørende for at forbedre beslutningstagningen vedrørende behandling.

Den kliniske evaluering af AK er udfordrende på grund af manglen på et vurderingsværktøj til at vejlede behandlingsstrategier. Læsioner klassificeres typisk fra grad I til III baseret på klinisk evaluerede karakteristika. Denne metode er subjektiv og viser lav reproducerbarhed i kliniske studier. For nylig er der sket en udvikling af ikke-invasive diagnostiske metoder, der muliggør undersøgelse af hudens underliggende strukturer. Specifikt har dynamisk optisk kohærenstomografi (D-OCT) vist sig nyttig til vurdering af hudens vaskularisering. Baseret på vaskulære forskelle har D-OCT gjort det muligt at skelne mellem forskellige typer hudkræft og deres forstadier, inklusive AK.

Formålet med denne afhandling var at bruge D-OCT til at identificere blodkarmorfologi i AK og kvantificere specifikke ændringer forbundet med de forskellige kliniske grader af AK I-III, sammenlignet med fotobeskadiget hud (PD). Derudover undersøgte vi vaskulære forskelle mellem behandlingsresistente og behandlingsresponsive AK efter feltrettet terapi med dagslys fotodynamisk terapi (dPDT).

De kvalitative vurderinger af D-OCT-scanninger fra AK I-III og PD (Studie I) afslørede, at vaskulariseringen i alle AK grader var mere intense og uorganiseret sammenlignet med PD hud. Disse analyser afslørede forskelle i vaskulære mønstre og retningen af karvækst, hvor karrene havde tendens til at konfigureres mod midten af læsionerne og omkring follikelåbninger. Sammenlignet med dermatoskopi var D-OCT særligt gavnlig til at skelne mellem tynde AK I og tykke AK III baseret på kvalitativt vurderede vaskulære forskelle.

Kombinationen af D-OCT med automatiseret kvantificering af blodkar (Studie II) gav lignende resultater. Kvantificering af parametre relateret til den totale karlængde og densitet samt antallet og de strukturelle karakteristika af karforgreninger, påviste øget vaskularisering og desorganisering af det vaskulære netværk i alle AK grader sammenlignet med PD hud. Disse automatiserede analyser overvandt også udfordringen med at visualisere blodkar i tykke AK III ved at muliggøre subregional karanalyse. Disse subregionale analyser viste også en korrelation mellem AK-tykkelse og øget karintensitet og desorganisering.

I Studie III blev D-OCT med automatisk vaskulær analyse anvendt til at undersøge vaskulære forskelle mellem behandlingsresistente og behandlingsresponsive AK under dPDT behandling. Disse analyser afslørede en øget vaskularisering og desorganisering af det vaskulære netværk i behandlingsresistente AK ved baseline sammenlignet med AK, der reagerede godt på behandlingen.

Samlet set demonstrerede denne afhandling, at D-OCT kan koble kliniske karakteristika med underliggende vaskulære forandringer i AK. Automatiserede vaskulære vurderinger giver standardiserede analyser, hvilket gør dem til et værdifuldt supplement til AK evaluering i både kliniske og forskningsmæssige sammenhænge. Derudover viser D-OCT potentiale i identifikationen af AK læsioner, der kræver yderligere behandling, hvilket kan forbedre behandlingsstratificering og langtidsresultater.

LIST OF PAPERS

This thesis is based on the following scientific studies:

I	Dynamic optical coherence tomography unveils subclinical, vascular differences across actinic keratosis grades I-III[1]. *Resubmitted with minor revision, Experimental Dermatology.*
II	Vascular feature identification in actinic keratosis grades I-III using dynamic optical coherence tomography with automated, quantitative analysis[2]. *Arch Dermatol Res*. 2024;316(7):391.
III	Vascular characteristics of treatment-resistant and responsive actinic keratosis identified with dynamic optical coherence tomography[3]. *Manuscript in preparation.*

These manuscripts serve as the foundation of this dissertation and will be referred to as Study I, Study II, and Study III.