(35)

The reliability and applicability of a macular thickness measurement in the diagnostic evaluation of primary open angle glaucoma

Ocena wiarygodności i przydatności metody pomiarów grubości siatkówki w okolicy plamki w diagnostyce jaskry pierwotnej otwartego kąta

Barbara Polaczek-Krupa, Iwona Grabska-Liberek

Department of Ophthalmology, Medical Centre for Postgraduate Education, Warsaw, Poland
Head: Assist. Professor Iwona Grabska-Liberek, MD, PhD

Streszczenie: Cel: ocena czułości, swoistości oraz współczynnika wiarygodności metody pomiarów grubości siatkówki w okolicy plamki oraz przydatności tych pomiarów w diagnostyce jaskry pierwotnej otwartego kąta.
Materiał i metoda: stu dziewięćdziesięciu czterech pacjentów (371 oczu) w wieku od 30 do 65 lat poddano szczegółowemu badaniu okulistycznemu oraz badaniu grubości siatkówki w okolicy plamki za pomocą analizatora grubości siatkówki. Badanie to obejmowało oznaczenie średniej grubości siatkówki w dołeczku, w dołku, w obszarze okołodołkowym oraz w tylnym biegunie. Otrzymane wartości liczbowe oceniono za pomocą analizy statystycznej, wyznaczając czułość, swoistość oraz iloraz wiarygodności metody.
Wyniki: wyznaczone wartości dodatniego i ujemnego ilorazu wiarygodności wyniosły odpowiednio dla poszczególnych obszarów: w dołeczku (2,374 i 0,456), w dołku (2,501 i 0,482), w obszarze okołodołkowym (6,161 i 0,099) oraz w tylnym biegunie (6,019 i 0,124).
Wniosek: metoda pomiarów grubości siatkówki w obszarze okołodołkowym oraz obszarze tylnego bieguna charakteryzuje się dużą czułością i swoistością, wysokim dodatnim współczynnikiem wiarygodności oraz bliskim zeru ujemnym współczynnikiem wiarygodności. Pomiar grubości siatkówki w tych obszarach może zatem znaleźć zastosowanie we wczesnym rozpoznawaniu jaskry pierwotnej otwartego kąta.
Słowa kluczowe: grubość siatkówki, plamka, analizator grubości siatkówki – RTA, czułość, swoistość, wiarygodność.
Abstract: Aim: The aim of the study was to evaluate the sensitivity and specificity of retinal thickness measurements in the macular region and the applicability of this method in the diagnosis of primary open-angle glaucoma.
Material and methods: A group of 194 subjects (371 eyes) aged 30 to 65 years underwent a comprehensive ophthalmic examination including the macular thickness measurement using the rerinal thickness, analyzer. The following parameters were determined: foveolar average thickness foveal average thickness, perifoveal average thickness and posterior pole average thickness. The data was analyzed statistically in order to determine the sensitivity, specificity and the likelihood ratio for the measurement method.
Results: We found the following positive and negative likelihood ratio values for the respective interest areas: foveolar average thickness (2.374 and 0.456), foveal average thickness (2.501 and 0.482), perifoveal average thickness (6.161 and 0.099) and posterior pole average thickness (6.019 and 0.124).
Conclusion: For the perifoveal and posterior pole regions, the method of retinal thickness measurement showed a high sensitivity and specificity as well as a high positive likelihood ratio and a near-zero negative likelihood ratio. The retinal thickness measurements can therefore be successfully applied in the diagnosis of primary open-angle glaucoma.
Key words: retinal thickness, macula, retinal thickness analyzer – RTA, sensitivity, specificity, validity.

The current diagnosis of primary open angle glaucoma (POAG) is based on the assessment of the optic nerve head, the neuroretinal rim and the retinal nerve fibre layer during the dilated slit lamp exam using a Volk lens. However, this evaluation is greatly dependent on the experience of the examiner it is difficult to interpret the findings because of the high inter-individual variation of optic disc anatomy. At present, widely applied diagnostic modalities include HRT laser scanning ophthalmoscopy and GDx scanning laser polarimetry (1). These methods are particularly helpful in the diagnosis of early glaucoma but the obtained results are often inconclusive, hence, direct ophthalmoscopystill remains an essential tool. Given this background, the search for alternative diagnostic methods continues. New developments include the retinal thickness analyser (RTA), which can be used for the assessment of retinal thickness in the macular region. The method is a new extension of the diagnostic armamentarium used in POAG in Poland. However, it seems that the measurements taken in the perifoveal region can offer the sensitivity and

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likelihood ratio comparable with the optic disc assessment, because the anatomy of the scleral canal does not interfere with the arrangement of nerve fibres and the distribution of retinal ganglion cells at this site (2). The altered macular thickness can therefore indirectly suggest the atrophy of retinal ganglion cell and retinal nerve fibre layers. Many published studies point to the correlation between the macular thickness and the presence of glaucomatous neuropathy, advocating the use of those parameters in diagnostic workup (3–5).

The aim of the study was to assess the sensitivity, specificity and the likelihood ratio of r a macular thickness measurement method and the applicability of such measurements in the diagnostic evaluation of primary open angle glaucoma.

Material and methods

We enrolled 194 subjects (371 eyes), aged 30–65, who presented at the Outpatient Clinic of the Department of Ophthalmology at the Medical Centre for Postgraduate Training in Warsaw between 2007 and 2008 for prophylactic checkups, to obtain a spectacle prescription for the evaluation of the suspected primary open angle glaucoma. The subjects were divided into 3 groups: A, B and C. Group A consisted of 50 patients (95 eyes, mean age 43.7 $\pm$ 9.0 years) with a diagnosis of POAG confirmed using the supplementary diagnostic methods. Group B consisted of 67 patients (128 eyes, mean age 43.2 $\pm$ 11.0 years) who were monitored for the suspected POAG without characteristic glaucomatous perimetry findings. Group C consisted of healthy controls whose diagnostic evaluation for POAG was negative (77 individuals, 148 eyes, mean age 46.3 $\pm$ 10.9 years). We presented a detailed description of the study population in earlier papers (6, 7).

All subjects underwent a detailed ophthalmic evaluation, which included history of glaucoma risk factors; visual acuity assessment (including appropriate spectacle correction), refraction error assessment using a Nikon autorefractometer, intraocular pressure measurement with a Goldmann's applanation tonometer (Tomey, USA), central corneal thickness measurement using the Reichert Technologies pachymeter (USA), anterior segment slit lamp evaluation including lens and cornear claritystatus,iridocorneal angle assessment using a 3-mirror Goldmann goniolens, dilated (1% tropicamide) fundus exam using a Volk lens (78 D). The optic disc was assessed for size, width and shape of the neuroretinal rim as well as hemorrhages. The scanning laser ophthalmoscopy (HRT II, Heidelberg Engineering, Germany), scanning laser polarimetry (GDx VCC, Laser Diagnostics Technologies, USA) as well asvisual field assessment with an automated Humphrey Matrix perimeter (Zeiss, Germany) were performed supplementarily.

We measured retinal thickness in the perifoveal region with a RTA (Talia Technology Ltd., Israel) following pupil dilation with a 1% tropicamide solution. The RTA operates based on the biomicroscopy principle. A helium-neon laser beam is projected on the retina through a dilated pupil and then registered as backscattered light, which forms two peaks representing the vitreoretinal and chorioretinal interfaces. The backscattered light reproduces retinal thickness in the interest area. Every scan covers the retinal area sized 3 x 3 mm and is composed of 16 optical cross-sections. Five scans cover an area of the posterior pole measuring 6 x 6 mm, which represents 20° of the central retina (8). In all groups, we evaluated the foveolar average thickness (VAV, an area of 300 μm diameter with its centre at the fixation point), the foveal average thickness (FAV, an area defined by a radius of 600 μm with its centre at the fixation point), the perifoveal average thickness (PFAV, a ring surrounding the fovea, with an external radius of 2500 μm) and the posterior pole average thickness (PPAV, an area sized 6 x 6 mm, excluding the fovea).

The entire ophthalmic examination, including RTA, was performed at the Department of Ophthalmology of the Medical Centre for Postgraduate Training (MCPT) in Warsaw. The study was approved by the Internal Review Boardof the MCPT in Warsaw (resolutions of 2nd March 2005 and 30th January 2008, No. 13/06). Although the study did not involve any invasive procedures, the patients had been informed about its aim and course, and had given their informed written consent.

Patient enrolment criteria were defined according to the guidelines of the European Glaucoma Society (1) and have been presented in detail in earlier papers (6, 7). The exclusion criteria were: advanced arterial hypertension, heart failure, diabetes mellitus, thyroid disease, previous cataract extraction or other ocular surgical or laser procedures, a history of central retinal vein occlusion, post-inflammatory or post-traumatic retinal degeneration, age-related retinal degeneration, and a refraction error exceeding 2,0 Dsph. We additionally excluded eyes in which retinal thickness measurement with an RTA device was impossible due to optic media opacification, inability to achieve adequate pupil dilation, or impaired visual acuity. Furthermore, we excluded subjects in whom the retinal thickness measurements were of poor quality; and those in whom the optic disc surface area, as measured by HRT, was found to be excessively small or excessively large (below 1.69 mm^2 or over 2.82 mm^2) (1).

We performed a statistical analysis of the measurement matrix (an Excel spreadsheet) (9). For all groups, we evaluated the patternof retinal thickness distribution in the respective areas. Histograms were plotted for all parameters, demonstrating that they have a normal distribution. The statistical significance (or insignificance) of the differences between the mean retinal thickness values in the respective areas was determined using the Student's *t* test. For patients with glaucoma, we assessed the sensitivity, specificity and likelihood ratio of retinal thickness measurement in the macular region. The cut-off values for calculations were based on the average retinal thickness values found in glaucoma suspects (group B). The sensitivity of the method was calculated as the proportion of patients with glaucoma who were correctly identified using the method; its specificity was reflected by the proportion healthy subjects who were correctly identified using the method. The likelihood ratio (LR) of the method was calculated from its sensitivity and specificity. If the positive LR is higher than 10 while the negative LR is lower than 0.1, a method can be used for the confirmation of the diagnosis of a condition. If values for the positive LR are within the range of 5–10 while values for the negative LR are within the range of 0.1–0.2, a method can be used as a highly useful diagnostic tool (9).

Measurement results

Table 1 shows the measurement results for the macular region thickness in the respective interest areas (VAV, FAV, PFAV

and PPAV) for patients with POAG (group A), patients with suspected POAG (group B), and healthy controls (group C). Table II presents the distribution of specific retinal thickness values in the respective interest areas (VAV, FAV, PFAV, PPAV), in the respective groups (A, B, C). The distribution curves are almost symmetrical and bell-shaped.

Grupa/ Group	VAV	FAV	PFAV	PPAV
A	139.0	149.9	173.0	168.1
B	147.6	157.1	187.3	182.5
C	160.9	171.2	201.0	195.7

Tab. I. Mean retinal thickness values for the respective interest areas: VAV, FAV, PFAV, PPAV in subjects from groups A, B and C (μm).
Abreviations: VAV foveolar average thickness, FAV foveal average thickness, PFAV perifoveal average thickness, PPAV posterior pole average thickness

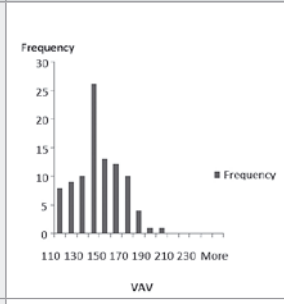
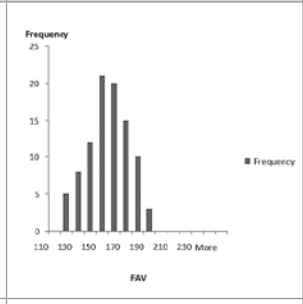
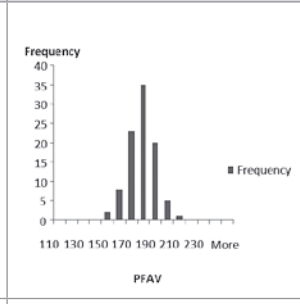
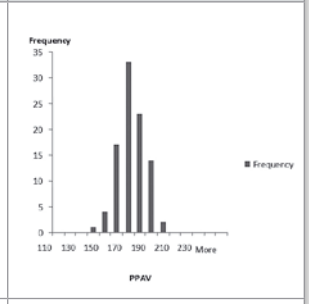
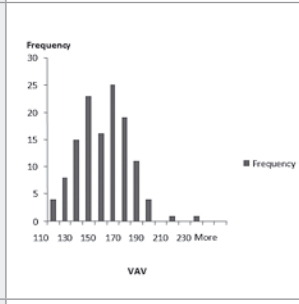
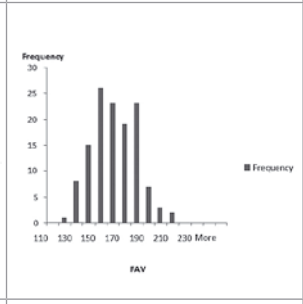
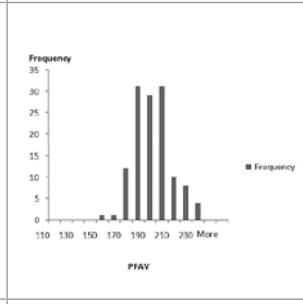
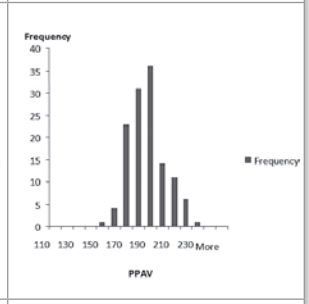
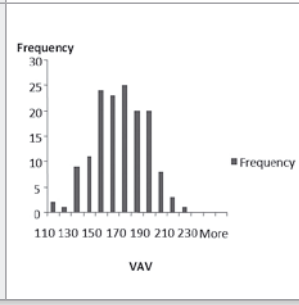
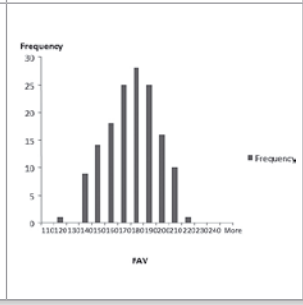
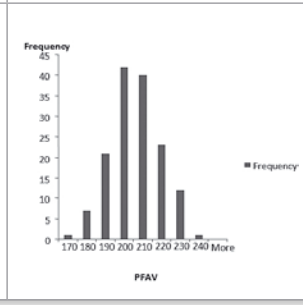
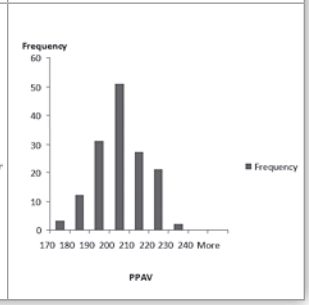
Tab. I. Wartości średnie pomiarów grubości siatkówki w poszczególnych obszarach VAV, FAV, PFAV, PPAV u pacjentów z grup A, B i C (μm).

The calculated values for sensitivity and specificity of the retinal thickness analysis method in the respective macular areas and the likelihood ratio values are presented in Table III.

Comparing retinal thickness between healthy controls (group C) and glaucoma patients (group A), we found that retinal thinning was more marked in the perifoveal and the posterior pole regions rather than around the fovea and foveola. Retinal thickness measurements around the fovea and foveola (VAV and FAV) are characterised by a higher dispersion, larger standard deviation and wider confidence interval found across all study groups (caused by fixation instability), as well as a significantly larger relative measurement error. Moreover, thickness reduction in this retinal region is lower in patients with POAG, hence, a higher diagnostic value should be attributed to thickness measurements of the perifoveal region and the posterior pole region (PFAV and PPAV).

Discussion

The presented groups of healthy subjects, POAG suspects and POAG patients were recruited according to the predefined criteria and subjected to detailed ophthalmic examinations. The three groups were comparable with regard sample size and mean age of subjects. All three groups differed significantly with regard to macular thickness (6, 7). In patients with POAG, the macular region was significantly thinner compared to patients monitored for suspected glaucoma and healthy controls. This shows that the macular region thickness differentiates

Group/ Grupa	VAV	FAV	PFAV	PPAV
A				
B				
C				

Tab. II. Frequency distribution for retinal thickness values in the respective interest areas (VAV, FAV, PFAV, PPAV) in groups A, B, and C.

Tab. II. Rozkłady częstości występowania określonych wartości grubości siatkówki we wszystkich badanych obszarach plamki VAV, FAV, PFAV, PPAV u pacjentów z poszczególnych grup – A, B i C.

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Wynik analizy/ Result of analysis		Grupa/ Group A	Grupa/ Group C	Razem/ Total
VAV				
Dodatni/ Positive		64	42	106
Ujemny/ Negative		31	106	137
Razem/ Total		95	148	243
Czułość/ Sensitivity		0.674		
Swoistość/ Specificity			0.716	
Iloraz wiarygodności/ Likelihood ratio	(+)			**2.374**
	(-)			**0.456**
FAV				
Dodatni/ Positive		61	38	99
Ujemny/ Negative		34	110	144
Razem/ Total		95	148	243
Czułość/ Sensitivity		0.642		
Swoistość/ Specificity			0.743	
Iloraz wiarygodności/ Likelihood ratio	(+)			**2.501**
	(-)			**0.482**
PFAV				
Dodatni/ Positive		87	22	109
Ujemny/ Negative		8	126	134
Razem/ Total		95	148	243
Czułość/ Sensitivity		0.916		
Swoistość/ Specificity			0.851	
Iloraz wiarygodności/ Likelihood ratio	(+)			**6.161**
	(-)			**0.099**
PPAV				
Dodatni/ Positive		85	22	107
Ujemny/ Negative		10	126	136
Razem/ Total		95	148	243
Czułość/ Sensitivity		0.895		
Swoistość/ Specificity			0.851	
Iloraz wiarygodności/ Likelihood ratio	(+)			**6.019**
	(-)			**0.124**

Tab. III. The sensitivity, specificity and likelihood ratio for the retinal thickness analysis method presented by group and interest area (VAV, FAV, PFAV andPPAV).

Tab. III. Zestawienie wartości czułości i swoistości metody analizy grubości siatkówki oraz wielkości ilorazu jej wiarygodności w poszczególnych obszarach plamki (VAV, FAV, PFAV, PPAV).

healthy individuals frompatients with glaucoma or with suspected glaucoma, because retinal thickness in the latter group differs from the one of healthy individuals as well as patients with a diagnosis of advanced glaucoma. Thus, retinal thickness in the macular region can be used as a good diagnostic indicator that differentiates between the healthy individuals and glaucoma patients.

The results of our study are consistent with earlier reports by Zeimer R. et al. (10), Czechowicz-Janicka K. et al. (11),

Brusini P. et al. (4), Salgarello T. et al. (5) Zhikuan Y. et al. (12) and Asrani S. et al. (13). However, their reports included only qualitative data evaluation. Therefore, the direct comparisons were hardly possible. Only Tanito M. et al. (14) have exactly measured the PVAV in POAG patients (185.7 μm) and healthy subjects (211.4 μm). Their measurement results were higher than ours (173.8 μm and 201.0 μm, respectively).

Table III presents the sensitivity and specificity values of retinal thickness analysis and the likelihood ratio for the respective macular thickness parameters (VAV, FAV, PFAV, PPAV). The method was found to be of the highest sensitivity and specificity for the perifoveal area (PFAV, 91.6% and 85.1%, respectively) and the posterior pole area (PPAV, 89.5% and 85.1%, respectively). The positive likelihood ratios for these interest areas were above 6 (PFAV 6.161, PPAV 6.019), while the negative likelihood ratios were close to zero (PFAV 0.099, PPAV 0.124). This means that the analysis provides useful information and can be a valuable diagnostic tool.

Conclusion

The described method of retinal thickness measurement in the macular region offers high sensitivity and specificity as well as a high positive likelihood ratio, especially in the perifoveal and posterior pole areas. Retinal thickness measurement in these areas can be applied for early POAG diagnosis as a valuable extension of the standard armamentarium used for the assessment of the optic disc and the peripapillary area.

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Reprint requests to (Adres do korespondencji):
Barbara Polaczek-Krupa, MD, PhD
Teaching Department of Ophthalmology, Medical Centre for Postgraduate Training,
Czerniakowska Str. 231
00-416 Warszawa
e-mail: basia.polaczek@gmail.com

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