Relationship between central corneal thickness and ganglion cell complex thickness in mild to moderate myopia

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ABSTRACT

Purpose: Myopia is not only a refractive error, but also a sight-threatening disease. In the study, we searched for a relationship between the central corneal thickness (CCT) and the retinal ganglion cell complex (GCC) thickness in patients with myopia.

Materials and Methods: This prospective cross-sectional study comprised 122 eyes of 122 subjects with mild to moderate myopia. The participants were divided into two groups according to the CCT; below 555 micrometer (Group 1) and above 555 micrometer (Group 2). The CCT was measured using an optical biometer device. All subjects also underwent slit-lamp examination and optical coherence tomography (OCT) imaging. The retinal nerve fiber layer (RNFL) thickness and the GCC thickness were automatically quantified.

Results: The retinal GCC and ganglion cell-inner plexiform layer (GC-IPL) thickness were decreased in Group 1 compared with Group 2 (p=0.002 and p=0.007, respectively). The RNFL thickness was statistically significantly decreased only in the superior-temporal quadrant (p=0.041). There was a significantly positive correlation between CCT and GCC and GC-IPL thickness (r=0.218, p=0.016, and r=0.200, p=0.027, respectively). We did not find any significant correlation between CCT and RNFL thickness (p>0.05).

Conclusions: There was a relationship between the CCT and GCC thickness in eyes with mild to moderate myopia.

Keywords: Central corneal thickness, Ganglion cell complex, Retinal nerve fiber layer, Inner plexifom layer, Myopia.

INTRODUCTION

As known, patients with myopia have a higher tendency to develop glaucoma.[1] The relationship between these two common ocular disorders may be related to the easily deformable lamina cribrosa due to myopia. Myopic changes include elongated axial length and increased vitreous cavity depth together with connective tissue changes which can increase the vulnerability of the optic nerve head to the glaucomatous damage.[2]

Central corneal thickness (CCT) is a substantial parameter in the diagnosis and treatment of glaucoma patients.[3-5] Thicker corneas result in artificially higher intraocular pressure readings.[6] It has been proposed that a thinner cornea is linked to the altered biomechanical and structural characteristics of the posterior sclera and the lamina cribrosa, which may cause a higher vulnerability of the retinal ganglion cells (RGC) to the glaucomatous damage.[7] Previous studies evaluating the correlation between the myopia and the CCT have shown conflicting results.[8]

Glaucoma is an optic neuropathy that can affect all components of the ganglion cell complex (GCC).[9,10] The ganglion cell layer (GCL) thickness is measured in the macular region, owing to the fact that over 50% of the ganglion cells are localized here and the RGC bodies are 10 to 20 times the diameter of their axons.[11-13] Due to tilting of the optic disc and atrophy of the peripapillary region, the retinal nerve fiber layer (RNFL) measurements may be prone to errors in patients with myopia. Therefore, the thickness of the ganglion cell layer (GCL) and inner plexiform layer (IPL) may enable us to detect glaucomatous eyes, besides the RNFL thickness.[11]

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Therefore, in this study, we aimed to search for a relationship between the CCT and the retinal GCC thickness in non-glaucomatous myopic eyes.

MATERIALS AND METHODS

This cross-sectional prospective study was in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Informed consents were obtained from all participants. Based on the evidence from the Ocular Hypertension Treatment Study (OHTS), the participants were divided into 2 groups; those who had CCT below 555 µm (Group 1) and above 555 µm (Group 2).[7]

Patients with myopia less than -6.00 diaopters (D) and astigmatism less than -2.00 D were included. Patients with an axial length over 26 mm, irregular corneal astigmatism, ocular inflammation, previous ocular interventions, history or signs of glaucoma or ocular hypertension, optic nerve disease or neurodegenerative disease, and media opacity affecting OCT image quality were excluded from the study. Only one eye of each participant was included according to the criteria described above. If both eyes met the criteria, a random eye was selected.

All patients underwent a full ophthalmologic evaluation including best-corrected visual acuity measurement, automated kerato-refractometer (Topcon Co., Tokyo, Japan), biomicroscopy, intraocular pressure measurement, and fundoscopy. The CCT measurement was performed with an optical biometry device (Lenstar LS 900, Hagg-Streit AG, Koeniz, Switzerland)).

Heidelberg spectralis OCT (software version 6.3.3.0, Heidelberg Engineering Inc., Germany) imagings were used to measure GCC and RNFL in the study groups. All measurements were made by an observer masked to the study. The OCT images were recorded under dim light conditions between 9:00 am and 12:00 pm in the same room. Before capturing the images, keratorefractive values of the subjects were entered into the software of the OCT device to estimate optical magnification. Heidelberg spectral domain-OCT applies an automatic modification process to reverse the ocular magnification effect, developing individual scan lengths based on 3 parameters (refraction, keratometry and axial length).

A scan circle with a diameter of 3.45 mm was centered at the optic disc. Nine B-scan images were captured and automatically averaged. Attention was paid to obtain good-quality scans with focused images, proper adjustment of the disc margins, and signal strength ≥20. The RNFL thickness parameters measured were; average RNFL thickness (a-RNFL thickness), superior-temporal (ST), temporal (T), inferior-temporal (IT), inferior-nasal (IN), nasal (N), and superior-nasal (SN) quadrant RNFL thicknesses (Figure 1).

The GCC protocol was used to measure the macular GCC thickness from the inner limiting membrane (ILM) to the inner plexiform layer (IPL). Layer segmentation was executed automatically using the new software for the Spectralis OCT, and it was checked to be adequate in the 61 B-scans of each imaged eye using the criteria of Ishikawa et al.[11] (Figure 1).

The statistical analyses were done using SPSS (Statistical Package for Social Sciences; version 15.0). A Shapiro-Wilk test was used to detect normal distribution. The differences between the groups were evaluated by Student T and Mann-Whitney U tests. Spearman correlation coefficients for the results were calculated. The data adjusted for age and corrected means were estimated with standard error and 95% confidence interval. Multiple

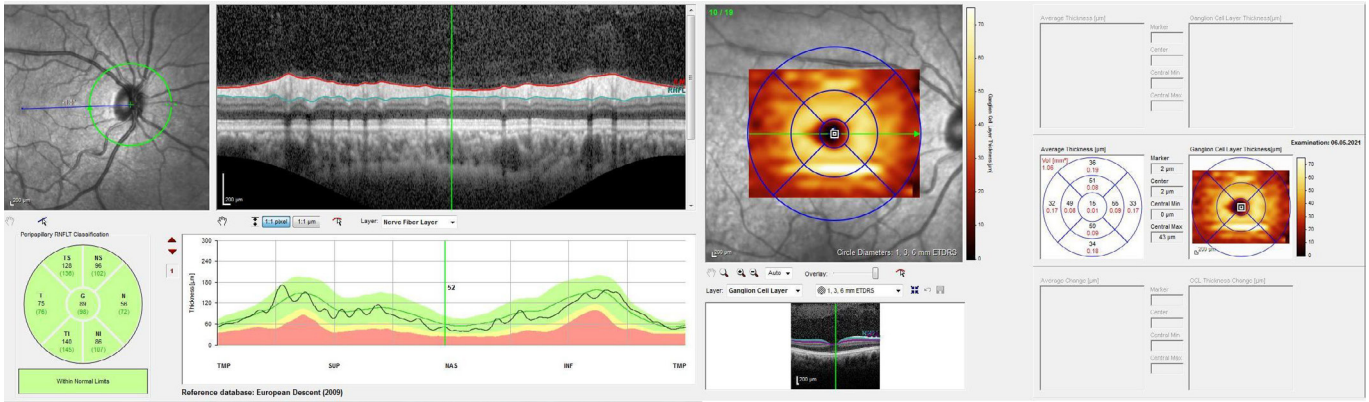

Figure 1: *The RNFL thickness parameters; average RNFL thickness, superior-temporal, temporal, inferior-temporal, inferior-nasal, nasal, and superior-nasal quadrant RNFL thicknesses with automated segmental GCC thickness.*

linear regression models were created to evaluate the relationship among the RNFL, GCC, GC-IPL thicknesses and age, CCT, axial length (AL), and spherical refraction values. "Enter method" was used as the variable selection method. The standardized and non-standardized regression coefficients of the models were presented together with the p values, and the risk factors affecting these variables were investigated. The statistical significance was set at a level of 5% ($p<0.05$).

RESULTS

In total, 122 eyes of 122 participants were included in the study. The mean age was 26.63±8.26 years (18-42) in Group 1 (n=60) and 25.25±7.94 years (18-42) in Group 2 (n=62). While 66.6% of Group 1 was female, percantage was 62% in Group 2. There were not any significant differences between groups in terms of age and gender ($p>0.05$).

The mean spherical refraction was 2.74±1.34 D in Group 1 and 2.68±1.22 D in Group 2 (p=0.959). The mean AL was 24.47±0.97 mm in Group 1 and 24.73±0.92 mm in Group 2 (p=0.183). Mean intraocular pressure was 15.45±2 mmHg in Group 1 and 16.88±2.1 mmHg in Group 2 (p=0.665). The mean cup to disc (C/D) ratio was 0.28±0.07 in Group 1 and 0.30±0.07 in Group 2 (p=0.146). The clinical and demographic characteristics of the participants were given in Table 1.

The mean CCT was measured as 517.48±23.2 micrometer in Group 1 and 572.29±21.62 micrometer in Group 2 ($p<0.001$).

The retinal GCC thickness was found to be statistically significantly decreased in Group 1 compared with Group 2 (p=0.002). The GC-IPL thickness was also statistically significantly decreased in Group 1 compared with Group 2 (p=0.007). The GCC thickness at superior, inferior and temporal quadrants were significantly thinner in Group 1 in comparison to Group 2. When the 2 groups were compared in terms of RNFL thickness, no statistically significant difference was found except for the superior-temporal quadrant (p=0.041). Table 2 presents the comparison of the GCC, GC-IPL and RNFL thicknesses between Group 1 and Group 2.

The CCT was statistically significantly correlated with the GCC and GC-IPL thicknesses (r=0.218, p=0.016, and r=0.200,p=0.027, respectively). There was no statistically significant correlation between the CCT and the RNFL thicknesses ($p>0.05$) (Table 3).

While there was a positive significant relationship between AL and GCC, GC-IPL thicknesses, a negative significant relationship was found between ST, SN, İN, İT and a-RNFL (β =0.371, $p<0.001$, β=0.392, $p<0.001$, β=-0.211, p=0.05, β=-0.263, p=0.014, β=-0.267, p=0.009, β=-0.219, p=0.043, β=-0.314, p=0.002, respectively). Age was related only with temporal RNFL (β=-0.197, p=0.036). There was a positive significant relationship between CCT and inferotemporal RNFL (β=0.185 p=0.034) (Table 4).

DISCUSSION

To our knowledge, this is the first study demonstrating a relationship between CCT and GCC and GC-IPL thicknesses in otherwise healthy mild to moderate myopic eyes. Eyes with mild to moderate myopia and thinner corneas revealed significantly decreased GCC and GC-IPL thickness. Except for the superior-temporal quadrant, there was no significant difference for the RNFL thickness.

Considering that myopia is a significant risk factor for the development of glaucoma, studies have shown that it can increase the risk by 2 to 3 folds and also the risk is associated with the amount of myopia.[14] Chen et al. proposed that

Table 1: *Clinical and demographic characteristics of the patient groups.*

	Group 1	Group 2	p-value
Age (years)	26.63±8.36	25.25±7.95	0.287
Spherical refraction (D)	2.74±1.34	2.68±1.22	0.959
Cylindrical refraction (D)	0.69±0.68	0.67±0.63	0.985
CCT (µm)	517.48±23.2	572.29±21.62	<0.001
IOP (mmHg)	15.45±2	16.88±2.1	0.665
Cup to disc ratio	0.28±0.07	0.30±0.07	0.146
AL (mm)	24.47±0.97	24.73±0.92	0.183

CCT: Central corneal thickness; IOP: Intraocular pressure, AL: Axial length

Table 2: *Comparison of GCC, GCC-IPL and RNFL thickness in the groups*

(µm±SD)	Group 1	Group 2	p-value
GCC thickness	44.36±9.35	50.03±10.18	0.002*
GCC-IPL thickness	33.28±7.81	37.43±8.42	0.007*
S-GCC	121.0±8.5	125.1±8.4	0.008*
I-GCC	116.2±11.2	120.9±8.5	0.011*
N-GCC	115.6±9.2	116.2±10.4	0.718
T-GCC	105.7±9.5	112.3±9.8	0.000*
a-RNFL thickness	99.88±10.09	99.51±9.13	0.998
T-RNFL thickness	74.83±11.09	74.48±12.03	0.634
ST-RNFL thickness	142.56±17.02	135.88±18.02	0.041*
SN-RNFL thickness	111±18.84	112.08±23.46	0.890
N-RNFL thickness	70.98±13.52	69.67±13.16	0.510
IN-RNFL thickness	106.41±21.15	114.12±26.32	0.281
IT-RNFL thickness	147.5±19.41	145.11±19.15	0.764

GCC: Ganglion cell complex; GC-IPL: Ganglion cell-inner plexiform layer; S-GCC :Superior GCC; I-GCC: Inferior GCC; N-GCC: Nasal GCC; T-GCC: Temporal GCC
a-RNFL: Average RNFL; Temporal (T); superior-temporal (ST); superior-nasal (SN); nasal (N); inferior-nasal (IN); inferior-temporal (IT)
*: Statistically significant p-value

Table 3: *Correlation analysis between age and CCT and other parameters.*

	Age		CCT	
	r	p	r	p
CCT	-0.133	0.144	1.000	0.000
AL	-0.178	0.050	0.113	0.214
GCC	-0.068	0.457	0.218	0.016
GC-IPL	-0.095	0.300	0.200	0.027
S-GCC	0.201	0.027	0.123	0.178
İ-GCC	0.138	0.130	0.107	0.243
N-GCC	0.070	0.441	-0.039	0.669
T-GCC	0.097	0.286	0.318	0.000
a-RNFL	0.074	0.417	0.007	0.943
T-RNFL	-0.158	0.082	-0.063	0.494
ST-RNFL	-0.006	0.948	-0.151	0.096
SN-RNFL	0.117	0.201	-0.021	0.816
N-RNFL	0.189	0.037	-0.069	0.447
İN-RNFL	0.162	0.074	0.102	0.264
İT-RNFL	0.032	0.726	-0.008	0.928

CCT: Central corneal thickness; AL: Axial length; GCC: Ganglion cell complex; GC-IPL: Ganglion cell-inner plexiform layer; S-GCC :Superior GCC; I-GCC: Inferior GCC; N-GCC: Nasal GCC; T-GCC: Temporal GCC; a-RNFL: Average RNFL; Temporal (T); superior-temporal (ST); superior-nasal (SN); nasal (N); inferior-nasal (IN); inferior-temporal (IT)

evaluating glaucoma in high myopic patients using only a database including low myopic measures could lead to misdiagnosis and that GCC thickness determined by a high myopic database should be used.[15] Wang et al. and Scuderi et al. have reported that macular GCC thickness has much more diagnostic power than the RNFL thickness in glaucoma patients with high myopia.[16,17]

The structural or elastic properties of the cornea were shown to be significant indicators for the overall structural

Table 4: *Standardized coefficients (β) and statistical significance values (p) from multiple linear regression models of the participants.*

	Age (y)		AL (mm)			SR(D)		CCT (µm)	
	β	P	β	P		β	P	β	P
ST-RNFL	-0.008	0.93	-0.211	0.05		0.014	0.897	0.014	0.897
SN-RNFL	0.046	0.613	-0.263	0.014		-0.053	0.615	0.033	0.711
N-RNFL	0.126	0.159	-0.19	0.068		-0.148	-0.148	-0.033	0.708
T-RNFL	-0.197	0.036	0.048	0.654		-0.146	0.18	-0.03	0.328
İN-RNFL	0.087	0.319	-0.267	0.009		-0.141	0.167	0.185	0.034
İT-RNFL	0.01	0.917	-0.219	0.043		-0.028	0.797	-0.005	0.957
a-RNFL	0.026	0.76	-0.314	0.002		-0.001	0.987	-0.156	0.124
GCC	0.101	0.251	0.371	<0.001		-0.132	0.199	0.143	0.105
GC-IPL	0.069	0.435	0.392	<0.001		-0.151	0.144	0.121	0.169

y:years, AL: Axial length, SR:Spherical refraction , D: Diopter, CCT: Central corneal thickness; GCC: Ganglion cell complex; GC-IPL: Ganglion cell-inner plexiform layer; S-GCC :Superior GCC; I-GCC: Inferior GCC; N-GCC: Nasal GCC; T-GCC: Temporal GCC; a-RNFL: Average RNFL; Temporal (T); superior-temporal (ST); superior-nasal (SN); nasal (N); inferior-nasal (IN); inferior-temporal (IT)

and elastic characteristics of the eye. In eyes with OHT, thinner cornea is an independent risk factor for conversion to glaucoma.[7,18] In eyes with known glaucoma, lower CCT seems to be a risk factor for progression.[19-21]

Previous studies have shown that the RNFL can be thinner in high myopic patients than in mild myopic patients.[22,23] Zhao et al. also found that as the amount of myopia increased, there was a thinning of the RNFL.[22] Similarly, Sezgin Akçay et al. analyzed the GCC and RNFL thickness in patients with varying amount of myopic refraction.[23] They showed that both RNFL and GCC thickness were decreased in eyes with high myopia. They also noted that there was no significant correlation between the GCC layer and the axial length in moderate myopia group. Henderson et al. evaluated the relationship between the CCT and RNFL thickness in healthy eyes and did not find any correlation.[24] They also searched for a relationship between the RNFL thickness and CCT in patients with ocular hypertension. The authors used scanning laser polarimetry for improving the accuracy of the technique for diagnosing glaucoma. The patients with OHT with thinner corneas had significantly thinner RNFL than patients with thicker corneas and healthy control subjects. Arranz-Marquez et al. measured the CCT and RNFL thickness in healthy subjects with mild to moderate myopia.[25] The mean spherical refractive error in their study group was greater than in our study group (-3.4±1.9 D and -2.74±1.34 D, respectively). They also found a positive significant correlation between the mean RNFL thickness and CCT.

There are very few studies evaluating the thickness of the retinal GCL in myopic eyes. In patients with amblyopia, Park and Oh measured increased thickness in the inner nuclear layer, IPL and GCL, particularly in myopic eyes, and reported that these findings may be attributable to the genetic factors.[26] Zereid et al. investigated the effect of refractive errors on the retinal thickness and found that the foveal thickness in the inner and outer retinal layers were increased, while the thickness in the inner and outer retinal layers of the parafoveal and perifoveal regions were decreased in moderate to high myopic eyes.[27] They linked the retinal thinning to the myopic elongation of the eye. In a very recent study, Ganekal et al. found that average GC-IPL and GC-IPL thickness of all sectors were significantly decreased in high myopic group compared to low myopic group.[28] None of the previous studies included corneal thickness as a parameter. In our study, the GCC and GC-IPL thickness were significantly decreased in myopic eyes with thinner corneas, without a generalized RNFL thinning. The CCT was statistically significantly correlated with the GCC and GC-IPL thicknesses.

Here, we may propose two different mechanisms; first, decreased GCC thickness can be related to the increased risk of glaucoma progression in myopic eyes with thinner corneas. Second, the decreased GCC thickness in myopic

patients with thinner corneas may itself be a risk factor for the development of glaucoma. The decreased GCC thickness measurement in mild to moderate myopic eyes with thinner corneas may therefore form a high risk group. As GCC thickness is well-known sign of early glaucomatous damage, decreased GCC thickness in myopic eyes supports the results of population-based studies. Longitudinal studies with longer follow-ups are needed to address this issue in future.

Our study had some limitations. First, including more participants with a wider range of the CCT, RNFL, and GCC thicknesses might have allowed for stronger correlations and analysis of subgroups. Second, the cut-off value for CCT was 555 micrometer. The reason for using this value was based on OHTS group data. We did not include a healthy control group or patients with glaucoma, as it has already been shown that healthy patients with thinner corneas or varying myopia could have GCC and RNFL changes.

CONCLUSIONS

In conclusion, current study showed that the GCC and GC-IPL thicknesses were decreased in eyes with myopia and thinner corneas. Therefore, before evaluating the thickness of the GCC and GC-IPL in glaucoma patients, not only the amount of myopia but also the CCT should be taken into the consideration as well. Still, prospective population-based studies are needed to reveal the effect of the CCT on the GGC and RNFL thicknesses in myopic eyes.

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