Spectral domain optična koherentna tomografija za odkrivanje glavkoma

Spectral domain optical coherence tomography for detecting glaucoma

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Ključne besede:
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Izvleček

Namen: *Ovrednotiti diagnostično zmožnost meritev debeline mrežnice makule in debeline mrežničnih vlaken (RNFL) ob papili vidnega živca, izmerjene s spectral domain optično koherentno tomografijo (SD–OCT) za odkrivanje glavkoma.*

Metode: *V to prospektivno klinično raziskavo je bilo vključenih 37 oči 20 bolnikov z glavkomom in 30 oči 16 zdravih posameznikov. S SD–OCT smo izmerili debelino mrežnice makule po standardnem protokolu "Macular Cube 512x128" in debelino RNFL ob papili vidnega živca po standardnem protokolu "Optic Disc Cube 200x200". Z določanjem površine pod Reciever Operating Characteristics (AROC) krivuljo in senzitivnosti pri določeni specifičnosti smo ocenili diagnostično zmožnost vseh merjenih parametrov za odkrivanje glavkoma. Najboljša parametra debeline mrežnice in debeline RNFL smo primerjali med sabo.*

Abstract

Purpose: *To evaluate the diagnostic ability of macular thickness parameters and peripapillary retinal nerve fiber layer (RNFL) thickness parameters for detecting glaucoma using spectral domain optical coherence tomography (SD–OCT).*

Methods: *37 eyes of 20 glaucoma patients and 30 eyes of 16 healthy subjects included in this study underwent macular and peripapillary RNFL scans with SD–OCT using standard scanning parameters. The "Macular Cube 512x128" scan protocol was used to measure the macular thickness. The "Optic Disc Cube 200x200" scan protocol was used for assessing the peripapillary region. The discrimination power of all parameters for detecting glaucoma was determined by the Area under Receiver Operating Characteristics (AROC) curve and sensitivity at fixed specificity, followed by a comparison of the best macular thickness*

Rezultati: *Med zdravimi posamezniki in bolniki z glavkomom so se pokazale signifikantne razlike pri vseh merjenih parametrih debeline RNFL ob papili vidnega živca in vseh parametrih debeline mrežnice makule, razen na področju fovee (p = 0,322). Največja AROC s senzitivnostjo pri > 90 % specifičnosti med meritvami debeline RNFL ob papili vidnega živca je bila pri povprečni debelini RNFL (AROC 0,95; senzitivnost 76 %). Največja AROC s senzitivnostjo pri > 90 % specifičnosti med meritvami debeline mrežnice makule je bila pri debelini spodnjega notranjega področja (AROC 0,90; senzitivnost 78 %). Med AROC teh dveh parametrov ni bilo statistično pomembne razlike (p = 0,208).*

Zaključek: *Pri ločevanju glavkomskih bolnikov in zdravih posameznikov s SD–OCT imajo parametri meritev debeline mrežnice makule primerljivo diagnostično vrednost s parametri meritev debeline RNFL ob papili vidnega živca.*

Results: *Significant differences between glaucoma patients and healthy subjects were found in all peripapillary RNFL thickness parameters and all macular thickness parameters, except in the fovea (p=0.322). The largest AROC with sensitivity at >90% specificity among the peripapillary RNFL thickness parameters was found for the average peripapillary RNFL thickness (AROC 0.95, sensitivity 76%). The largest AROC with sensitivity at >90% specificity among the macular parameters was found for the inferior inner macular thickness (AROC 0.90, sensitivity 78%). There was no statistically significant difference between the AROCs of these two parameters (p=0.208).*

Conclusion: *To discriminate glaucoma patients from healthy subjects using SD–OCT, macular thickness parameters had high diagnostic ability which was comparable to that of the peripapillary RNFL thickness parameters.*

INTRODUCTION

Glaucoma is the second most common cause of acquired blindness worldwide, therefore its early diagnosis and treatment are of crucial importance (1). As the affected population does not have reliable symptoms for disease assessment, there has been a tendency to develop objective diagnostic methods for diagnosing and monitoring the disease. The features of glaucoma include pathological loss of retinal ganglion cells which are correlated to changes in the retinal nerve fiber layer (RNFL) and the optic nerve head. Considering that the RNFL and the ganglion cells constitute 30% to 35% of the macular retinal thickness and are thickest in the macular region, it was proposed that glaucomatous damage may be more readily detected in this region (2). To assess structural glaucomatous damage, earlier imaging technologies focused on the peripapillary RNFL, but only the recent advancement in optical coherence technology by spectral domain optical coherence tomography (SD–OCT) revived the idea of scanning the macular region. Recent studies have reported that the macular thickness parameters of SD–OCT were as good as the RNFL thickness parameters for detecting glaucoma (3,4,5,6,7,8,9,10,11).

The aim of this study was to carry out measurements of the peripapillary RNFL thickness and the macular thickness using SD–OCT in glaucoma patients and healthy subjects and to compare the diagnostic ability of macular thickness parameters for the detection of glaucoma with those of peripapillary RNFL thickness parameters.

MATERIALS AND METHODS

In this non–randomized prospective study performed in the Department of Ophthalmology at the University Clinical Centre Maribor, we included patients with open angle glaucoma (OAG) and healthy subjects of comparable age and gender. Informed

consent was obtained from all subjects involved in the study.

General medical and ophthalmological history was taken from all subjects. Each subject underwent a full ophthalmological clinical exam acquiring best corrected visual acquity (BCVA) (decimal equivalents of Snellens visual acuity), slit–lamp biomicroscopy, direct and indirect ophthalmoscopy to assess the optic nerve head and the RNFL (to assess the cup/disc ratio – C/D), gonioscopy, and intraocular pressure (IOP) measurement using the Goldmann aplantation tonometry. All subjects underwent baseline standard achromatic perimetry with the Humphrey's Field Analyzer HFA 750 II (Carl Zeiss–Humphrey Systems) using the C30–2 SITA standard testing protocol. The visual fields were considered reliable if false–positive and false–negative errors did not exceed 30% and fixation errors did not exceed 25%.

The eyes of glaucoma patients were included in the research, if they had BCVA ≥0.63, open angles on gonioscopy, characteristic glaucoma optical neuropathy with any diffuse or local neuroretinal rim thinning, any disc hemorrhage, and/or any RNFL defects, with corresponding visual field defects defined as mean deviation (MD) and pattern standard deviation (PSD) outside 95% normal confidence limits and the glaucoma hemifield test outside normal limits.

The control group of healthy subjects were required to have BCVA ≥0.63, IOP ≤21 mmHg, open angles on gonioscopy, normal–appearing optic nerve head and normal visual fields.

We excluded subjects who had eye trauma or any other disease such as diabetic retinopathy, age–related macular degeneration or uveitis. Eyes with unclear optic media were also excluded from the study.

All included subjects were scanned with the spectral domain Cirrus™ OCT, model 4000, software version 6.0.2.81 (Carl Zeiss Meditec Inc.). The "Optic Disc Cube 200x200" scan protocol was used for assessing the peripapillary region. This constructs a cube of data by acquiring 200 horizontal scan lines, each composed of 200 A–scans. After image acquisition, the machine's glaucoma protocol "ONH and RNFL OU Analysis" was used to automatically find the optic disc and place a calculation circle of 3.46 mm in diameter around it evenly. Subsequently, layer–seeking algorithms defined the RNFL inner and outer boundaries for the entire cube. The "Macular Cube 512x128" scan protocol was used to measure the macular thickness. This constructs a cube of 128 horizontal scan lines, each composed of 512 A–scans. The analysis was done with the "Macular thickness: Macular Cube 512x128" protocol. The minimum acceptable signal strength score in both measurements was 7.

The distribution of the results was checked with the Shapiro–Wilk test. The Student–T test for normally distributed and the Mann–Whitney U test for abnormally distributed variables were used to analyze the differences between the healthy subjects and the glaucoma patients. The Area under the Receiver Operating Characteristics (AROC) curve of each measured parameter was analyzed to assess its power to discriminate glaucoma patients from healthy subjects. The statistical analysis was performed using SPSS 20 for Windows (SPSS Inc., Chicago IL, USA). An AROC comparison was carried out using the method of DeLong et al (12). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 67 eyes of 36 individuals were examined in the study. These included 37 eyes of 20 glaucoma patients and 30 eyes of 16 healthy subjects. There were no statistically significant differences in age, gender, BCVA and IOP between the healthy subjects and glaucoma patients (Table 1). In the glaucoma group there were 3 eyes with pseudoexfoliative glaucoma, 3 eyes with pigmentary glaucoma, and 31 eyes with primary open angle glaucoma.

The results of peripapillary RNFL thickness parameters are shown in Table 2. Statistically significant

differences between healthy subjects and glaucoma patients were found in the average peripapillary RNFL thickness, superior, nasal, inferior and temporal quadrants. The largest AROC (0.95) with 76% sensitivity at 93% specificity was found for the average peripapillary RNFL thickness.

Results of the macular thickness parameters are shown in Table 3. Statistically significant differences between healthy subjects and glaucoma patients were found in the average macular thickness, the superior inner macula (SIM), the nasal inner macula (NIM), the inferior inner macula (IIM), the temporal inner macula (TIM), the superior outer macula (SOM), the nasal outer macula (NOM), the inferior outer macula (IOM) and the temporal outer macula (TOM) ($p < 0.05$), but not in the fovea ($p = 0.322$). The largest AROC (0.90) with 78% sensitivity at 93% specificity was found for the inferior inner macular thickness.

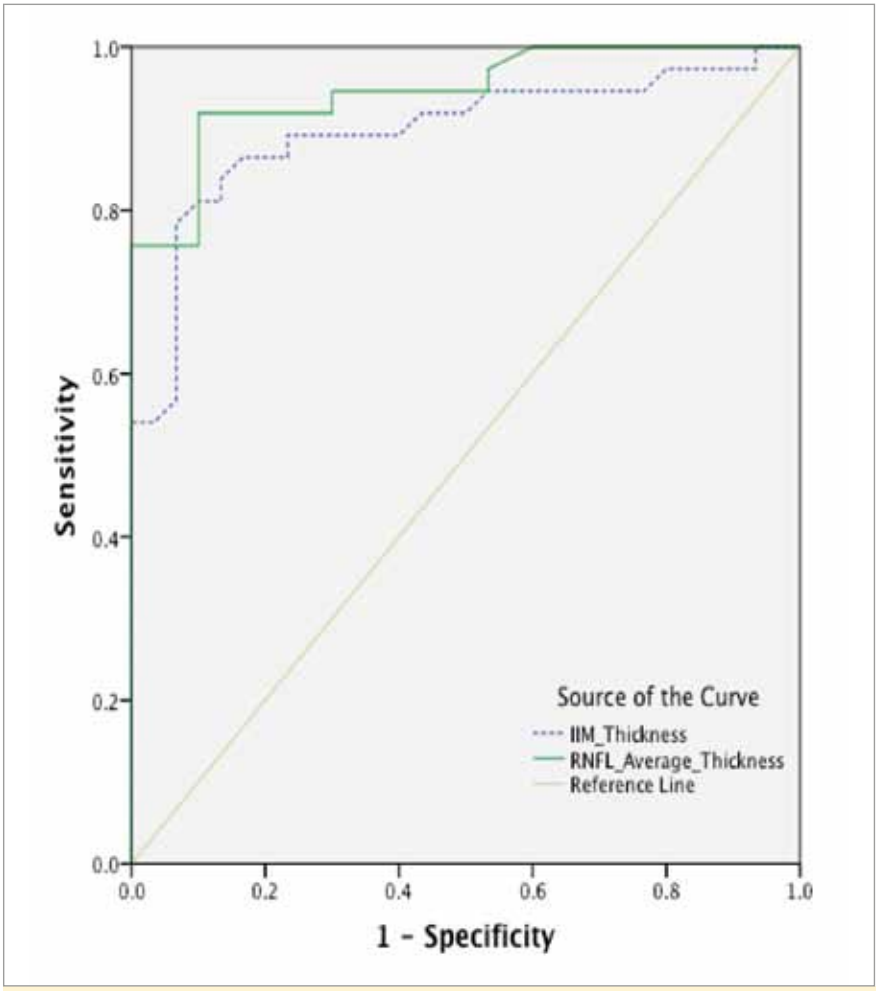

Figure 1. *Area under Receiver Operating Characteristics (AROC) curve for discriminating glaucoma patients from healthy individuals using spectral domain optical coherence tomography. AROC curves of parameters with the largest AROC in peripapillary RNFL thickness and macular thickness, respectively, are shown. IIM_Thickness (dotted line) demonstrates the inferior inner macular thickness; RNFL_Average_Thickness demonstrates the average peripapillary thickness.*

Table 1: *Baseline characteristics*

	Healthy (n = 30)	Glaucoma (n = 37)	p
Age (years)	64.30±9.91	65.05±10.67	0.767
Gender (M/F)	11/19	20/17	0.161
BCVA	0.99±0.05	0.97±0.08	0.297
IOP (mmHg)	15.83±1.95	15.81±2.97	0.972
MD (dB)	-0.48±1.57	-7.69±6.97	0.000
PSD (dB)	2.59±1.05	7.65±4.21	0.000

n – number of eyes; BCVA – best corrected visual acuity (decimal equivalent of Snellens visual acuity); IOP – intraocular pressure; M/F – male/female; MD – mean deviation; PSD – pattern standard deviation

Table 2: *Results of SD-OCT peripapillary RNFL thickness parameters (µm)*

	Healthy (n =30)	Glaucoma (n = 37)	p	AROC	SN/SP (SP>90%)	SN/SP (SP>80%)
Average (µm)	92.11±8.97	65.83±12.94	0.000*	0.95	76/93	92/83
Superior (µm)	110.90±14.61	76.08±19.78	0.000*	0.91	68/93	76/83
Nasal (µm)	74.00±11.20	60.38±15.28	0.000†	0.78	57/93	57/90
Inferior (µm)	120.33±15.75	76.86±23.37	0.000†	0.93	78/93	78/86
Temporal (µm)	63.20±9.39	50.00±10.53	0.000*	0.83	68/93	68/83

*n – number of eyes; p – p-values for evaluating the differences between glaucoma patients and healthy subjects with * Student-T test and † Mann-Whitney U test; AROC – Area under the Receiver Operating Characteristics; SN/SP – sensitivity at fixed specificity for discriminating glaucoma patients from healthy subjects.*

Table 3*: Results of SD-OCT macular thickness parameters (µm)*

	Healthy (n = 30)	Glaucoma (n = 37)	p	AROC	SN/SP (SP>90%)	SN/SP (SP>80%)
Average (µm)	290.12±9.85	272.24±18.21	0.000*	0.82	62/93	76/83
Fovea (µm)	258.63±17.05	268.16±29.61	0.322†	0.43	11/93	16/83
SIM (µm)	324.00±12.01	295.51±22.33	0.000†	0.89	73/93	81/87
NIM (µm)	327.43±11.41	303.95±26.58	0.000†	0.80	57/93	70/83
IIM (µm)	322.40±14.88	286.38±29.55	0.000†	0.90	78/93	87/83
TIM (µm)	310.13±13.02	286.27±19.83	0.000*	0.86	65/93	76/83
SOM (µm)	276.67±9.13	253.41±15.68	0.000†	0.89	76/93	78/87
NOM (µm)	295.50±12.34	271.54±24.05	0.000†	0.83	70/93	70/90
IOM (µm)	267.83±13.11	246.73±22.73	0.000†	0.79	57/93	65/83
TOM (µm)	259.97±11.06	242.30±14.74	0.000†	0.85	35/93	76/83

*n – number of eyes; p – p-values for evaluating the differences between glaucoma patients and healthy subjects with * Student-T test and † Mann-Whitney U test; AROC – Area under the Receiver Operating Characteristics; SN/SP – sensitivity at fixed specificity for discriminating glaucoma patients from healthy subjects; SIM – superior inner macula; NIM – nasal inner macula; IIM – inferior inner macula; TIM – temporal inner macula; SOM – superior outer macula; NOM – nasal outer macula; IOM – inferior outer macula; TOM – temporal outer macula.*

The AROC curves of the peripapillary RNFL thickness and the macular thickness parameters with the largest AROC, thus for the average peripapillary RNFL thickness and for the inferior inner macular thickness, respectively, are shown in Figure 1. A comparison of the average peripapillary RNFL thickness AROC and the inferior inner macular thickness AROC showed no statistically significant difference (p = 0.208).

DISCUSSION

In our study, the parameters of macular and peripapillary RNFL scans using SD–OCT showed similar discrimination power between glaucoma patients and healthy individuals. The best discrimination performance was shown for the inferior inner macular thickness measurement and the average value of

peripapillary RNFL thickness measurements.
The studies by Nakatani et al and by Bowd et al which focused on the detection of early glaucoma by measuring peripapillary RNFL thickness using SD–OCT, show that the inferior region of the optic disc is most commonly affected and that the best glaucoma identification performance was shown in the inferior peripapillary quadrant (13,14). The study by Nakatani et al included 32 eyes of early glaucoma patients and 32 healthy controls (13). The AROC for the inferior quadrant was 0.82, with 53% sensitivity at 91% specificity (13). The AROC for the average RNFL thickness measurement was 0.76 and had a 50% sensitivity at 91% specificity (13).

In their study, Bowd et al examined 56 eyes of early glaucoma patients and 38 eyes of healthy controls (14). They formed two groups of patients based on standard automated perimetry and optic disc appearance (14). In both groups, the inferior quadrant had the largest AROC, being 0.89 in the standard automated perimetry group and 0.91 in the optic disc appearance group, and had 69% and 79% sensitivity, respectively, at 91% specificity (14). The average RNFL thickness measurement had AROC values of 0.85 and 0.89, respectively, and 65% and 74% sensitivity, respectively, at 91% specificity in each group (14).

A large prospective study by Na et al including 424 eyes of glaucoma patients with established disease, as in our study, and 297 eyes of healthy controls, compared macular thickness and peripapillary RNFL thickness parameters for diagnosing glaucoma (15). This study showed the highest diagnostic ability for the average peripapillary RNFL thickness, with an AROC of 0.958 and 87.1% sensitivity at 94.5% specificity, among all peripapillary RNFL thickness parameters and for the inferior quadrant, an AROC of 0.956 and 86.6% sensitivity at 94.4% specificity, among the sectoral measurements (15).

A recent study by Lisboa et al compared different SD–OCT scanning protocols for diagnosing preperimetric glaucoma. They followed 142 eyes of 91 patients suspected of having glaucoma based on the appearance of the optic disc. At the time of imaging all participants had no visual deficits. 48 eyes of 42 participants showed progressive optic disc damage, but no visual field loss. 94 eyes of 49 untreated patients without any evidence of progressive change in the appearance of the optic disc during more than 10 years follow–up were used as controls. Among peripapillary thickness measurements, the largest AROC values of 0.89 and 0.85 were found for the average peripapillary RNFL thickness and the inferior quadrant, respectively. The average peripapillary RNFL thickness measurement showed 70.1% sensitivity at 95% specificity and the inferior quadrant peripapilary RNFL thickness measurement showed 50% sensitivity at 95% specificitiy (16).

The results of peripapillary RNFL parameters in the studies by Nakatani et al, Bowd et al and Na et al are in agreement with the results of peripapillary RNFL parameters in our study. In all studies, high AROCs for the inferior quadrant parameter and the average peripapillary RNFL parameter were seen. The inferior quadrant parameter had a higher AROC in early glaucoma patients and the average peripapillary RNFL parameter had a higher AROC in patients with established disease. The study by Lisboa et al shows a higher AROC for the average peripapillary RNFL parameter compared to the inferior quadrant parameter. This could be due to the study design which included only preperimetric glaucoma patients with optic discs of suspicious appearance.

Na et al also published a retrospective study focusing on the detection of glaucoma progression. They examined 127 eyes of 75 patients and compared different peripapillary and macular parameters. They concluded that the highest reduction in thickness was noted in the inferior RNFL quadrant and inferior outer macula, and that serial measurement of parameters in the peripapillary region as well as the macular region permits identification of progression in glaucomatous eyes (17).

The results of macular thickness measurements in the study by Na et al and by Parikh et al show the

largest AROC for macular thickness of the inferior outer sector, while our results provide the largest AROC for macular thickness of the inferior inner macular sector (15,18). According to Hood et al, the whole inferior segment of the macula is affected early in the development of glaucoma (19), but in the latest study by Na et al, the authors suggest that structural damage is present first in the optic disc region and appears later in the macular region (20).

In the study by Na et al, the inferior outer sector had an AROC of 0.88 and 71.6% sensitivity at 94.4% specificity and the inferior inner sector had an AROC of 0.77 and 65.5% sensitivity at 83.3% specificity (15). Although they included a large sample of patients and healthy controls, the patients had a considerably lower mean age, 57.9 years compared to 64.3 years in our study, and had better visual field test results, mean MD was –5.02 dB compared to –7.69 dB in our study and mean PSD was 6.22 dB compared to 7.65 dB in our study (15).

The study by Parikh et al included 56 early glaucoma patients and 75 healthy controls and the diagnostic ability of the macular thickness paramaters for detecting glaucoma with time–domain OCT was evaluated (18). The AROC of the inferior outer macula in their study was 0.66 and had 58% sensitivity at 75% specificity. The AROC for the inferior inner macula was 0.61 and had 44% sensitivity at 56% specificity. The results of visual field testing were considerably better than in our study, mean MD was –3.55 dB and mean PSD was 3.69 (18). The diagnostic ability of the macular thickness parameters for detecting glaucoma in the study of Parikh et al was considerably lower compared to the same parameters in our study. This could be attributed to the inclusion of early glaucoma patients and the use of time–domain OCT in their study.

The comparison of the parameters with the best AROC among peripapillary RNFL thickness parameters and macular thickness parameters, respectively, in our study showed no significant differences and high diagnostic ability for both parameters. Earlier studies comparing peripapillary RNFL thickness parameters and macular thickness parameters using time–domain OCT showed the higher diagnostic ability of the peripapillary RNFL thickness parameters over the macular thickness parameters (21,22,23). The study by Na et al, in which a SD–OCT tomograph was used, concludes that peripapillary RNFL thickness parameters were generally superior for diagnosing glaucoma, adding that macular thickness parameters are superior in eyes with larger optic discs and in cases of low signal strength (15). The latest study by Yoon et al, comparing the macular and peripapillary thickness parameters acquired using SD–OCT among discs of different sizes, showed no significant differences among different disc sizes or between the peripapillary and macular regions (24). The study by Nakatani et al, also performed using SD–OCT, concluded that the macular thickness parameters had a high and comparable discriminating power when assessed alongside peripapillary RNFL thickness measurements (13). In the macular thickness parameters, the highest AROC of 0.79 was found for the inferior outer macular thickness and the temporal outer macular thickness, but the latter had a 63% sensitivity at 91% specificity, compared to 38% sensitivity at 91% specificity for the inferior outer macular thickness (13). At 81% specificity, the sensitivity for the temporal outer macular thickness remained at 63%, but for the inferior outer macula it increased to 59% (13). The AROC for inferior inner macular thickness was 0.78, the sensitivity at 91% specificity was 36% and at 81% specificity it was 59% (13). The study by Lisboa et al concluded that peripapillary RNFL parameters performed significantly better than macular parameters for diagnosing glaucoma, which may have been due to the inclusion of preperimetric glaucoma patients. They point out that in advanced glaucoma, the macula has a higher chance of being involved and measurements of macular parameters will probably give better performance for glaucoma diagnosis (16). Although there are differences among these parameters, they are small and in agreement with the results of our study.

On the basis of the results of our own and other studies we can conclude that to discriminate glaucoma patients from healthy subjects using SD–OCT, macular thickness parameters have a high diagnostic ability which is comparable to the peripapillary RNFL thickness parameters. Studies have confirmed the existence of glaucomatous damage to the macula, however, further studies based on larger samples should be performed to define the exact role of macular thickness parameters in glaucoma detection.

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