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Relationship between optic nerve head topography and nerve fiber layer thickness with central corneal thickness in patients with primary open-angle glaucoma

Повезаност топографских параметара главе оптичког нерва и дебљине слоја нервних влакана ретине са централном дебљином рожњаче код пацијената са примарним глаукомом отвореног угла

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SUMMARY

Introduction/Objective In patients with primary open-angle glaucoma (POAG) we explored the relationship between optic nerve head (ONH) topography parameters and retinal nerve fiber layer (RNFL) thickness with central corneal thickness (CCT).

Methods This retrospective study included 97 patients (97 eyes) with primary open-angle glaucoma. Patients were divided into a thin CCT<540µm (45 eyes) and a thick CCT≥540µm (52 eyes) group, using ultrasonic pachymeter. Topographic measurements of the ONH parameters and RNFL thickness was performed using optical coherence tomography (OCT). The outcomes were compared with the thin and thick CCT and correlated with the thin CCT of the subjects.

Results There were significantly lower mean intraocular pressure (IOP) (p<0.0001) and CCT (p<0.0001) in patients with thin CCT compared to patients with thick CCT. Statistically significant differences of ONH parameters were found in thin cornea group compared to thick cornea group in: cup/disc area ratio (p<0.03), vertical cup/disc ratio (p<0.01) and rim volume (p<0.01). Statistically significant differences of RNFL thickness were found in thin cornea group compared to thick cornea group in: average (p<0.001), superior (p<0.03), inferior (p<0.03) and nasal (p<0.01). Significant positive correlation was found between thin CCT and OCT parameters in: optic disc area (r=0.429, p=0.003), cup/disc area ratio (r=0.287, p=0.05), horizontal cup/disc ratio (r=0.472, p<0.001), vertical cup/disc ratio (r=0.578, p<0.001), average RNFL (r=0.796, p<0.001), superior RNFL (r=0.665, p<0.001), inferior RNFL (r=0.650, p<0.001), nasal RNFL (r=0.611, p<0.001) and temporal RNFL thickness (r=0.601, p<0.001).

Conclusion POAG patients with thin cornea will probably develop larger glaucoma changes than those with a thicker cornea. Ultrasonic pachymetry measurements of CCT and OCT analysis of ONH topography parameters and RNFL thickness provide significant information in early diagnosis and monitoring progression of POAG.

Keywords: intraocular pressure; ultrasonic pachymetry; optical coherence tomography

САЖЕТАК

Увод/Циљ Истраживали смо повезаност између топографских параметара главе оптичког нерва (*ONH*) и дебљине слоја нервних влакана ретине (*RNFL*) са централном дебљином рожњаче (*CCT*) код пацијената са примарним глаукомом отвореног угла (*POAG*).

Методе У ову ретроспективну студију укључено је 97 пацијената (97 очију) са примарним глаукомом отвореног угла. Пацијенти су подељени на групу са тањом рожњачом (*CCT*<540µm, 45 очију) и дебљом рожњачом (*CCT*≥540*µm*, 52 ока), мерени ултразвучном пахиметријом. Топографска мерења *ONH* параметара и дебљине RNFL рађена су оптичком кохерентном томографијом (*OCT*). Резултати су упоређивани са тањом и дебљом *CCT* и корелирани са тањом *CCT* учесника студије.

Резултати Утврђене су статистички значајно ниже вредности интраокуларног притиска (*IOP*) (p<0,0001) и *CCT* (p<0,0001) код пацијената са танком *CCT* у поређењу са пацијентима са дебљом *CCT*. Код ONH параметара добили смо статистички значајну разлику у групи са танком рожњачом у поређењу са групом са дебљом рожњачом код: површине cup/disc односа (p<0,03), вертикалног cup/disc односа (p<0,01) и rim волумена (p<0,01). Пронађена је статистички значајна разлика код дебљине *RNFL* у групи са танком рожњачом у поређењу са групом са дебљом рожњачом код: средње (p<0,001), горње (p<0,03), доње (p<0,03) и унутрашње (p<0,01) дебљине *RNFL*. Утврђена је статистички значајна позитивна корелација танке *CCT* и *OCT* параметара код: *optic disc* површине (*r*=0,429,p=0,003), површине *cup/disc* односа (*r*=0,287,p=0,05), хоризонталног *cup/disc* односа (*r*=0,472,p<0,001), вертикалног *cup/disc* односа (*r*=0,578,p<0,001), средње дебљине *RNFL* (*r*=0,796,p<0,001), горњег *RNFL* (*r*=0,665,p<0,001), доњег *RNFL* (*r*=0,650,p<0,001), унутрашњег *RNFL* (*r*=0,611,p<0,001) и спољашњег *RNFL* квадранта (*r*=0,601,p<0,001).

Закључак Пацијенти са *POAG* и тањом рожњачом вероватно ће развити веће глаукомне промене од оних са дебљом рожњачом. Ултразвучном пахиметријом мерен *CCT* и *OCT* анализирани топографски *ONH* параметри и дебљина *RNFL*, пружају значајне информације у раној дијагнози и праћењу прогресије код *POAG*.

Кључне речи: интраокуларни притисак; ултразвучна пахиметрија; оптичка кохерентна томографија

INTRODUCTION

Primary open angle glaucoma (POAG) is the disorder of the structural and functional changes of the optic nerve [1].

Glaucoma change of optic nerve may manifest as a morphological damage in the optic nerve head (ONH) as well as a decrease in the thickness of the retinal nerve fiber layer (RNFL) [2].

Optical coherence tomography (OCT) is usually used method for evaluation of structural glaucoma damage [3, 4]. OCT is non-contact and high resolution device which provide a cross-sectional image, good for quantitative evaluation of the ONH and RNFL [5]. It is repeatable and time saving procedure.

Central corneal thickness (CCT) is a risk factor for the development of POAG and a predictive factor for conversion ocular hypertension (OHT) to POAG [1]. It has been reported that thick cornea provide falsely elevated IOP, which may cause a false POAG diagnosis, whereas thin cornea provide an opposite result, which hide the risk of developing POAG [6]. Herendon et al. [7] reported that CCT was an important parameter of glaucoma ONH structural change. Hewitt et al. [8] also found that, in glaucoma eyes, thin CCT was related to increased vertical cup/disc ratio (VCDR).

The aim of this study was to determine whether thin CCT is associated with specific ONH topography parameters and RNFL thickness, measured by OCT in POAG patients.

METHODS

The study was a retrospective on documented 97 patients (97 eyes) with POAG in Ophthalmology practice Family Čivčić, Belgrade. The research was done in accordance with Helsinki Declaration and with the approval of the Local Ethics Committee.

Exclusion criteria were: myopia ≥ - 6 D, secondary glaucoma, POAG advanced glaucoma stage, drusae of the optic nerve head and other anomalies of the optic nerve head, other ocular diseases, history of previous ocular surgery and laser tretman, trauma, systemic comorbidites that may affect the visual field, patients with unreliable visual field (defined as false-negative errors>33%, false-positive errors >33%, and fixation losses >20%), MD ≥ - 10 dB.

In all participants we examine best corrected visual acuity (BCVA), slit-lamp biomicroscopy, intra-ocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy, a dilated fundus evaluation using indirect ophthalmoscopy with 90 D lens, and a 24-2 threshold test using a standard automated perimetry AP-1000 Tomey (Tomey, Nagoya, Japan). In addition, CCT was measured with ultrasonic pachymeter SP-100 Tomey (Tomey, Nagoya, Japan). ONH analysis (disc, cup and rim area, cup and rim volume, cup/disc (C/D) ratio, horizontal and vertical C/D ratio) with RNFL measurements (average and four quadrants RNFL thickness), was performed using spectral domain OCT (SOCT Copernicus Plus, Optopol Technology, Zawiercie, Poland).

POAG patients were classified into two groups according to their median CCT: thin CCT<540μm (45 eyes) and thick CCT ≥ 540μm (52 eyes).

Demographic and clinical characteristics and OCT parameters were compared with the two groups according to the CCT value, using unpaired t-test (Microsoft Excel, Office 2010). Pearson's correlation coefficients (r) were calculated to assess the associations between thin CCT and optic disc morphological parameters. Statistical analysis of Pearson's correlation coefficients were performed by JASP version 0.12.2 (Jeffrey's Amazing Statistics Program, Amsterdam, The Netherlands). The significance level was set at p value of <0.05.

RESULTS

This study included 97 eyes of 97 patients with medically controlled POAG. Of these, 39 (40.21%) patients were male and 58 (59.79%) patients were female. The average age of the examined population was 57.18±13.05 (range 26-78) years. Demographic and clinical characteristics of patients with POAG were compared with the two groups according to the CCT value (Table 1). There were statistically significant difference in mean IOP and CCT between the groups (p<0.0001). IOP with prescribed therapy was significantly higher in patients with thick CCT compared to patients with thin CCT (17.92±2.40 mmHg vs. 15.62±2.39 mmHg, p<0.0001). CCT was significantly higher in patients with thick CCT compared to patients with thin CCT (569.65±22.06µm vs. 512.44±20.39µm, p<0.0001). We found no statistically significant difference between the groups in terms of age, gender and MD (p=0.053, p=0.65, p=0.007).

Table 2 shows a comparison of ONH parameters obtained by OCT between two studied groups. There were statistically significant differences between thin CCT and thick CCT in these stereometric parameters: cup/disc area ratio (0.48±0.15 vs. 0.42±0.11, p<0.03), vertical cup/disc ratio (0.71±0.12 vs. 0.69±0.10, p<0.01) and rim volume (0.12±0.06 mm³ vs. 0.15±0.05 mm³, p<0.01). ONH parameters showed that cup/disc area ratio and vertical cup/disc ratio were significantly larger and rim volume significantly smaller in POAG patients with thin CCT compared to patients with thick CCT.

The average and quadrant RNFL thickness were compared between the thin CCT and thick CCT. Statistically significant differences were found in thin cornea group compared to thick cornea group in: average (102.88±11.04µm vs. 110.32±10.83µm, p<0.001), superior (118.42±16.76µm vs. 125.57±15.82µm, p<0.03), inferior (118.44±19.38µm vs 126.59±16.93µm, p<0.03) and nasal (78.33±12.39µm vs 84.15±11.16µm, p<0.01) RNFL thickness (Table 3). The average and quadrants (superior, inferior, nasal) RNFL thickness were significantly lower in thin cornea group compared to thick cornea group in POAG patients.

There was no statistically significant difference in optic disc area (p=0.45), horizontal cup/disc ratio (p=0.15), cup area (p=0.18), cup volume (p=0.21), rim area (p=0.11) and temporal RNFL thickness (p=0.31) between the two groups (Table 2 and 3).

Table 4 gives the correlation coefficient between OCT parameters (ONH parameters and RNFL thickness) and thin CCT. There was a positive correlation with all OCT parameters. Statistical significance was found in: optic disc area (r=0.429, p=0.003), and cup/disc area ratio (r=0.287, p=0.05). High statistical significance was found in: horizontal cup/disc ratio (r=0.472, p<0.001), vertical cup/disc ratio (r=0.578, p<0.001), average RNFL (r=0.796, p<0.001), superior RNFL (r=0.665, p<0.001), inferior RNFL (r=0.650, p<0.001), nasal RNFL (r=0.611, p<0.001) and temporal RNFL thickness (r=0.601, p<0.001).

DISCUSSION

OCT provide objective and reliable data of ONH and RNFL with a high reproducibility in glaucoma and healthy eyes [9].

CCT has been demonstrated as a important risk factor for development and progression of ocular hypertensive to primary open-angle glaucoma patients [10]. The Ocular Hypertension Treatment Study (OHTS) discovered that the risk for development of glaucoma is larger in eyes with thin CCT and lower in eyes with thick CCT [10]. The present study showed a significantly lower mean IOP (p<0.0001) and CCT (p<0.0001) in POAG patients with thin cornea compared to patients with thick cornea. Patil M et al. [11] have demonstrated that the mean CCT in the normal group (554.38±17.67μm) and the glaucoma group (554.15±16.39μm) was similar and was significantly lower than the mean CCT in the OHTN group (568.18±30.52μm, p<0.01). Bulut M et al. [12] found that the CCT in the

POAG group (545.6±29.7μm) and the healthy control group (551.9±26.2μm) was significantly higher than the CCT in the NTG group (519.0±25.7μm, $p<0.001$). Marić V et al. [13] found in glaucoma suspect patients significantly lower mean CCT in adult than in children (547±35μm vs. 578±35, $p<0.032$).

In the current study ONH parameters showed that cup/disc area ratio and vertical cup/disc ratio were significantly larger and rim volume significantly smaller in POAG patients with thin CCT compared to patients with thick CCT. Anton A et al. [14] and Dagdalen K et al. [9] showed that rim parameters were significantly smaller and C/D ratio significantly greater in glaucomatous eyes than in normal and OHT eyes.

Several studies using OCT showed that the mean RNFL thickness and superior and inferior sector thickness are valuable measurement parameters in the differentiation of glaucoma. Kaushik S et al. [15] found that the RNFL in ocular hypertensives with CCT≤555μm was thinner than in those with thicker corneas. Anton A et al. [14] and Dagdalen K et al. [9] discovered that mean RNFL thickness and superior and inferior RNFL thickness were thinner in glaucoma eyes than in eyes with ocular hypertension and normal eyes. Chen MJ et al. [16] found that the most RNFL thickness (except at the nasal quadrant) were significantly lower in preperimetric glaucoma eyes compared to normal eyes. Bulut M et al. [12] discovered that mean RNFL thickness were thinner in NTG group than in POAG and healthy control group. In the present study, the average and quadrants (superior, inferior, nasal) RNFL thickness were significantly lower in thin cornea group compared to thick cornea group in POAG patients.

In our study a significant positive correlation was found between thin CCT and OCT parameters in: optic disc area ($p=0.003$), cup/disc area ratio ($p=0.05$), horizontal cup/disc ratio ($p<0.001$), vertical cup/disc ratio ($p<0.001$), average RNFL ($p<0.001$), superior RNFL ($p<0.001$), inferior RNFL ($p<0.001$), nasal RNFL ($p<0.001$) and temporal RNFL thickness

(p<0.001). In the recent study Öztürker ZK et al. [17] found a significant positive correlation between thin CCT and inferior RNFL thickness (r=0.353, p<0.005) in patients with POAG. Wangsupadilok B et al. [18] found a significant positive correlation between CCT and RNFL thickness in all quadrants and average RNFL thickness, with highest correlation for average RNFL thickness (r=0.487, p=0.001) in POAG patients.

CONCLUSION

POAG patients with thin cornea will probably develop larger glaucoma changes than those with a thicker cornea. Ultrasonic pachymetry measurements of CCT and OCT analysis of ONH topography parameters and RNFL thickness, provide significant information in early diagnosis and monitoring progression of POAG. It is required to do larger prospective study to confirm these findings.

Conflict of interest: None declared.

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Table 1. Demographic and clinical characteristics of patients with primary open-angle glaucoma

Parameters	**CCT< 540µm (n = 45)** $\bar{x}$ **± SD**	**CCT≥ 540µm (n = 52)** $\bar{x}$ **± SD**	***p***
Age (years)	59.93 ± 12.81	54.80 ± 12.91	0.053
Gender (M/F), n	17/28	22/30	0.65
Mean IOP (mmHg)	15.62 ± 2.39	17.92 ± 2.40	< 0.0001
CCT (µm)	512.44 ± 20.39	569.65 ± 22.06	< 0.0001
MD (dB)	-3.72 ± 1.57	-3.22 ± 1.1	0.077

M/F – male/female; IOP – intra-ocular pressure; CCT – central corneal thickness; *p* – unpaired t – test; MD – mean deviation

Table 2. Optic nerve head topography parameters classified by central corneal thickness (CCT)

Optic nerve head parameters	**CCT< 540µm (n = 45) $\bar{x} \pm$ SD**	**CCT≥ 540µm (n = 52) $\bar{x} \pm$ SD**	***p***
Optic disc area (mm²)	1.72 ± 0.4	1.78 ± 0.36	0.45
Cup/disc area ratio	0.48 ± 0.15	0.42 ± 0.11	< 0.03
Horizontal cup/disc ratio	0.67 ± 0.13	0.63 ± 0.12	0.15
Vertical cup/disc ratio	0.71 ± 0.12	0.69 ± 0.10	< 0.01
Cup area (mm²)	0.84 ± 0.33	0.76 ± 0.27	0.18
Cup volume (mm³)	0.21 ± 0.13	0.18 ± 0.10	0.21
Rim area (mm²)	0.87 ± 0.29	0.97 ± 0.31	0.11
Rim volume (mm³)	0.12 ± 0.06	0.15 ± 0.05	< 0.01

p – unpaired t-test

Table 3. Retinal nerve fiber layer (RNFL) thickness classified by central corneal thickness (CCT)

RNFL thickness	CCT< 540µm (n = 45) $\overline{x} \pm$ SD	CCT≥ 540µm (n = 52) $\overline{x} \pm$ SD	p
Average (µm)	102.88 ± 11.04	110.32 ± 10.83	< 0.001
Superior (µm)	118.42 ± 16.76	125.57 ± 15.82	< 0.03
Inferior (µm)	118.44 ± 19.38	126.59 ± 16.93	< 0.03
Temporal(µm)	63.15 ± 9.81	71.47 ± 11.03	0.31
Nasal (µm)	78.33 ± 12.39	84.15 ± 11.16	< 0.01

p – unpaired t-test

Table 4. Optical coherence tomography parameters in relationship to thin central corneal thickness (CCT)

OCT parameters	**Correlation coefficient (r)**	***p***
Optic disc area (mm^2)	0.429	0.003
Cup/disc area ratio	0.287	0.05
Horizontal cup/disc ratio	0.472	< 0.001
Vertical cup/disc ratio	0.578	< 0.001
Cup area (mm^2)	0.227	0.126
Cup volume (mm^3)	0.118	0.429
Rim area (mm^2)	0.268	0.069
Rim volume (mm^3)	0.108	0.472
Average RNFL (µm)	0.796	< 0.001
Superior RNFL (µm)	0.665	< 0.001
Inferior RNFL (µm)	0.650	< 0.001
Nasal RNFL (µm)	0.611	< 0.001
Temporal RNFL (µm)	0.601	< 0.001

OCT – optical coherence tomography; RNFL – retinal nerve fiber layer; r – Pearson's correlation coefficient; *p* – value

