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A new method to assess foveal morphology with optical coherence tomography

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Abstract

Purpose. To measure foveal morphology using optical coherence tomography (OCT).

Methods. Three examiners classified normal subjects and patients with macular edema and epiretinal membranes from a normative database (299 OCT scans) and a study sample (80 OCT scans) on the basis of the foveal depression appearance (reference classification). The following parameters were measured for each OCT scan: Central Foveal Thickness (CFT), Central Subfield Thickness (CST), Central Subfield Volume (CSV), Centrofoveal Index (CI), Parafoveal Index (PI), and Foveal Indices (FI1, FI2, FI3). Foveal depression of OCT scans in the study sample were classified based on the values of OCT parameters using Bayesian statistics (test classifications).

Results. Agreement between reference and test classifications was of 70% for CFT, 58.7% for CST, 60% for CSV, 80% for CI, 72.5% for PI, 88.7% for FI1, 96.2% for FI2 and 97.5% for FI3.

Conclusions. IF3 seems to provide a reliable measure of the foveal morphology. ***Clin Ter 2019; 170(3):e192-198. doi: 10.7417/CT.2019.2132***

Key words: *optical coherence tomography, retinal diseases, macular edema, epiretinal membranes*

Introduction

The optical coherence tomography (OCT), providing both quantitative and qualitative information, is the most useful tool to manage patients with macular edema and epiretinal membranes. Central subfield thickness (CST) is the most used parameter to measure objectively changes in foveal thickness. Since retinal thickness is weakly related to visual acuity in macular edema (1), it is also useful to consider other qualitative parameters in order to plan for the most appropriate management of patients.

The foveal shape is one qualitative parameter used to describe macular edema and epiretinal membranes. In both diseases foveal shape may change resulting in a reduced, absent or inverted depression. As with other qualitative parameters, the foveal shape is not measurable and cannot be directly derived from the CST (Fig. 1).

Some authors have measured the foveal depression using OCT with the addition of complex mathematical models but none of these methods has found practical application so far (2-6).

In this study we investigated whether a method based on OCT parameters, derived from macular thicknesses, could be used to assess reliably the foveal depression in subjects with normal macula, macular edema and epiretinal membranes. The values of each parameter have been assessed with the help of a statistical analysis software to classify the OCT scans on the basis of foveal morphology (test classification). Software derived classifications were then compared with morphological classifications made by expert examiners (reference classification). The agreement between test and reference classifications has been used to assess the reliability of the OCT parameters in measuring foveal morphology.

Materials and Methods

The Ethics Committee approval was obtained. We selected 379 OCT scans performed on 379 eyes of 338 patients, from an SD-OCT RVue system database (software version: A5, 1,0,90; Optovue, Fremont, CA, USA), which was in action at our Hospital from 2011 to 2013. OCT scans acquired with MM5 grid scan mode were used for the study. The MM5 scan mode is used to generate a retinal thickness map of the macula covering an area of 5 x 5 mm with horizontal and vertical scans. The scans are spaced 0.25-mm apart in the central 3-mm-area and 0.50-mm apart in the 3-mm to 5-mm-area.

Scans were collected from normal and abnormal maculas, due to different pathologies such as diabetic macular edema, cystoid macular edema secondary to retinal venous occlusion and epiretinal membranes. Only OCT maps where the center of the fovea was identifiable were selected. In patients without central fixation, the examiner used the reprocessing software of the system to manually reposition the center of the OCT map on the center of the fovea. Only scans with no artifacts were selected. Scans from patients

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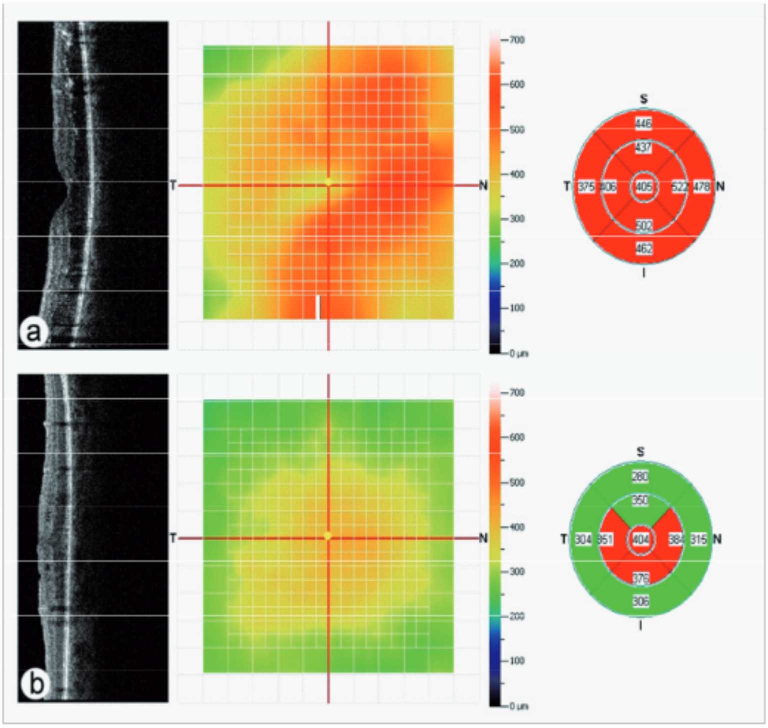

Fig. 1. OCT scans and macular thickness maps with ETDRS grid. (a) Scan of a patient with diabetic macular edema, preserved foveal depression and central subfield thickness of 405 µm. (b) Scan of patient with cellophane maculopathy, absent foveal depression and central subfield thickness of 404 µm.

with age-related macular degeneration, myopic macular degeneration and macular hole were excluded from the study. Scans were classified by two independent examiners based on the morphology of the foveal depression into four morphological classes (reference classification): preserved, reduced, absent and inverted (Fig. 2).

The two examiners have classified the foveal depression assessing the central (vertical and horizontal) B-scans and the macular map. OCT scans classified differently have been reevaluated by a third examiner establishing the definitive morphological class.

OCT examinations were divided randomly into two groups, a Normative database of 299 scans and a Study sample consisting of 80 scans. Using ETDRS grid as a topographic reference, in each macular map were measured some "simple" OCT parameters: central foveal thickness (CFT); CST, within the inner 1-mm-diameter subfield; the thickness between the inner 1-mm-diameter circle and the middle 3-mm-diameter circle of the four inner parafoveal subfields: superior (ISS), nasal (INS), inferior (IIS) and temporal (ITS); the volume of the central subfield (CSV). For each macular map both centrofoveal index (CI), given by the ratio CFT / CST, and parafoveal index (PI), given by the ratio CST / (ISS + INS + IIS + ITS) × 1/4 were calculated. Finally, three foveal indices (FI) given by the following combinations: FI1 = CI + PI; FI2 = CI^2 + PI; FI3 = CI^3 + PI were calculated. CI, PI, FI1, FI2 and FI3, were defined "combined" OCT parameters.

For each value of the OCT parameters we calculated the most likely foveal morphology class. For this purpose we used the conditional probability method based on Bayes' theorem that defines the probability of a "conditioned" event following an other "conditioning" event (7).

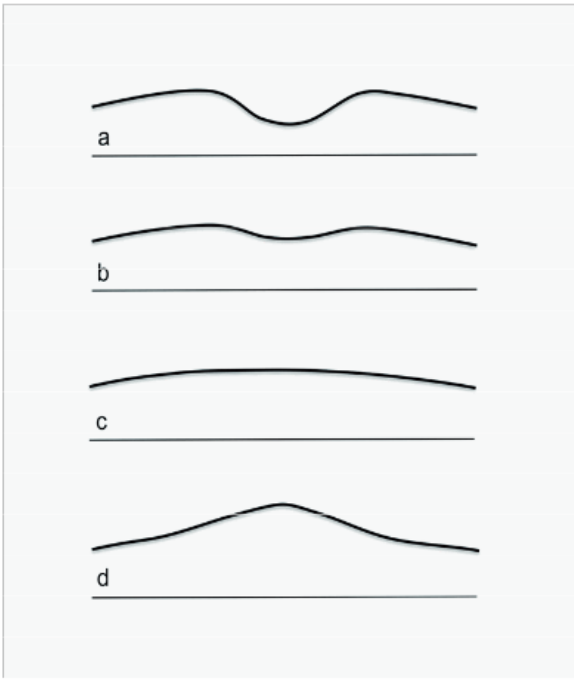

Fig. 2. Morphologic patterns of foveal depression: (a) preserved; (b) reduced; (c) absent; (d) inverted.

The statistical software R (R Core Team 2016, R Foundation for Statistical Computing, Vienna, Austria) was programmed (see Appendix 1) to calculate the probability of fitting a morphologic class for each OCT scan of the sample study ("conditioned" event) based on the distribution of the OCT parameters in the normative database ("conditioning" event). A test classification of the OCT scans based on their foveal shape was generated by the software for each of the evaluated OCT parameters. Finally, the agreement between reference and test classifications was assessed using cross-tables.

Results

The normative database of 299 OCT scans resulted from 299 eyes of 269 patients (mean age: 69.1 ± 11.6 years; 138 M, 131 F). The study sample of 80 OCT scans resulted from 80 eyes of 69 patients (mean age: 68.2 ± 10.2 years; 39 M, 30 F). OCT scans classified differently by the initial examiners and then reevaluated by the third examiner were 7 out of 299 (2.34%) from the normative database and 5 out of 80 (6.25%) from the study sample.

Table 1 shows the eyes divided by diagnosis and foveal shape for both the Normative database and the Study sample. Table 2 shows the mean values and standard deviations of CFT, CST and CSV divided by foveal depression class for both the Normative database and the Study sample. Table 3 shows the 10th and 90th percentile of OCT parameters values measured from the Normative database divided by foveal depression class. The overlap between percentiles of different morphologic classes was larger for "simple" than for "combined" OCT parameters, and IF3 showed less overlap than all other parameters. Table 4 shows the percentages of agreement between the reference classification, elaborated by the examiner, and the test classification, elaborated by the software. IF2 and IF3 have obtained the highest percentage of agreement with 96.25% and 97.5% respectively.

Table 1. Eyes from Normative database group and Sample study group divided by diagnosis and foveal shape.

	Diagnosis	Preserved	Reduced	Absent	Inverted	Total
Normative Database Eyes	Normal	55	27	0	0	82
	Cellophane	16	19	28	1	64
	Macular Pucker	1	4	26	17	48
	Macular Edema	6	18	22	59	105
	Total	78	68	76	77	299
Sample Study Eyes	Normal	17	3	0	0	20
	Cellophane	4	5	10	0	19
	Macular Pucker	1	2	11	5	19
	Macular Edema	4	10	3	5	22
	Total	26	20	24	10	80

Appendix 1

Programming language of statistical software R

```
estimated<-function(norma,data,coef){
q<-norma[,coef]
print(summary(q))
Absent<-norma$Foveal.Depression =="Absent"
Reduced<-norma$Foveal.Depression =="Reduced"
Preserved<-norma$Foveal.Depression =="Preserved"
Inverted<-norma$Foveal.Depression =="Inverted"
tot<-length(norma$Foveal.Depression)
subA<-density(norma[Absent,coef],from=min(norma[Absent,coef]),to=max(norma[Absent,coef]))
subR<-density(norma[Reduced,coef],from=min(norma[Reduced,coef]),to=max(norma[Reduced,coef]))
subP<-density(norma[Preserved,coef],from=min(norma[Preserved,coef]),to=max(norma[Preserved,coef]))
subI<-density(norma[Inverted,coef],from=min(norma[Inverted,coef]),to=max(norma[Inverted,coef]))
pA<-sum(Absent)/tot
print(paste("pA=",pA))
pR<-sum(Reduced)/tot
print(paste("pR=",pR))
pP<-sum(Preserved)/tot
print(paste("pP=",pP))
pI<-sum(Inverted)/tot
print(paste("pI=",pI))
funA<-approxfun(subA$x,subA$y)
funR<-approxfun(subR$x,subR$y)
funP<-approxfun(subP$x,subP$y)
funI<-approxfun(subI$x,subI$y)
data$prob<-0.00
for (i in 1:length(data[,coef])){
x<-round(data[i,coef],1)
print(x)
pxa<-funA(x)
print(paste("pxa=",pxa))
if(is.na(pxa)){pxa<-0}
pxr<-funR(x)
if(is.na(pxr)){pxr<-0}
pxp<-funP(x)
if(is.na(pxp)){pxp<-0}
pxi<-funI(x)
if(is.na(pxi)){pxi<-0}
if((pxa+pxr+pxp+pxi)==0){
data$pred[i]<-"Out Range"
next
}
pax<-(pxa*pA)/((pxa*pA)+(pxr*pR)+(pxp*pP)+(pxi*pI))
print(pax)
prx<-(pxr*pR)/((pxa*pA)+(pxr*pR)+(pxp*pP)+(pxi*pI))
print(prx)
ppx<-(pxp*pP)/((pxa*pA)+(pxr*pR)+(pxp*pP)+(pxi*pI))
print(ppx)
pix<-(pxi*pI)/((pxa*pA)+(pxr*pR)+(pxp*pP)+(pxi*pI))
print(pix)
data$prob[i]<-max(pax,prx,ppx,pix)
probi<-c(pax,prx,ppx,pix)
maxi<-which(probi==max(probi))
depress<-c('Absent','Reduced','Preserved','Inverted')
data$pred[i]<-depress[maxi]
}
data$pred<-factor(data$pred,levels=c("Inverted","Absent","Reduced","Preserved"))
print(table(data$Foveal.Depression,data$pred))
boxplot(norma[,coef]~norma$Foveal.Depression,main=coef)
return(data)
}
```

Table 2. Mean values and standard deviations of "simple" OCT parameters divided by foveal shape for Normative database group and Study sample group.

		Preserved	Reduced	Absent	Inverted	Total
Normative Database	N. eyes	78	68	76	77	299
	CFT mean ± SD (µm)	235.57 ±43.27	295.11 ±66.80	402.81 ±70.03	582.26 ±107.82	380.90 ±153.27
	CST mean ± SD (µm)	286.5 ±51.49	326.86 ±73.56	408.78 ±69.50	552.55 ±104.08	395.28 ±128.39
	CSV mean ± SD (mm³)	0.22 ±0.04	0.27 ±0.06	0.31 ±0.05	0.43 ±0.08	0.31 ±0.10
Sample Study	N. eyes	26	20	24	10	80
	CFT mean ± SD (µm)	234.26 ±44.91	327.75 ±71.46	395.25 ± 46.13	521.1 ±78.28	341.78 ± 109.44
	CST mean ± SD (µm)	286.03 ±55.62	365.6 ±86.60	404.04 ±48.72	503.1 ±80.7	368.46 ±95.56
	CSV mean ± SD (mm³)	0.22 ±0.04	0.28 ±0.06	0.31 ±0.03	0.39 ±0.06	0.28 ±0.07

CFT: central foveal thickness; CST: central subfield thickness; CSV: central subfield volume; SD: standard deviation

Table 3. Tenth and ninetieth percentiles of all OCT parameters values measured from Normative Database divided by foveal depression class. Overlapping values between different classes are in bold.

Foveal depression	CFT (µm)		CST (µm)		CSV(mm³)		CI		PI		FI 1		FI 2		FI 3	
	10th	90th	10th	90th	10th	90th	10th	90th	10th	90th	10th	90th	10th	90th	10th	90th
Preserved	192,4	**281,6**	234	**339,3**	0,18	**0,26**	0,75	**0,87**	0,74	**0,92**	1,54	1,75	1,37	1,62	1,24	1,52
Reduced	**237,1**	**435,4**	**260,6**	**472,1**	**0,20**	**0,37**	**0,86**	0,95	**0,86**	1,10	1,76	**2,04**	1,65	**1,97**	1,56	**1,91**
Absent	**309,3**	**497,9**	**317,9**	**495,8**	**0,24**	**0,38**	0,96	**1,01**	**0,97**	1,09	**1,94**	2,1	**1,91**	2,11	**1,88**	2,11
Inverted	**456,8**	739,2	**426**	685,8	**0,33**	0,53	1,01	1,1	1,13	1,32	2,13	2,39	2,14	2,48	2,16	2,58

CFT: central foveal thickness; CST: central subfield thickness; CSV: central subfield volume; CI: Centrofoveal Index; PI: Parafoveal Index; FI: Foveal Index.

Table 4. Cross-tables evaluating the agreement, expressed in percentages, between reference (ref) and test (test) classification of OCT scans from the Study Sample group for all parameters. The bold numbers refer to the OCT scans correctly classified by the software.

	Central foveal thickness (70%)				**Central subfield thickness (58.75%)**				**Central subfield volume (60%)**				**Centrofoveal Index (80%)**			
	I test	A test	R test	P test	I test	A test	R test	P test	I test	A test	R test	P test	I test	A test	R test	P test
I ref	**6**	4	0	0	**4**	6	0	0	**8**	2	0	0	**3**	7	0	0
A ref	0	**22**	2	0	2	**19**	3	0	5	**19**	0	0	0	**19**	5	0
R ref	1	7	**7**	5	2	8	**3**	7	4	10	**0**	6	0	2	**18**	0
P ref	0	1	4	**21**	0	4	1	**21**	0	5	0	**21**	0	0	2	**24**
	Parafoveal Index (72.5%)				**Foveal Index 1 (88.75%)**				**Foveal Index 2 (96.25%)**				**Foveal Index 3 (97.5%)**			
	I test	A test	R test	P test	I test	A test	R test	P test	I test	A test	R test	P test	I test	A test	R test	P test
I ref	**5**	4	0	0	**8**	2	0	0	**10**	0	0	0	**10**	0	0	0
A ref	0	**24**	0	0	0	**22**	2	0	0	**24**	0	0	0	**22**	2	0
R ref	1	10	**8**	1	0	2	**18**	0	0	3	**17**	0	0	0	**20**	0
P ref	0	2	3	**21**	0	0	3	**23**	0	0	0	**26**	0	0	0	**26**

Foveal depression morphology: (I) Inverted; (A) Absent; (R) Reduced; (P) Preserved.

Discussion

Central retinal thickness is the most used measure when performing an OCT scan of the macula. In patients with macular edema or epiretinal membranes structural alterations of the neuroepithelium and foveal depression changes are also described. These changes are not measurable but are defined by the examiner in terms of categories or subjective judgments. Measuring foveal depression changes together with central retinal thickness, could improve the management of patients with macular diseases. Quantitative measures reduce subjective mistakes and enable accurate comparison reading.

In our study we evaluated the ability to assess foveal depression changes by “simple” (CST, CFT, CV) and “combined” OCT parameters (CI, PI, FI1-2-3), the latter derived from a mathematical combination of the macular thicknesses. The aim to develop “combined” parameters is to get more information than what is provided by an individual thickness value. FIs contain information derived from the analysis of six different values of retinal thickness, both centrofoveal (CST, CFT) that parafoveal (ISS, INS, IIS, ITS). Moreover, FI2 and FI3 give greater importance to centrofoveal area by using the exponent.

For each value of the OCT parameters we calculated the most likely foveal shape class using Bayes’ theorem. This method allowed us to calculate the conditional probability that a value of OCT parameters fits a foveal shape class (conditioned event) knowing the probability of observing that value given the foveal shape class (conditioning event). The software correctly classified into the four foveal shape classes the highest number of OCT scans when it was based on FI2 and FI3 values, reaching a degree of agreement with the examiner’s classification of 96.25% and 97.5%, respectively. A few errors occurred when the software had to distinguish between reduced and absent foveal depression. In fact, examining how the FI values are distributed in the four morphologic classes of Normative database (Table 3), the only overlap between percentiles that we noted was for reduced and absent foveal depression classes. Between these two classes, FI3 showed less percentile overlap, ranging between 1.88 and 1.91. On the contrary, all other OCT parameters showed more pronounced percentile overlapping between different classes of foveal depression.

A FI3 value of 1.52 or less indicates a preserved foveal profile, regardless of central retinal thickness. As shown in Figure 1, although the CST of the two OCT scans is the same, the FI3 of the patient with preserved profile is 1.39 while the FI3 of the patient with absent foveal depression is 2.10. In this way IF3 values, together with macular thickness, could be part of daily OCT reports and possibly it could be used for research purposes during clinical trials.

The methods described in literature to measure foveal shape use complex mathematical models to process OCT data. Dubis et al. (2) used a difference of Gaussians function to measure the foveal shape of normal and myopic eyes. The authors calculated a mathematical function by processing data from time-domain OCT scans and they were able to get from the equation some measures of the fovea such as depth, diameter and slope. Since a single function is unable to describe the asymmetries present in opposite foveal sectors, Scheibe et al. used multiple functions all from the center of the fovea and with equiangular radial distribution (3). Other authors reported techniques to measure foveal

shape based on customized software used to process the OCT scans (4-6).

All these methods have had little practical applications because they cannot be used in presence of any macular disease and are strictly dependent on additional data processing. On the contrary, FI3 comes from macular thickness values that any OCT system can easily measure and possibly process with only minor updates to the software. The reliability of FI3 in describing the foveal shape depends on how accurately the examiner is able to classify the OCT scans of the normative database. Using two or more independent examiners could improve the accuracy of the measurements.

In our study we considered normal eyes and eyes with macular edema and epiretinal membranes where the center of the fovea was recognizable. Therefore the measurement of foveal morphology with FI3 is not applicable to patients with macular degeneration and when the foveal center is not identifiable on the OCT maps.

In conclusion, the "combined" OCT parameters, particularly FI3, seem able to measure the degree of foveal depression reliably in normal eyes and in eyes with macular edema and epiretinal membranes. The method described can be applied to any available OCT device, if a normative database specific for that system is created. In the future, further studies will be needed to evaluate the clinical value and the scope of application in measuring foveal shape with "combined" OCT parameters.

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