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Emerging Technologies

Correlating Optical Coherence Tomography and Other Noninvasive Imaging Features With Atrophic and Hypertrophic Skin Photoaging

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ABSTRACT

Background: According to morphological and clinical differences, atrophic (AP) and hypertrophic (HP) skin photoaging types have been reported. The current study examines the correlation between optical coherence tomography (OCT) and dynamic-OCT (D-OCT) features in subjects with skin photoaging types classified as AP, HP, or controls. Furthermore, we aim to define the correlations between OCT/D-OCT and other noninvasive skin imaging features (standardized clinical photography and reflectance confocal microscopy [RCM]).

Methods: We explored the correlations between skin photoaging types, OCT/D-OCT, and noninvasive skin imaging features. A total of 58 patients were clinically classified as AP ($n = 17$), HP ($n = 24$), or controls ($n = 17$).

Results: AP subjects showed higher D-OCT vessel assets and vessel densities ($p < 0.05$) compared to HP and control subjects. A significant correlation was established between standardized clinical evidence of wrinkles and RCM collagen scores. Dermal variations in HP subjects represent the underlying substrate of wrinkles.

Conclusions: Despite the limited cohort, these results contribute to the current knowledge of morphologic differences between AP and HP subjects. Treatment should consider morphologic changes according to skin photoaging phenotypes for optimal personalized medicine.

1 | Introduction

The process of skin aging involves a complex series of phenomena. Skin aging has been related to intrinsic factors, such as the passing of time (chronoaging), and exposure to extrinsic factors, such as sun exposure (photoaging) [1–3]. Photoaging has recently been classified as either atrophic photoaging (AP), characterized by an increased risk of dyspigmentation, erythema, telangiectasia, fine wrinkling, and a tendency to develop precancers and invasive skin cancers, or hypertrophic photoaging

(HP), characterized by increased photoaging scale severity, deep/coarse wrinkles, homogeneity of skin color, and increased elastosis [4–6].

The characteristics of AP and HP have also been described using noninvasive skin imaging tools [7]. Automated features count estimated with standard photography suggested that AP is significantly associated with increased red and brown areas compared to HP and control subjects. Using reflectance confocal microscopy (RCM), HP has been characterized by increased collagen scores compared to AP [7]. However, AP and HP have not yet been characterized with RCM combined with optical coherence tomography (OCT) and dynamic-OCT (D-OCT).

This study aims to describe OCT and D-OCT characteristics in AP, HP, or control skin photoaging types. Furthermore, we aim to define the potential correlation of OCT features with standardized clinical photography and RCM.

2 | Materials and Methods

2.1 | Study Design and Population

This post hoc study was performed with data from a prospectively conducted genetic study of correlations between MC1R and skin photoaging features revealed with noninvasive imaging techniques [7, 8]. The local ethics committee approved the study protocol (no. 33/16, protocol no. 2560), and all participants provided written informed consent. The study was conducted according to the principles of the Declaration of Helsinki.

This prospective study was conducted between June and August 2016 at the Dermatology Unit of the University of Modena and Reggio Emilia, with an original sample of 100 middle-aged women (age range 31–58 years) from Italy. Criteria for inclusion specified subjects of Caucasian origin, without any known dermatological disorders (including personal or family skin cancer history), without a history of any other previous cancers or any facial interventions, including injection of fillers or laser procedures within the last 6 months, or any facial plastic surgery. The criteria specified the exclusion of patients < 49 years old from the previous study since this has been considered the age at which photoaging signs start showing [6].

Moreover, subjects were instructed not to apply facial cleansers or cosmetic agents for at least 12 h before the arranged dermatological examination.

2.2 | OCT and D-OCT Assessment

All subjects were assessed using noninvasive skin imaging with OCT and D-OCT [9, 10]. OCT and D-OCT enable the exploration of the skin at depths of up to 1–2 mm; however, they do not provide cellular-level resolution. OCT images were acquired through the OCT VivoSight examination (Michelson Diagnostics Ltd., Orpington, UK) of the right cheek (5 mm below the zygomatic arch) [7]. The vessels were studied in horizontal (parallel to the skin surface) D-OCT images at both 300 and 500 μm depth. The vascular network was assessed with the ImageJ software (Image Processing and Analysis in Java, freeware 2014 version USA) and reported as "vessel density." [7–9] ImageJ-based vessel quantification has been validated in prior studies, comparing it with histological and confocal microscopy assessments [9]. Additionally, vascular features also included "vessel asset," estimated according to a previously validated 4-point photo numeric scale based on the quantity and dilation of the vascular network (from 0 = low vascular network to 3 = high vascular network) [7–9]. The features assessed at OCT and D-OCT are outlined in Table S1.

Two expert readers (BDP, SC) evaluated the OCT and D-OCT images, and in case of disagreement, a third expert (SG) was consulted.

2.3 | Skin Photoaging Phenotype Classification

Skin photoaging phenotype classification was performed according to erythema and coarse/pronounced wrinkles, as previously described by Sachs et al. [6] Study participants were grouped as AP, prominent erythema (no prominent coarse wrinkles); HP, prominent coarse wrinkles (no prominent erythema); or controls (no pronounced wrinkles or pronounced erythema).

The distribution of standardized clinical photography (with automated features count; VISIA) and RCM skin photoaging features have been previously described [7, 11]. The VISIA parameters were UV and brown spots, wrinkles, and red areas. The RCM features were mottled pigmentation, irregular honeycombed pattern, big sebaceous gland, polycyclic papillary contours, reticular, coarse, and huddle collagen, curled fibers, and RCM collagen (alteration) score. RCM enables the cytoarchitectural evaluation of the skin, although it can reach up to 250 μm depth exploration. The definitions of the RCM criteria analyzed are reported in Table S1.

The raters were masked to patient classification.

2.4 | Statistical Methods

Mean and percentage frequency were used to express population characteristics. Fisher's exact or χ^2 tests were used to assess group differences for categorical data. Pearson's correlation, expressed as the r coefficient, was calculated to find associations between noninvasive skin imaging features observed with OCT/D-OCT, RCM, and VISIA. A p-value of 0.05 was used to determine statistical significance. Data were analyzed using SPSS (version 24, Armonk, NY).

3 | Results

3.1 | Characteristics of the Study Population

A total of 58 women were included in the study and grouped into AP ($n = 17$), HP ($n = 24$), and controls ($n = 17$). There were no differences between the groups in terms of age and other aging risk factors, including smoking habits and alcohol intake (data not shown).

3.2 | Photoaging, OCT, and D-OCT

The OCT features observed, according to the photoaging classification, are presented in Table 1.

No significant differences were found between the OCT and D-OCT features of the dermis and epidermis. However, AP subjects were attributed significant differences in higher vessel assets ($p=0.042$) and densities ($p=0.0017$).

3.3 | Correlation Between Noninvasive Skin Imaging Features

We observed multiple correlations between noninvasive skin parameters in AP and HP subjects (Tables S2 and S3; Figure 1).

In AP subjects, vessel density at 300 and 500 μm depth, estimated with D-OCT, was significantly correlated with red areas ($r=0.418$ and $r=0.450$, $p<0.05$) (Figure 1a–c). Furthermore, vessel density at 300 and 500 μm was strongly associated ($r=0.790$; $p<0.01$). Additional significant correlations were observed between curled fibers and RCM collagen score ($p<0.01$) as well as between mottled pigmentation and red areas ($p<0.05$) (Table S2).

In HP subjects, a significant correlation between wrinkles and RCM collagen score was observed ($r=0.477$, $p<0.05$) (Figure 1e-f). Vessel density at 300 μm was correlated with red areas (VISIA; $r=0.526$, $p<0.05$). Other significant correlations were observed between the RCM epidermal irregular honeycombed pattern and curled fibers ($r=0.686$, $p<0.01$) and red areas ($r=0.673$, $p<0.01$). Correlations between huddle collagen, curled fibers, and RCM collagen score were observed. Additionally, a correlation between vessel density at 500 μm and huddle collagen, curled fibers, and RCM collagen score was revealed ($r=0.639$, $p<0.01$ and $r=0.519$, $p>0.05$, respectively) (Table S3).

4 | Discussion

This study reports a significant correlation between clinically classified AP and higher vessel asset/density observed with D-OCT, compared to HP and control subjects. Our data support previous findings of increased telangiectasia and red areas associated with AP in the literature [6, 7]. Additionally, red areas (VISIA) are associated with vessel density revealed with D-OCT, and although this observed correlation falls in the moderate range ($r=0.418$, 0.450), this is consistent with prior research linking vascular density to photoaging signs, as measured with different techniques [12, 13]. Further studies are needed to establish clinical cutoffs, but these findings suggest that noninvasive vascular imaging may aid phenotype classification. The increased vascular skin component of AP subjects,

TABLE 1 | OCT and D-OCT imaging features of the study population, grouped according to skin photoaging type.

	Total, *n* (%)	AP, *n* (%)	HP, *n* (%)	Control, *n* (%)	
	***N*=58**	***N*=17**	***N*=24**	***N*=17**	***p***
OCT					
Epidermal thickness (μm), *mean ± SD (range)*	0.04 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	0.261
DEJ, *visible*	54 (93.1)	15 (88.2)	23 (95.8)	16 (94.1)	0.64
Disruption of collagen fibers					
Normal	2 (3.4)	1 (5.9)	0	1 (5.9)	0.584
Fragmented—few	14 (24)	5 (29.4)	6 (25)	3 (17.6)	
Fragmented—moderate	29 (50)	7 (41.2)	11 (45.8)	11 (64.7)	
Fragmented—many	13 (22.4)	4 (23.5)	7 (29.2)	2 (11.8)	
D-OCT (at 300 μm)					
Vessel asset					
Low	15 (25.9)	1 (5.9)	8 (33.3)	6 (35.3)	0.042
Mild	35 (60.3)	12 (70.6)	14 (58.3)	9 (52.9)	
Moderate	7 (12.1)	3 (17.6)	2 (8.3)	2 (11.8)	
High	1 (1.7)	0	1 (4.2)	0	
Vascular density, *pixel mean ± SD*	5235 ± 4220.3	7596.2 ± 5862[a,b]	4560.1 ± 3021.7[a]	3826.8 ± 2692.3[b]	0.017

Abbreviations: AP, atrophic photoaging; DEJ, dermo-epidermal junction; D-OCT, dynamic-optical coherence tomography; HP, hypertrophic photoaging; OCT, optical coherence tomography; RCM, reflectance confocal microscopy.
[a]Statistically significant for the comparison AP versus HP; *p*-value <0.05.
[b]Statistically significant for the comparison AP versus control; *p*-value <0.05.

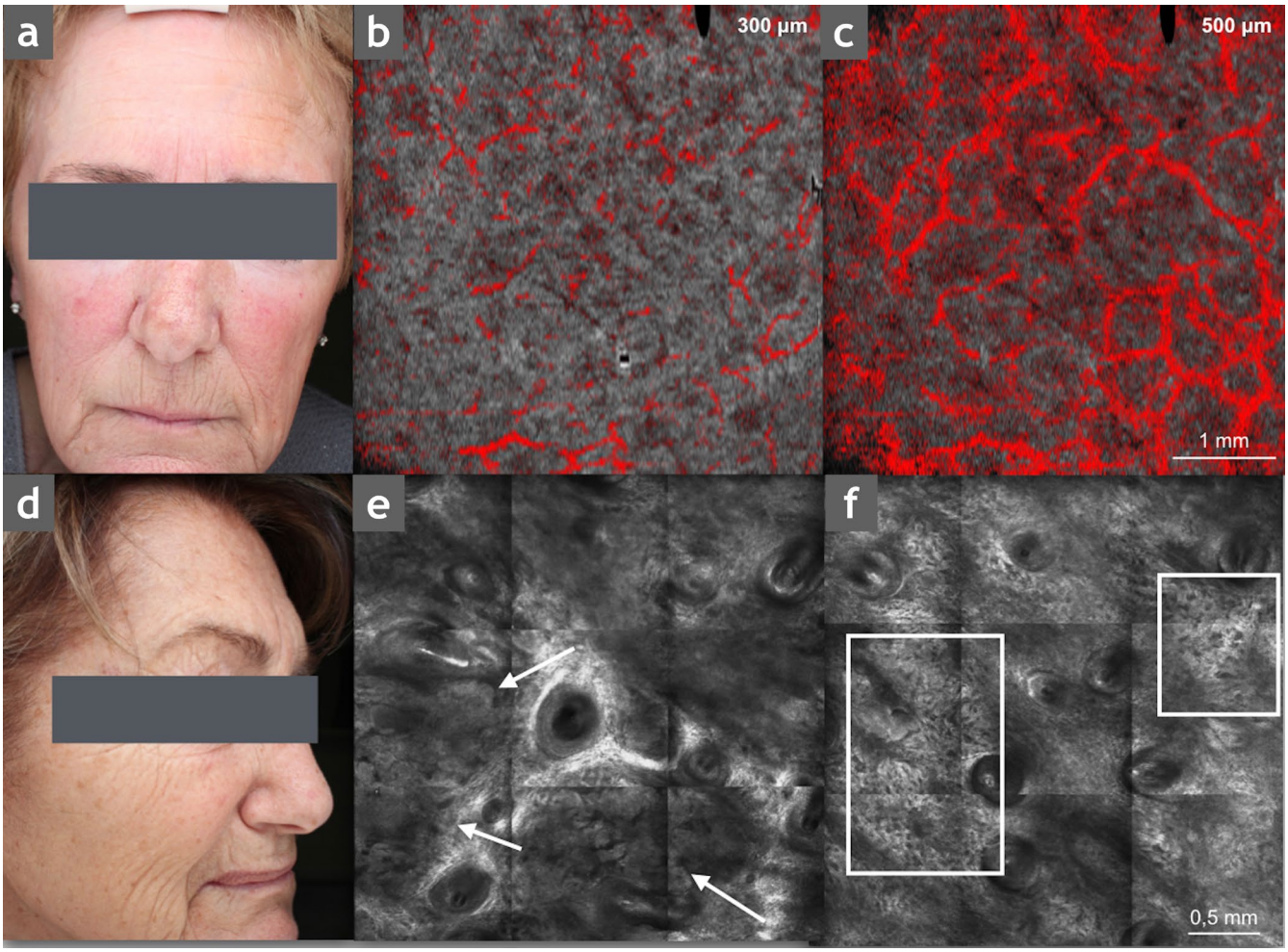

FIGURE 1 | Atrophic (a–c) and hypertrophic (d–f) skin photoaging. (a) Clinical picture of a female patient with atrophic skin photoaging showing prominent erythema. (b, c) Related horizontal D-OCT images at 300 µm, 500 µm. (d) Clinical picture of a female patient with hypertrophic skin photoaging showing prominent coarse wrinkling and related reflectance confocal microscopy (RCM) images, (e) RCM showing huddle collagen (arrows), and (f) curled fibers (square).

related to a response to photo exposure, has been correlated with an increased risk of skin cancers, particularly nonmelanoma skin cancers (NMSC) [6]. Increased telangiectasias observed in the AP group have been hypothesized to be associated with collagen fragmentation, which leads to alterations in the dermal extracellular matrix, making blood vessels more represented [6]. Additionally, a previous study highlighted that the loss of collagen VII in male subjects classified as AP promotes skin tumor migration and invasion through a mechanism involving disorganized keratinocyte differentiation. Therefore, these pathways could also be relevant to the development of NMSC [14]. Not surprisingly, photodynamic therapy, employed in both photoaging and NMSC treatments, has been shown to improve telangiectasia by up to 87% [15]. Vascular lasers, employed in treating basal cell carcinomas to target hemoglobin, produce selective photothermolysis of the vessels [16]. An emerging role of injectables (hyaluronic acid, botulinum toxin) in vessel reduction has been recently reported [17, 18].

Interestingly, we describe the previously unreported correlation between clinical evidence of wrinkles (revealed with VISIA) and RCM collagen score in HP subjects. Current literature reports the role of the reduction of functional dermal components in the appearance of wrinkles [14, 19]. However, this study provides the first morphologic evidence that the underlying substrate for wrinkle appearance in HP subjects is related to variations occurring at the dermal level. According to these results, laser or injectable treatments aiming at collagen remodeling [20, 21] can be considered in rejuvenation treatments of HP subjects to improve wrinkles.

We previously showed a trend towards HP subjects having an increased number of wrinkles compared to AP subjects [7]. According to Langton et al. [13], similar reductions of fibrillin-rich microfibrils were observed in all HP and female AP subjects compared to male AP subjects. This may explain why there was no significant difference in wrinkles in the HP and AP subjects (all females) in our study population.

The main limitations of this study are related to the small population size and gender selectivity (female subjects only), as well as the retrospective post hoc design and potential biases in subject selection. However, our study size is in line with the study population analyzed by Sachs et al. ($n = 53$) [6].

Previous studies supported the use of multiple imaging modalities (VISIA, RCM, OCT/D-OCT) to provide a comprehensive evaluation of the characteristics of the skin (i.e., wrinkles, pigmentation), vascular and structural (i.e., collagen) skin changes associated with photoaging [7–10]. However, these studies did not differentiate between distinct photoaging phenotypes. Additionally, each imaging modality has inherent limitations. While OCT/D-OCT excels in vascular assessment, it lacks cellular resolution. RCM provides detailed collagen and epidermal features but is limited to superficial layers ($<250\,\mu m$). Standardized photography captures macro-level pigmentation changes but lacks histologic correlation. These differences must be considered when interpreting findings across techniques. In our study, the combination of these techniques highlighted the correlation between clinical evidence of wrinkles and RCM collagen score in HP subjects, as well as the increased quantity of vessels in the AP subjects.

This study contributes to our current knowledge of different morphologic details, revealing different response pathways to photo exposure. In the era of personalized medicine, optimal treatment should focus on the morphologic differences in skin photoaging patterns.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.