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Lid-parallel conjunctival fold (LIPCOF) morphology imaged by optical coherence tomography and its relationship to LIPCOF grade

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ABSTRACT

Purpose: Lid-parallel conjunctival folds (LIPCOF) are a well-accepted clinical sign in dry eye diagnosis. Commonly, LIPCOF is classified by grading the number of folds observed by slit-lamp microscope. This study investigated the relationship between subjective grading scale and LIPCOF morphology imaged by optical coherence tomography (OCT).
Methods: Temporal and nasal LIPCOF of 42 subjects (mean age 27.3 ± 8.4 (SD) years; 13 M, 29 F) were observed and classified by an experienced optometrist using the Pult LIPCOF grading scale (0: no permanent, lid-parallel conjunctival fold; 1: one fold; 2: two folds, 3: three or more folds). Additionally, LIPCOF cross-sectional area (LIPCOF-A) and fold count (LIPCOF-C), as imaged by OCT (Cirrus HD; Carl Zeiss Meditec, Jena, Germany), were analysed with ImageJ 1.50 (http://rsbweb.nih.gov/ij). Correlations between subjective grading and LIPCOF-A and LIPCOF-C were analysed by Spearman correlation, differences between subjective grading and LIPCOF-C were analysed by Wilcoxon test.
Results: For temporal and nasal sectors, mean subjective LIPCOF grade was 1.43 ± 0.86 grade units and 0.57 ± 0.80 grade units, mean LIPCOF-C was 1.67 ± 0.82 folds and 0.69 ± 0.78 folds, and mean LIPCOF-A was 0.0676 ± 0.0236mm^2 and 0.0389 ± 0.0352 mm^2, respectively. Subjective temporal and nasal LIPCOF grade was significantly correlated to LIPCOF-C ($r = 0.610$, $p < 0.001$ and $r = 0.645$, $p < 0.001$, respectively), and to LIPCOF-A ($r = 0.612$, $p < 0.001$ and $r = 0.583$, $p < 0.001$, respectively). LIPCOF-C was not statistical different to subjective LIPCOF grade ($p = 0.07$ and $p = 0.239$; temporal and nasal sectors, respectively).
Conclusions: OCT allows for better imaging of finer details of LIPCOF morphology, and especially of LIPCOF area. OCT evaluation of LIPCOF area correlated well with subjective grading and appears to be a promising objective method for LIPCOF classification.

1. Introduction

Lid-parallel conjunctival folds (LIPCOF) are small folds in the infero-temporal and infero-nasal quadrants of the bulbar conjunctiva, parallel to the lower lid margin, and were first described by Höh et al. [1] in 1995. Subsequent studies have shown that patients with increased LIPCOF grade are more likely to suffer from dry eye disease [1–6]. Their appearance seems to be related to increased shear forces between the bulbar conjunctiva and palpebral conjunctiva of the eyelid during blinking [7]. Commonly, LIPCOF are observed with a slit-lamp microscope using high magnification (x25), and with no fluorescein instilled, in the area perpendicular to the temporal and nasal limbus above the lower lid (Fig. 1.) [4,8–11].

Slit-lamp findings of LIPCOF can be classified by a fold-height-based grading scale [1], or by counting the number of folds (Table 1) [12]. Care has to be taken to differentiate LIPCOF from microfolds, which are less well organised and are around three times smaller than a LIPCOF [8,10,11]. LIPCOF may be a form of conjunctivochalasis, but are assumed to present a mild form of this condition and should be carefully differentiated and reported as such in clinical observation and research to avoid confusion. Conjunctivochalasis typically shows a much larger cross-sectional area and also occurs also in the central region of the lower lid [10,11,13,14]. Like conjunctivochalasis, LIPCOFs are assumed to influence the tear volume distribution along the lower lid and

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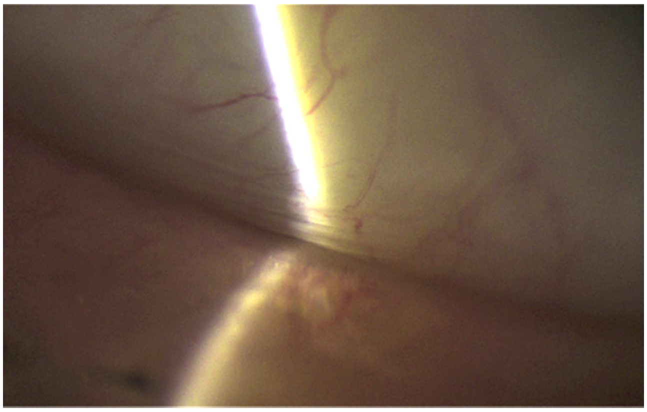

Fig. 1. Slit-lamp image of LIPCOF grade 3 at the temporal position.

Table 1
Optimised grading scale of LIPCOF.

LIPCOF Grade	
0	No conjunctival folds
1	One permanent and clear parallel fold
2	Two permanent and clear parallel folds (normally < 0.2 mm)
3	More than two permanent and clear parallel folds (normally > 0.2 mm)

therefore alter tear meniscus parameters [10,11,15–17].

Beside the commonly-used slit-lamp observation, new techniques, like Scheimpflug imaging or optical coherence tomography (OCT), have been used in recent studies to visualise LIPCOF [5,10,17,18]. In addition to counting of the fold numbers, these techniques allow imaging of the cross-sectional area of the LIPCOF and their degree of coverage by the tear film [10,17].

Although these previous studies have enabled imaging of the cross-sectional area of observed LIPCOF, no attempt has been made to correlate this aspect of OCT imaged LIPCOF morphology with LIPCOF grading using subjective observation. Consequently this study investigated the relationship between OCT derived LIPCOF morphology metrics and a subjective grading of slit-lamp observed LIPCOF.

2. Material and methods

2.1. Subjects

Forty-two subjects (male = 13, female = 29) were recruited from the staff and students of the Höhere Fachschule für Augenoptik Köln, (Cologne School of Optometry), Cologne, Germany. The mean age was 27.3 years (standard deviation, ± 8.4 years). Subjects were excluded if they were pregnant or breast-feeding; had a current or previous condition known to affect the ocular surface or tear film; had a history of previous ocular surgery, including refractive surgery, eyelid tattooing, eyelid surgery, or corneal surgery; had any previous ocular trauma, were diabetic, were taking medication known to affect the ocular surface and/or tear film, and/or had worn any types of contact lenses less than two weeks prior to the study. All subjects gave written informed consent before participating in the study. All procedures obtained the approval of the Cardiff School of Optometry and Vision Sciences Human Ethics Committee and were conducted in accordance with the requirements of the Declaration of Helsinki.

2.2. Procedures

LIPCOF evaluation was performed, without fluorescein, in the area tangential to the temporal and nasal limbus, on the bulbar conjunctiva above the lower lid, using a slit-lamp microscope and x25 magnification (BQ900, Haag-Streit, Koeniz, Switzerland) (Fig. 1). LIPCOF grade was classified by an experienced optometrist (SB) using the Pult LIPCOF grading scale (folds count: 0, no permanent, lid-parallel conjunctival fold; 1, one fold; 2, two folds, 3, three or more folds) (Table 1) [12]. Additionally, lid-parallel folds at the same locations were imaged using an OCT (Cirrus HD; Carl Zeiss Meditec, Jena, Germany). This instrument uses spectral-domain OCT (SD – OCT), with a wavelength of 840 nm to achieve an axial resolution of 5 µm. Cross-sectional images of the nasal and temporal LIPCOFs were taken using the anterior segment five lines raster method. OCT images were stored as JPEG files and analysed with ImageJ 1.50 (http://rsbweb.nih.gov/ij). On the OCT images, LIPCOF cross-sectional area (LIPCOF-A) was analysed by the segmented-line function in ImageJ, where only the area of the conjunctival fold, but not the area of tear meniscus, was marked (Fig. 2). Furthermore, the visible folds on the OCT images were counted (LIPCOF-C) (Fig. 3 a–d).

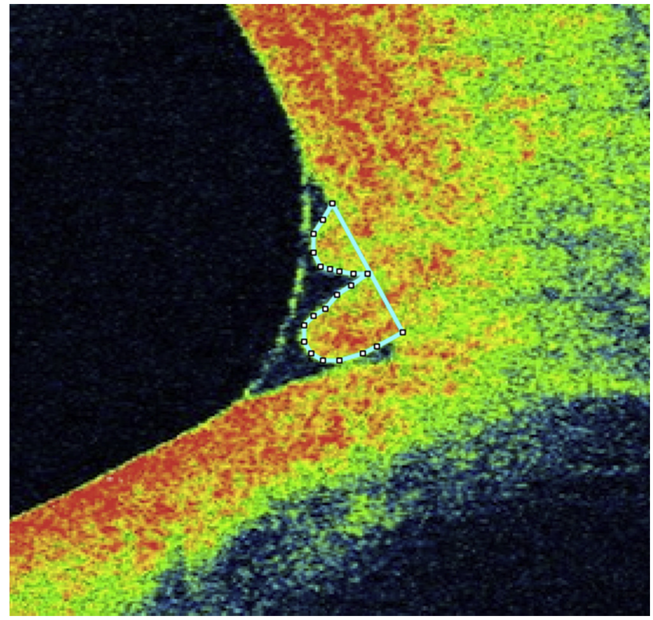

Fig. 2. OCT image of LIPCOF grade 2 with ImageJ segmented line tool (blue line) to measure LIPCOF cross-sectional area.

2.3. Statistical analyses

Data were tested for normality using the Shapiro-Wilk test. As LIPCOF grade was not normally distributed, the correlations between slit-lamp LIPCOF grade, LIPCOF cross-sectional area (LIPCOF-A) and LIPCOF count (LIPCOF-C) were assessed using Spearman's Rank coefficient. Differences between subjective grading and LIPCOF-C were analysed by Wilcoxon test.

3. Results

The mean subjective temporal and nasal LIPCOF grade was 1.43 ± 0.86 grade units and 0.57 ± 0.80 grade units, the mean LIPCOF-C was 1.67 ± 0.82 folds and 0.69 ± 0.78 folds, and the mean LIPCOF-A was 0.0676 ± 0.0236mm^2 and 0.0389 ± 0.0352 mm^2, respectively (Table 2).

Subjective temporal and nasal LIPCOF grading was significantly correlated to LIPCOF-C ($r = 0.610$, $p < 0.001$ and $r = 0.645$, $p < 0.001$, respectively) and to LIPCOF-A ($r = 0.612$, $p < 0.001$ and $r = 0.583$, $p < 0.001$, respectively) (Figs. 4 and 5).

LIPCOF-C was not statistically different to subjective temporal and

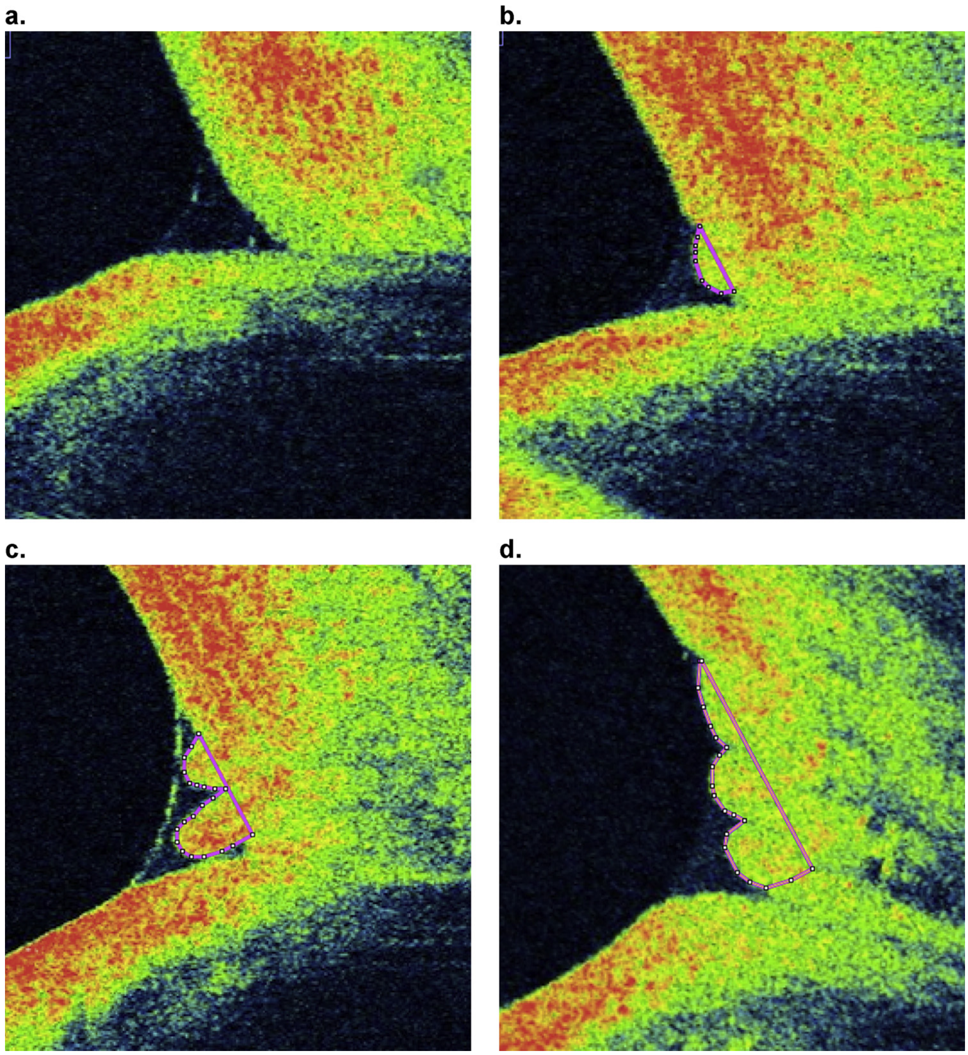

Fig. 3. a Example of LIPCOF Grade 0. LIPCOF cross-sectional area: 0.000mm^2. Fig. 3b Example of LIPCOF Grade 1. LIPCOF cross-sectional area: 0.0363mm^2. Fig. 3c Example of LIPCOF Grade 2. LIPCOF cross-sectional area: 0.078mm^2. Fig. 3d Example of LIPCOF Grade 3. LIPCOF cross-sectional area: 0.108mm^2.

Table 2
LIPCOF grading and measurement with the different methods.

Methods	Temporal	Nasal
Slit-lamp LIPCOF Grade	1.43 ± 0.86	0.57 ± 0.80
OCT LIPCOF Grade	1.67 ± 0.82	0.69 ± 0.78
OCT LIPCOF cross-sectional area [mm^2]	0.0676 ± 0.0236	0.0389 ± 0.0352

nasal LIPCOF grade ($p = 0.07$ and $p = 0.239$, respectively).

4. Discussion

The subjective slit-lamp LIPCOF gradings, based on appearance, for these subjects match the established phenotype pattern, with the temporal LIPCOF grade (1.43 ± 0.86 grade units) being significantly higher than the nasal grade (0.57 ± 0.80 grade units) [9,19]. This difference in appearance between the nasal and temporal sectors also describes a 3-dimensional morphological difference, and this is the first study in which OCT has been used to analyse not only the number of folds, but also the cross-sectional area of the folds. The study found moderate/strong correlations between the OCT-derived number of folds and the subjective LIPCOF grade, and moderate/strong correlations between the OCT-derived cross-sectional area of observed folds and the subjective grade. These findings support the use of OCT to better understand LIPCOF morphology.

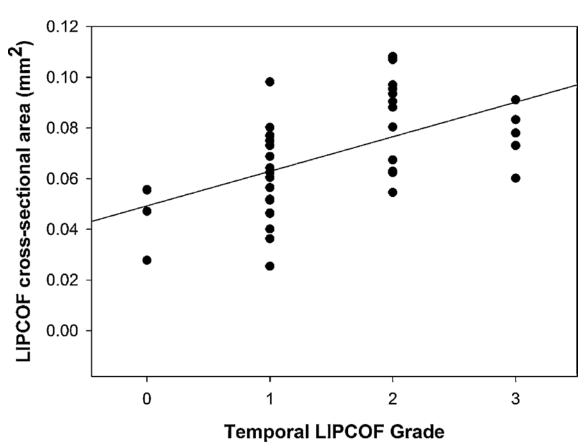

Fig. 4. Relationship between temporal slit-lamp LIPCOF Grade and OCT LIPCOF cross-sectional area (Spearman-Rank-Order coefficient, $r = 0.612$; $p < 0.001$).

A better understanding of LIPCOF morphology is important for understanding the clinical consequences of LIPCOF presence and grade.

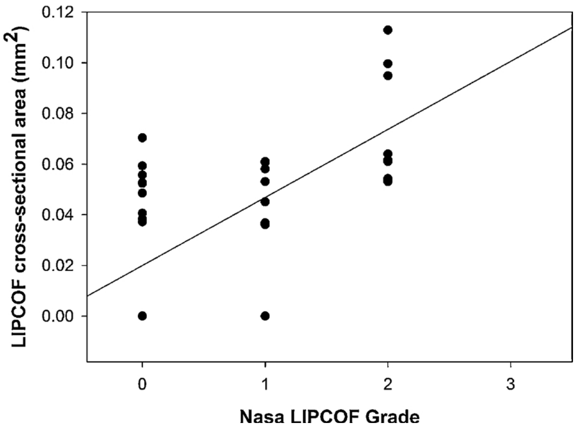

Fig. 5. Relationship between nasal slit-lamp LIPCOF Grade and OCT LIPCOF cross-sectional area (Spearman-Rank-Order coefficient, r = 0.583; $p < 0.001$).

Like conjunctivochalasis, the presence of LIPCOF results in irregularity of the lower tear meniscus, interferes with tear flow, and can influence the measurement of tear meniscus parameters [10,11,16,17,20,21]. Optical coherence tomography therefore allows not only an objective grading of LIPCOF severity similar to subjective LIPCOF grading, but it also provides a quantitative measurement of the conjunctival protrusion. In turn, this morphological description can be related to tear meniscus parameters that are influenced by LIPCOF, and which are thought to be related to the interactive mechanism between LIPCOF, tear volume, friction, and dry eye disease symptoms. Moreover, by considering the cross-sectional morphology, OCT might be helpful in differentiating between similar looking slit-lamp findings, such as microfolds, LIPCOF and conjunctivochalasis.

Previous attempts have been made to study this interactive mechanism. For example, Veres et al. [5] compared a subjective LIPCOF grade (Höh et al. [1]) to three different methods of quantifying the tear film which was imaged used a Fourier-domain OCT. Method 1 was based on the height of the lower tear meniscus immediately after a voluntary complete blink (LTMH), Method 2 on the LTMH 3 s after blink, and Method 3 on the degree of tear film coverage of the LIPCOF. All three methods showed a moderate correlation with the Höh et al. [1] slit-lamp derived subjective grade, which is also based on lower tear meniscus height (r = 0.470–0.473, $p < 0.01$). However, they did not attempt to measure the cross-sectional LIPCOF area on the OCT images.

Pult and Riede-Pult [17] were the first to measure cross-sectional LIPCOF area using a modified Scheimpflug camera (Pentacam HD; Oculus Optikgeräte GmbH, Wetzlar, Germany). In concordance with this study, they found subjective LIPCOF grading was significantly correlated with Scheimpflug imaged cross-sectional area. For the cross-sectional LIPCOF area they reported mean values of 0.035mm^2 temporally and 0.006mm^2 nasally. These values are smaller than those found in this study; however, this can by attributed to the lower LIPCOF degrees in their study and to the poorer resolution of Scheimpflug images in comparison to OCT images. Only one recent conference paper has reported on the repeatability of subjective LIPCOF grading, which they found was limited [22]. Further studies are needed to assess the repeatability of LIPCOF cross-sectional area and fold count, as imaged by OCT.

Since LIPCOFs have been described as a mild sub-type of conjunctivochalasis [23], being able to image conjunctival folds by OCT may help to differentiate between LIPCOF and conjunctivochalasis. This has not been directly tested, but Gumus et al. [15] applied Fourier-domain OCT to evaluate the cross-sectional area of conjunctivochalasis before and after conjunctival cauterisation. They found that the mean cross-sectional conjunctivochalasis area decreased from 0.247 ± 0.24mm^2 to 0.054 ± 0.79mm^2 after cauterisation. In contrast, in this study, mean cross-sectional LIPCOF areas of 0.068 ± 0.02 mm^2 temporally and 0.039 ± 0.04mm^2 nasally were measured, which suggests that pre-cauterised conjunctivochalasis could be differentiated from LIPCOF. Furthermore, it seems that the cross-sectional conjunctivochalasis area after cauterisation might be similar to the mean cross-sectional LIPCOF area.

Gumus et al. [13] also considered how the prevalence and severity of conjunctivochalasis changed with age. Comparing the cross-sectional area of conjunctivochalasis in three different age groups (29.2 ± 4.1; 49.5 ± 5.4 and 65.9 ± 5.6 years) showed an increase for temporal area from 0.03 ± 0.02 mm^2 to 0.14 ± 0.04mm^2 to 0.23 ± 0.05mm^2, and for nasal area from 0.01 ± 0.01mm^2 to 0.04 ± 0.01mm^2 to 0.08 ± 0.02 mm^2 [13]. In this study, the mean age of the subjects was 27.3 ± 8.4 years with a cross-sectional LIPCOF area of 0.068 ± 0.02 mm^2 temporally and 0.039 ± 0.04mm^2 nasally, which corresponds with the findings of the Gamus et al young and middle-aged conjunctivochalasis groups. The conclusion is that conjunctivochalasis severity increases with aging. From this it might be hypothesised that LIPCOF and conjunctivochalasis are similar findings in younger and mid-aged patients, while the findings differ in the elderly population. This would match with previous findings that LIPCOF is not age-related [1,13]. Hence, an analysis of the cross-sectional area of the conjunctival fold could be a helpful tool to differentiate between LIPCOF/conjunctivochalasis severity, as defined by the amount of conjunctival tissue that protrudes into the lower tear meniscus.

5. Conclusions

OCT allows for better imaging of the finer details of LIPCOF morphology, and especially of LIPCOF area. OCT evaluation of LIPCOF area correlates well with subjective grading and appears to be a promising objective method for LIPCOF classification. OCT imaging of conjunctival folds may also provide a method for differentiation between LIPCOF and conjunctivochalasis in older subjects.

Conflict of interest

None.

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