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ORIGINAL ARTICLE

Subfoveal Choroidal Thickness and Its Intereye Differences in Fuchs Uveitis Syndrome Evaluated Using Optical Coherent Tomography

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ABSTRACT

Purpose: To measure the subfoveal choroidal thickness (SFCT) and assess intereye subfoveal choroidal thickness difference (ISFCTD) in patients with unilateral Fuchs Uveitis Syndrome (FUS) compared with healthy controls.

Methods: Forty-two patients with unilateral FUS were included in this observational retrospective study. SFCT in both eyes was measured in patients and controls using optical coherent tomography. The measurements were analyzed and compared as follows: for SFTC-affected eye vs fellow eye (FUS); affected eye (FUS) vs right control eye; fellow eye (FUS) vs left control eye; for ISFCTD – FUS patients vs controls. In addition, measurement error analysis was performed.

Results: No significant differences in SFCT between the compared eyes were found ($p > .05$). The mean ISFCTD was 57.24 ± 40.8 µm in FUS patients and 30.33 ± 25.48 µm in controls ($p < .,001$).

Conclusion: The ISFCTD was higher in FUS patients than in controls. There were no statistically significant differences in SFCT between the compared eyes.

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KEYWORDS
Choroidal thickness; Fuchs uveitis syndrome; optical coherence tomography; choroidal thickness intereye difference; choroid

Introduction

Fuchs uveitis syndrome (FUS) is also known as Fuchs heterochromy, Fuchs heterochromic iridocyclitis, Fuchs iridocyclitis or Fuchs heterochromic cyclitis.[1–6] These differences in terminology reflect different opinions concerning the etiology and the clinical picture of the disease. FUS is a rare type of mainly unilateral uveitis that accounts for 1–12.3% of all uveitis cases.[7] The typical age at presentation is 30–40 years.[4,7] The incidence is 0.9 per 100 000 per year and both genders are equally affected.[4,7] The diagnostic criteria include diffuse keratic precipitates, vitreal debris, mild anterior uveitis without posterior synechia and macular edema, and iridial stromal atrophy resulting in heterochromy.[4,5,8] Although FU is classified as anterior uveitis, there are reports of changes localized to the posterior segment of the eye.[8–12]

Optical Coherent Tomography (OCT) is a widely used, noninvasive, accurate and fast method for the diagnosis of most posterior pole retinal abnormalities.[13,14] The Enhanced Depth Imaging (EDI) option in spectral domain (SD)-OCT and penetration of swept source (SS)-OCT allow visualizing the choroid.[13,14] OCT has been used in a number of studies to evaluate subfoveal choroidal thickness (SFCT) in a variety of ocular diseases.[15–18]

Recently, the diagnosis of FUS is based purely on clinical findings. Also, there are no tools available to predict progression tempo or next aggravations. In spite of those facts, there are different trials trying to identify any useful diagnostic tool for prognosis and treatment. Promising one is SFCT – in literature, there are studies concerning that topic, showing noticeable differences.[9–11]

Because of small samples in all of those works, and substantial differences between ethnic groups in SFCT in healthy individuals, we decided to conduct our own study with larger groups in Polish population. In addition, we also wanted to check if intereye SFCT difference (ISFCTD) among patients with FUS differs from one in healthy individuals. Our hypothesis was that SFCT in affected eye is significantly different from healthy eye among patients and healthy controls without such difference in control group. Second hypothesis was that ISFCTD will be higher in patients with FUS in comparison to control group. If those hypotheses would be confirmed, this work could be a basis for next, prospective trials for correlating SFCT and/or ISFCTD with length, recurrence and severity of FUS which could turn in useful tool for clinicians.

To the best of our knowledge, to date there have been only 3 studies, from Turkey and Italy,[9–11] evaluating SFCT in FUS in small samples of patients and no studies concerning ISFCTD comparisons.

Material and Methods

The purpose of this study was to measure SFCT and intereye subfoveal choroidal thickness difference (ISFCTD) in patients with unilateral FUS for comparison with healthy controls.

The study is based on the review of the medical records of patients treated in the First Department of Ophthalmology, Medical University of Warsaw in the years 2015–2018. Seventy-

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two records were identified and initially reviewed based on the diagnosis on admission. The control group consisted of 63 healthy volunteers who were employees of the First Department of Ophthalmology, Medical University of Warsaw.

The inclusion criteria for FUS patients were: diagnosed unilateral FUS (based only on clinical findings) and an insight into the eye fundus sufficient for its visualization on clinical examination (information derived from the medical records). Bilateral FUS, insufficient visualization of the choroid with OCT, previous ocular surgery, other eye diseases, and cardiovascular diseases were the exclusion criteria. Two subgroups, of affected eyes and of fellow eyes, were distinguished. In the control group, both eyes of each participant had to be free from eye disease and the exclusion criteria were insufficient visualization of the choroid with OCT, previous ocular surgery, cardiovascular disease and BCVA <1.0. Again two subgroups were established, one comprising right eyes (RE) and the other left eyes (LE). To identify potential study patients as meeting inclusion criteria and matching none of the exclusion criteria, the medical records were reviewed to obtain such data as the final diagnosis, age, sex, past ocular/systemic medical histories, and ocular anterior and posterior segment findings. Identification of the affected and fellow eyes was also based on the medical record review. Subsequently, OCT scans of the study patients were extracted from the OCT database and analyzed. Only 7-line scans obtained with spectral-domain optical coherence tomography (SD-OCT) using enhanced depth imaging (EDI) technique (Heidelberg Spectralis) were included in the evaluation. If a patient had more than one OCT examination, the scan with the best visualization of the choroid was chosen. Measurements were performed manually on a line scan passing through the fovea directly beneath its center, using a built-in software caliper. SFCT was defined as the distance between the outermost hyperreflective line of the retinal pigment epithelium (RPE) and the chorioscleral junction or in its absence, reflects from the last choroidal vessels. When there was no sharp internal or external border, the measurement accuracy was evaluated (within sections of <5 μm, <10 μm, <20 μm, <50 μm and >100 μm). In other cases, we assumed a measurement accuracy at 1 μm, which is the accuracy of the tool. A representative measurement is shown in Figure 1.

Next, the measurement error was calculated as the measurement accuracy divided by the choroidal thickness (expressed as percentage). For further analysis, only subjects with a measurement error below 5% in both eyes were included.

The study inclusion process is presented in the flowchart (Figure 2).

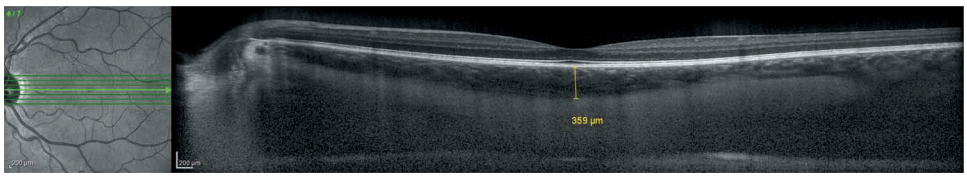

Figure 1. Representative measurement of SFCT with a built-in caliper, Heidelberg Spectralis.

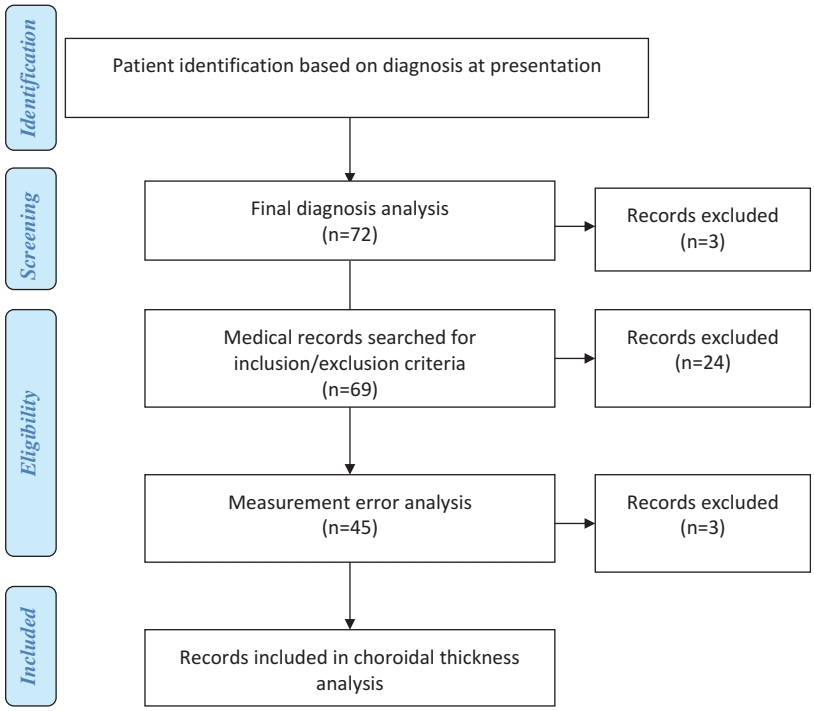

Figure 2. Flow chart presenting the study inclusion process.

Statistical analysis was performed with Statistica ver. 13.1, data analysis software package (StatSoft Polska) and the programming language and environment to statistical calculation R (R Foundation for Statistical Computing, Vienna, Austria). A value of $p < .05$ was considered to be statistically significant for all analyses.

Statistical analyses were performed for the following comparisons in the following groups of eyes:

SFCT: the affected eye (AE) vs the fellow eye (FE); AE vs the control right eye (RE); FE vs the control left eye (LE), intereye SFCTD in FUS vs intereye SFCTD in controls. For each compared group of eyes the following information was provided: size (N) and the minimum (min), maximum (max), mean, median and standard deviation (SD) of the measurements. The Shapiro-Wilk W-test was performed to identify the normality of distribution. Statistical tests are shown in Table 1.

In all cases of normal distribution in the comparisons, the homogeneity of variance was assessed with Bartlett's test, and if $p < .05$ correction for unequal variances was implemented.

Results

A total of 72 patients with unilateral FUS were initially identified and subsequently 27 patients were excluded due to either insufficient quality of the choroid visualization on the scan or because they matched the exclusion criteria. Another 3 patients were excluded because of a very high measurement error. Ultimately, 42 patients (27 females, 15 males), mean age 41.6 ± 13.41 years, were included in the statistical analyses. The control group consisted of 63 healthy volunteers (43 females, 20 males)., mean age 38 ± 16.55 years. Demographics and sizes of both groups are shown in Table 2.

The mean and median SFCT in FUS patients and controls did not significantly differ although the SFTC values tended to be higher in FUS patients. In the FUS group, the standard deviation was noticeably higher, especially in the fellow eye measurements. The results are shown in Table 3.

Statistical analysis showed no significant differences in the SFCT in any of the comparisons and nearly two-fold significantly higher ISFCTD in FUS patients compared with controls ($p < .001$). The results are summarized in Table 4 and in box plots in Figures 3 and 4.

Table 1. Use of statistical tests in comparisons between groups.

		Groups	
		Paired	Unpaired
Distribution	Normal	Paired Student's -t test	Unpaired Student's-t test
	Other than normal	Wilcoxon signed-rank test	U Mann-Whitney test

Table 2. Demographics and sample size.

	N	Age (mean, years)	Age (SD, years)	F (%)	M (%)
FUS	42	41.60	13.41	63	37
Controls	63	38.00	16.55	68	32

Abbreviations: FUS = Fuchs uveitis syndrome group; N = sample size; SD = standard deviation; F = females; M = - males

Table 3. Summary of SFCT and ISFCTD results (μm).

		N	Mean	Median	Min	Max	SD
SFCT	AE	42	313.14	318	143	560	98.92
	FE	42	328.81	325	62	526	106.06
	RE	63	307.59	303	101	453	77.38
	LE	63	309.79	309	107	484	78.68
ISFCTD	FUS	42	57.24	51	3	186	40.80
	Controls	63	30.33	22	0	127	25.48

Abbreviations: SFCT = subfoveal choroidal thickness; ISFCTD = intereye subfoveal choroidal thickness difference; AE = affected eye (FUS group); FE = fellow eye (FUS group); RE = right eye (control group); LE = left eye (control group); FUS = Fuchs uveitis syndrome group

Table 4. Summary of statistical analysis results for all comparisons.

	Comparison	P-value (mean)	Mean difference (95% CL)
SFCT	AE vs FE	0.149*	−15.67 (−37.19–5.85)
	AE vs RE	0.748*	5.56 (−28.66–39.77)
	FE vs LE	0.324**	5.56 (−28.66–39.77)
ISFCTD	FUS vs control	<0.001***	21.00 (12.00–33.00)

*- paired Student's t-test; **- paired Student's t-test with correction for unequal variances; ***- U Mann–Whitney test;

Abbreviations: SFCT = subfoveal choroidal thickness; ISFCTD = intereye subfoveal choroidal thickness difference; AE = affected eye (FUS group); FE = fellow eye (FUS group); RE = right eye (control group); LE = left eye (control group); FUS = Fuchs uveitis syndrome group.

Discussion

SFCT

To the best of our knowledge three studies only, two from Turkey and one from Italy, have assessed the subfoveal choroidal thickness in patients with Fuchs uveitis syndrome.[9–11] The study of Balci and Ozsutsus had a control group and the studies of Kardes et al. and Carquaglia et al. involved the comparison between the affected and fellow eye in FUS patients.[9–11] There was also a study concerning healthy individuals in Turkish population that can be used to access the control group for Balci and Ozsutsus work.[19] Interestingly, there was a large difference in SD between study of Balci and Ozsutsus and Tuncer et all (the SD was approximately 30% lower in the study of Balci and Ozsutsus).[9,19] The low SD and small-size study groups may produce apparent statistical significance, which may be difficult to prove in studies involving larger patient groups and a high SD as in the study of Tuncer et al. The study of Kardes et al. was also conducted also in Turkish patients and its findings were consistent with the study of Balci and Ozsutsus. The study of Carquaglia et al. reported findings from eight Italian patients with very large differences between individual measurements.[10] Such a small study group with a high variance and absence of a control group carries a high risk of bias and it is difficult to compare the Italian findings with the studies from Turkey and our study. Information concerning all above works are collected in Table 5 (age and sample size) and Table 6 (mean SFCT for affected eye, unaffected eye and control group)

Although the cited studies demonstrate thinning of the SFCT in the affected eye in comparison to the fellow eye,[9–11] Balci and Ozsutsu reported lower SFCT values in the affected eyes when compared with healthy controls.[9] Both studies differ from our findings. There may be several reasons for that. One could be the difference in sample size – 42 patients with FUS and 63 healthy

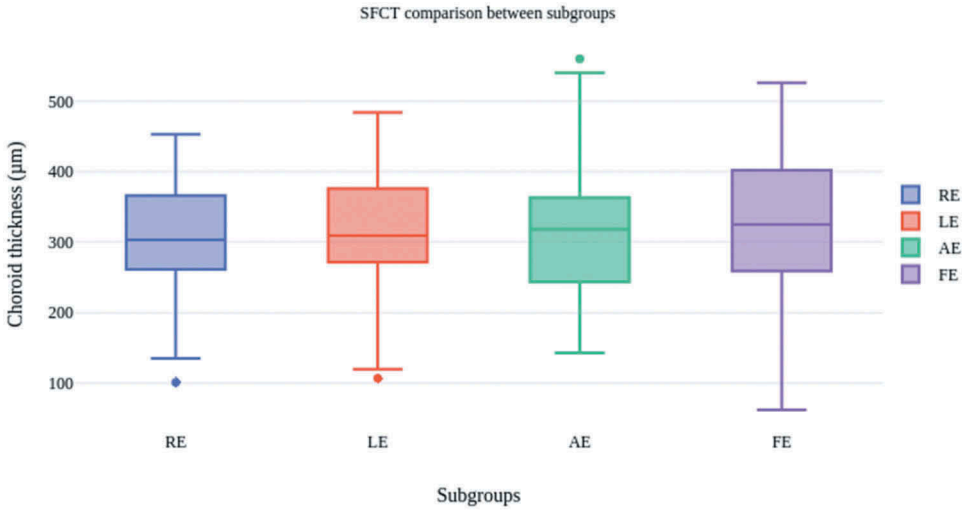

Figure 3. SFCT comparison between eyes.
Abbreviations: SFCT = subfoveal choroidal thickness; AE = affected eye (FUS group); FE = fellow eye (FUS group); RE- = right eye (control group); LE = left eye (control group)

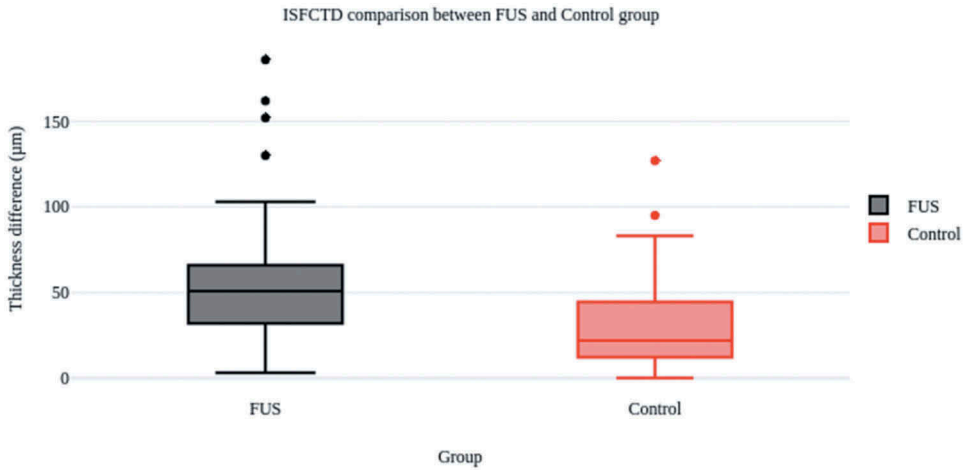

Figure 4. ISFCTD comparison between FUS group and controls.
Abbreviations: ISFCTD = intereye subfoveal choroid thickness difference; FUS = Fuchs uveitis syndrome group

Table 5. Comparison between different studies – group sizes.

Authors	Country	FUS group (mean, SD, years)	AE	FE	Mean age of control group (mean, SD, years)	Control group
Balci and Ozsutsus	Turkey	36.2 ± 8	15	15	35.5 ± 6.2	20
Kardes et al.	Turkey	35.2 ± 4.8	25	25	-	-
Carquaglia et al.	Italy	43 ± 10.99	8	8	-	-
Tuncer et al.	Turkey	-	-	-	49.01 ± 19.19	
Our work	Poland	41.60	43	43	38.00	63

Abbreviations: AE = affected eye (FUS group); FE = fellow eye (FUS group).

Table 6. Comparison between different studies – mean SFCT (µm).

Authors	Country	AE	FE	Control group
Balci and Ozsutsus	Turkey	276.7 ± 22.9	313.6 ± 26.8	318 ± 40.1
Kardes et al	Turkey	296.47 ± 32.29	324.47 ± 26.73	-
Carquaglia et al	Italy	255.62 ± 91.32	347.50 ± 91.55	-
Tuncer et al	Turkey	-	-	265.86 ± 60.32
Our work	Poland	313.14 ± 98.92	328.81 ± 106.06	307.59 ± 77.38

Abbreviations: SFCT = subfoveal choroidal thickness; AE = affected eye (FUS group); FE = fellow eye (FUS group).

controls in our study and no more than 25 patients and only one control group (Balci and Ozsutsu – 15 FUS patients and 20 controls,[9] Kardes et al. – 25 patients and no control group,[11] Carquaglia et al. – 8 patients and no control group.[10]) Another reason could be different ethnicities of the study populations. As advised by Bafiq et al. comparing their own results with studies in other populations without considering the differences between them may lead to a high risk of bias.[20] Balci and Ozsutsus only used a control group and their results differ from ours. Neither of those studies included analysis of the measurement error which when performed could have resulted in the exclusion of some of the measurements.[9–11] This effect could be especially significant in studies with very small patient groups as every measurement has then a very high impact on the final results. In addition, neither of those studies, ours included, takes into consideration the duration of FUS.[9–11] Assuming that choroidal thinning is associated with chronic inflammation and autoimmune response, it would be also logical to assume that this effect becomes more pronounced over time.[9–11] In that case, studies in patients with a longer history of FUS would present higher differences in SFCT between the affected eye, fellow eye and controls. Severity and recurrence of the condition also would have a high impact on the results. Hypothetically, if the duration of FUS in patients enrolled in the present study were shorter or FUS symptoms milder than those presented in other studies, it might explain the observed discrepancies. The stage of FUS when an OCT scan is obtained (an SCFT value higher during aggravation and lower during remission) could also be a factor. Inclusion of patients in different stages of FUS could result in no statistical differences in the mean SFCT values with a high SD that was shown in the present study. To conclude, the discrepancies between our findings and the literature could result from different causes, either objective (ethnically different populations evaluated in particular studies) or related to the study design (sample size, measurement accuracy, duration of FUS, its stage and severity, and the time of OCT capturing). To confirm the impact of these factors on the measurements, further prospective studies comparing the results with normative databases of specific populations should be conducted.

ISFCTD

To the best of our knowledge, there are no published studies comparing ISFCTD between patients with FUS and healthy individuals. Hypothetically, a higher ISFCTD could be explained by the absence of disease in the fellow eye, but it is disproved by a greater dispersion relative to the mean of the SFTC values in the fellow eyes versus control eyes which is not observed in the affected eyes versus controls. Those results show that although there are no apparent symptoms, in FUS the fellow eyes differ from the eyes of healthy individuals at least in greater variability of choroidal thickness. It is difficult to draw firm conclusions from those findings and more dedicated studies are needed to address the issue of intereye differences in subfoveal choroidal thickness in FUS.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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