

# Central Corneal Thickness in Glaucoma Subgroups and Ocular Hypertension and the Factors Affecting Central Corneal Thickness\*

Glokom ve Oküler Hipertansiyonda Merkezi Kornea Kalınlığı ve Merkezi Kornea Kalınlığını Etkileyen Faktörler

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## ABSTRACT

**Purpose:** To evaluate the central corneal thickness (CCT) values in Primary Open Angle Glaucoma (POAG), Pseudoexfoliation Glaucoma (PXG), Normal Tension Glaucoma (NTG), Ocular Hypertension (OHT), and normal subjects, and to study the relationship of age, gender, intraocular pressure (IOP) and systemic diseases with CCT.

**Materials and Methods:** A total of 286 patients and 50 control subjects were included in our prospective study. All the patients were questioned for family history of glaucoma and presence of systemic diseases. IOP and CCT were measured using Goldmann applanation tonometer and ultrasound pachymeter, respectively

**Results:** Only CCT values of NTG ( $527.8 \pm 21.4 \mu\text{m}$ ) and OHT ( $578.6 \pm 24.1 \mu\text{m}$ ) were statistically significantly different from the values of the control group ( $545.9 \pm 39.3 \mu\text{m}$ ). Age and IOP were found to be statistically important factors those affecting CCT in multivariate analysis. Systemic diseases were found to have no significant effect on CCT values. The NTG group had significantly higher rates of diabetes mellitus, hypertension, and hyperlipidemia, while we found no relationship between migraine and NTG in our cases. The rate of positive family history of glaucoma was found to be significantly higher in OHT patients than other cases and normal subjects.

**Conclusions:** NTG and OHT patients have significantly lower and higher CCT values, respectively. There was a moderate thinning of cornea by ageing. DM and HT did not seem to have a relation with CCT.

**Key Words:** Central corneal thickness, intraocular pressure, ocular hypertension, glaucoma, systemic disease.

## ÖZ

**Amaç:** Primer açık açılı glokom (PAAG), psödoeksfolyatif glokom (PXG), normotansif glokom (NTG), oküler hipertansiyon ve kontrol grubundaki merkezi kornea kalınlığı (MKK) değerleri ve yaş, cinsiyet, göz içi basıncı (GİB) ve sistemik hastalıklar ile MKK arasındaki ilişkiyi değerlendirmek.

**Gereç ve Yöntem:** Bu ileriye dönük çalışmaya 286 hasta ve 50 kontrol dahil edildi. Tüm hastalardan aile hikayesi ve sistemik hastalık varlığı sorgulandı. Goldmann aplanasyon tonometresi ile GİB, ultrason pakimetri ile MKK ölçüldü.

**Bulgular:** MKK değerleri yalnızca NTG ( $527.8 \pm 21.4 \mu\text{m}$ ) ve OHT ( $578.6 \pm 24.1 \mu\text{m}$ ) grubunda kontrol grubundan ( $545.9 \pm 39.3 \mu\text{m}$ ) istatistiksel olarak anlamlı farklı bulundu. Multivariate analizde yaş ve GİB, MKK etkileyen faktörler olarak bulundu. Sistemik hastalıkların MKK değerleri üzerinde anlamlı etkisi bulunmadı. Diyabet, hipertansiyon ve hiperlipidemi NTG grubunda anlamlı yüksek idi. Bizim vakalarımızda migren ve NTG arasında ilişki bulunmadı. Pozitif aile hikayesi oranı diğer glokom grupları ve kontrol grubuna göre OHT grubunda anlamlı yüksekti.

**Tartışma:** MKK değerleri NTG grubunda anlamlı düşük, OHT grubunda ise yüksek bulundu. Yaşla beraber korneanın orta derecede incelendiği saptandı. Diyabet ve hipertansiyonun MKK ile ilişkisi bulunmadı.

**Anahtar Kelimeler:** Merkezi kornea kalınlığı, göz içi basıncı, oküler hipertansiyon, glokom, sistemik hastalık.

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## INTRODUCTION

Intraocular pressure (IOP) is the most important risk factor of glaucoma that can be measured objectively and decreased by anti-glaucoma treatment. Goldmann applanation tonometer is still the golden standard method for IOP measurement but it can even be influenced by central corneal thickness (CCT) and other ocular factors. When Goldmann and Schmidt first described this tonometer, they assumed a standard CCT of 500  $\mu\text{m}$  and emphasized that theoretically the measurements might be influenced by the variation in CCT.<sup>1</sup>

Previous studies investigating the relationship between the IOP and CCT have been carried out since 1970.<sup>2-5</sup> Hansen and Ehlers showed a positive linear relationship between IOP and CCT.<sup>6</sup> Due to the increasing popularity of refractive surgery and findings of numerous recent studies indicating that thinner corneas could lead to lower IOP measurements erroneously, IOP-CCT relationship has received more attention.<sup>7-10</sup> The Early Manifest Glaucoma Trial revealed that 1mmHg lowering of IOP had decreased the visual field progression by about 10 percent.<sup>11</sup> According to the results of the *Ocular Hypertension Treatment Study* (OHTS), higher IOP and lower CCT values at the first visit are important risk factors for the conversion from ocular hypertension to open angle glaucoma.<sup>12</sup> Therefore, it became more important than ever to find out the factors that might influence the IOP measurement, which is very critical in glaucoma diagnosis, follow-up, and treatment.

In this study, we aimed to investigate the differences between the mean value of CCT for glaucoma subgroups and OHT and to evaluate the relation of age, gender, IOP, and systemic diseases with CCT.

## MATERIALS AND METHODS

A total of 336 subjects (160 males, 47.6%; 176 females, 52.4%) were recruited prospectively for the study. Cases, referred to the glaucoma department of our hospital with suspected glaucomatous optic nerve damage or high IOP values, were examined with a complete ophthalmological examination consisting of assessment of best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement by Goldmann applanation tonometer, gonioscopy with Goldmann three-mirror lens, dilated fundus examination with +90 D lens, visual field analysis by Humphrey automatised perimeter, and CCT measurements. The distribution of the patients into different diagnostic groups was as follows: Primary Open Angle Glaucoma (POAG),  $n=120$ ; Pseudoexfoliation Glaucoma (PXG),  $n=62$ ; Ocular Hypertension (OHT),  $n=53$ ; and Normal Tension Glaucoma (NTG),  $n=51$ . The diagnostic criteria for POAG, PXG, NTG, and OHT are shown in Table 1. Subjects over 40 years of age seen in daily visits who admitted for refractive correction or presbyopia were selected randomly for the control group. CCT was measured using Tomey AL-1000 ultra-

sound bio-pachymeter (Tomey Corporation, Japan) by the same technician, and IOP was measured with Goldmann applanation tonometer by the same physician to avoid interobserver variations. For both measurements, the mean of three readings was recorded. To avoid diurnal variation, measurements of CCT and IOP performed between 9 and 11 a.m. were recorded.

All the subjects were informed about the study, and their consents were taken. Institutional Ethics Committee approval was obtained. Subjects who had previous history of contact lens wear, any ocular surgery or trauma and eyes which had corneal diseases, high spherical ( $>\pm 3.0$  D) or cylindrical ( $>\pm 1.0$  D) refractive error were excluded from the study. All the patients were asked about family history of glaucoma and the presence of any systemic disorders.

For statistical analysis; independent sample t-test, Analysis of Variance (ANOVA) with Tukey HSD test for post-hoc analysis, Pearson correlation, Mann-Whitney U, and Chi-square tests were used. Multivariate linear regression analysis was performed in order to evaluate the effect of age, gender, the presence of diabetes mellitus (DM) or hypertension (HT) and IOP on CCT for the total group. Other systemic diseases such as bronchial asthma, coronary artery diseases, hyperlipidemia, thyroid diseases, and migraine were not included in the models due to the low number of cases. All the statistical analyses were performed by SPSS Version 13.0 (SPSS Incorporation, Chicago, USA) statistical analysis software.  $p < 0.05$  was considered statistically significant.

## RESULTS

The CCT values of the right and left eyes were very significantly correlated for the total group ( $r=0.908$ ,  $p=0.00$ ) and each of the subgroups (POAG:  $r=0.929$ ,  $p=0.00$ ; PSXG:  $r=0.833$ ,  $p=0.00$ ; OHT:  $r=0.924$ ,  $p=0.00$ ; NTG:  $r=0.675$ ,  $p=0.00$ ; Control:  $r=0.911$ ,  $p=0.00$ ) when evaluated separately. The IOP values for the right and left eyes were also significantly correlated for the total group ( $r=0.795$ ,  $p=0.00$ ) and each of the subgroups (POAG:  $r=0.661$ ,  $p=0.00$ ; PSXG:  $r=0.666$ ,  $p=0.00$ ; OHT:  $r=0.836$ ,  $p=0.00$ ; NTG:  $r=0.655$ ,  $p=0.00$ ; Control:  $r=0.791$ ,  $p=0.00$ ). Therefore, only

**Table 1:** Diagnostic criteria for POAG, PSXG, OHT, and NTG.

|   | POAG        | PSXG | OHT         | NTG         |
|---|-------------|------|-------------|-------------|
| IOP $\geq 21$ mmHg <sup>a</sup>                     | +           | +    | +           | $\emptyset$ |
| Glaucomatous optic nerve damage                     | +           | +    | $\emptyset$ | +           |
| Glaucomatous visual field defects                   | +           | +    | $\emptyset$ | +           |
| Gonioscopy  | Open        | Open | Open        | Open        |
| Psx <sup>b</sup> at the angle/lens anterior capsule | $\emptyset$ | +    | $\emptyset$ | $\emptyset$ |

<sup>a</sup> At least three measurements IOP $\geq 21$  mmHg

<sup>b</sup> Pseudoexfoliation (Psx) material.

**Table 2:** The age, gender, right eye IOP and CCT values for each group.

|         | Number of subjects (n) | CCT ( $\mu\text{m}$ ) (Mean $\pm$ SD) | Age (years) (Mean $\pm$ SD) | IOP (mmHg) (Mean $\pm$ SD) | Male/Female ( $n_M/n_F$ ) |
|---------|------------------------|---------------------------------------|-----------------------------|----------------------------|---------------------------|
| POAG    | 120                    | 554.7 $\pm$ 33.7                      | 57.5 $\pm$ 11.5             | 17.5 $\pm$ 4.1             | 55/65                     |
| PSXG    | 62                     | 530 $\pm$ 38.1                        | 68.0 $\pm$ 7.6              | 18.1 $\pm$ 3.7             | 27/35                     |
| OHT     | 53                     | 578.6 $\pm$ 24.1                      | 48.7 $\pm$ 7.5              | 24.2 $\pm$ 1.8             | 26/27                     |
| NTG     | 51                     | 527.8 $\pm$ 21.4                      | 53.2 $\pm$ 8.6              | 15.6 $\pm$ 2.8             | 28/23                     |
| Control | 50                     | 545.9 $\pm$ 39.3                      | 54.4 $\pm$ 7.6              | 15.6 $\pm$ 2.1             | 24/26                     |
| Total   | 336                    | 549.2 $\pm$ 36.2                      | 56.7 $\pm$ 11.1             | 16.9 $\pm$ 4.1             | 160/176                   |

CCT and IOP values of the right eyes were evaluated for statistical purposes. The age, gender, right eye IOP and CCT values for each group are shown in Table 2.

Among the groups other than control subjects, the oldest (mean age: 68.0 $\pm$ 7.6 years) and the youngest (mean age: 48.7 $\pm$ 7.5 years) groups were the cases with PXG and OHT respectively.

The mean CCT values of the control group differed significantly from the CCT of NTG and OHT, but not from the POAG or PXG (ANOVA, Post-hoc Tukey test,  $p=0.00$ ). OHT group had the highest and NTG group had the lowest mean CCT values. The distribution of mean CCT values among groups is shown in Graphic.

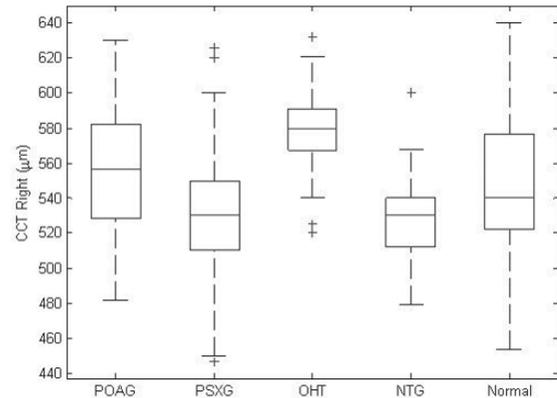
The mean CCT values were 549.4 $\pm$ 38.2  $\mu\text{m}$  for male and 548.9 $\pm$ 34.3  $\mu\text{m}$  for female cases (Independent sample t-test,  $p=0.90$ ).

We found a moderately significant negative correlation between age and CCT values (Pearson correlation test,  $r=-0.227$ ,  $p=0.00$ ).

Among all the subgroups, NTG seemed to have significantly higher rates of DM (47.1%), HT (54.9%), and hyperlipidemia (23.5%) (Chi-square test,  $p=0.00$  for all). No statistically significant relationship was determined between NTG and migraine (Chi-square test,  $p=0.41$ ). The rate of family history of glaucoma (41.2%) was significantly higher in OHT group (Chi-square test,  $p=0.00$ ).

The prevalences of systemic diseases were 20% for DM, 30.4% for HT, 17.1% for coronary artery diseases, 7.7% for thyroid diseases, 6.9% for hyperlipidemia, 6.6% for bronchial asthma, and 3.1% for migraine. When the total group was evaluated, the CCT values of the patients with any of the chronic diseases did not differ from the CCT values of the patients without any of the diseases (Independent sample t-test and Mann-Whitney U tests,  $p>0.05$ ).

In the multivariate analysis, when the relation of age, sex, IOP, DM and HT with CCT was evaluated for the total group; the age ( $\beta=-0.261$ ,  $p=0.00$ ) and IOP ( $\beta=0.369$ ,  $p=0.00$ ) were determined to be the predictors of CCT.

**Graphic:** The distribution of CCT values among groups.

## DISCUSSION

Intraocular pressure is one of the most important parameters in the diagnosis and follow-up of glaucoma. Its measurement with Goldmann applanation tonometry may be influenced by some factors such as anterior corneal curvature, corneal thickness, scleral rigidity, etc. Nevertheless, CCT is often considered the main source of error in measuring IOP.<sup>13-14</sup> Ehlers et al.<sup>3</sup> have detected 5 mmHg changes in IOP for 70  $\mu\text{m}$  CCT variation. In their meta-analysis, Doughty and Zaman<sup>15</sup> have reported the relationship as 2.5 mmHg IOP change per 50  $\mu\text{m}$  CCT variation. In a study performed for the myopic patients that underwent excimer laser surgery, there was a decrease of 0.26 mmHg in IOP per 10  $\mu\text{m}$  corneal thinning.<sup>16</sup>

Gordon et al<sup>12</sup> emphasized that in a multivariate analysis, CCT was an independent risk factor for glaucoma conversion of OHT. According to 5 year follow-up results of the OHTS, glaucomatous damage seemed to be present in 36% of patients with thinner corneas, whereas only 13% of patients with thicker corneas suffered from the same problem. These recent findings increased the importance of CCT and turned it into an important parameter in the diagnosis, classification, and follow-up of glaucoma patients.

The aim of our study was to determine the mean CCT values for glaucoma subtypes and to assess the effect of age, gender, and systemic diseases like DM and HT on CCT. Among our cases, NTG group had the lowest (527.8 $\pm$ 21.4  $\mu\text{m}$ ) and OHT group had the highest (578.6 $\pm$ 24.1  $\mu\text{m}$ ) CCT values similar to the results of some previous studies.<sup>17-19</sup> Yagci<sup>20</sup> and Ventura<sup>21</sup> have found the lowest CCT for PXG group in their studies. Nevertheless, the study of Yagci did not include NTG patients.

When all the groups were investigated for the mean age; PXG group had the oldest cases and OHT had the youngest once. The appearance of pseudoexfoliation material increases with age; thus, higher incidence of PXG at older ages is reasonable. This is similar to the results of some of the earlier studies<sup>20, 21</sup> in the study of

Singh et al<sup>18</sup>, NTG group was the oldest, but they did not have a PXG group.

There were no statistically significant differences between CCT readings of males and females. Findings of many studies are similar to our results<sup>22-24</sup>; however, a few studies have reported difference in CCT values between sexes.<sup>25, 26</sup>

Flammer<sup>27</sup> discusses that vascular endotheliopathy and dysregulation play a role in the pathogenesis of NTG. Our findings indicate that NTG patients have a higher incidence of DM, HT, and hyperlipidemia, which might cause vascular pathology. Primary vasospasm is the main cause for different kinds of diseases like migraine, Raynaud's phenomenon and peripheral vasospasm. It is triggered by primary aberrant neuronal activity, various neuropeptides and vasoactive substances and may cause primary alterations in blood flow<sup>28,29</sup> NTG is also associated with primary vasospasm other than systemic vascular diseases suggesting an underlying vascular insufficiency.<sup>30,31</sup> Because of a similar pathogenesis, migraine may be a risk factor for the development of NTG. But in our study, NTG patients did not have a significantly higher rate of migraine. The reason of this result is not clear but it might be due to the lack of migraine diagnosis in those patients possibly having symptoms of chronic headache.

The rate of positive family history of glaucoma was significantly high in OHT patients. It could be because family members who were misdiagnosed with glaucoma had thicker corneas, giving rise to higher IOP measurements. This could also be the reason for the presence of glaucoma in family history. In our study, the rate of positive family history was 41%, which is a little higher compared to approximately 34% in OHTS. Although the rate of family history in our study is reasonable, according to OHTS it is not a risk factor to predict glaucoma conversion.<sup>12</sup>

The presence of DM did not seem to affect the CCT values in our study. Inoue<sup>32</sup> and Larsson<sup>33</sup> emphasized that CCT of patients with type 2 DM did not differ from CCT values of non-diabetic subjects. However, Larsson et al<sup>33</sup> found higher CCT values only for type 1 DM patients. Our result is parallel to the results of both studies because the patients had type 2 DM in our study. However in OHTS group, diabetic patients had thicker corneas but not greater than 10 $\mu$ m.<sup>25</sup>

No significant differences were detected between CCT values of the patients with and without HT. Brandt et al<sup>25</sup> did not find any relation between CCT and HT but warned about the racial differences. Many studies reported that systolic blood pressure (SBP) was significantly correlated with IOP.<sup>34, 35</sup> According to Carel et al's study<sup>34</sup>, there were weak correlations of IOP with heart rate and with SBP. But Rochtchina et al<sup>35</sup> reported a strongly positive association of IOP with SBP. CCT is also known to

have a very strong correlation with IOP.<sup>6</sup> However; there is little evidence about HT in which SBP is higher than normal and its relationship with CCT in current literature. Our result may be a useful addition to relevant literature.

Age-CCT relationship is a controversial subject. Similar to the results of some reports in the literature, we determined a significant moderate negative correlation.<sup>24-26</sup> However, studies reporting no correlation<sup>22, 36</sup> also exist. In their meta-analysis, Doughty and Zaman<sup>15</sup> emphasized that CCT values did not change by ageing for Caucasians but decreased after 60 years of age in African Americans. Our subjects were mostly over 40 years of age (i.e. the number of younger subjects was not sufficient); therefore, it may not be possible to make a general conclusion based on the age-CCT relationship found in our study.

The higher IOP values, if not normalized with CCT values, may lead clinicians to misdiagnosis of glaucoma manifestation and application of unnecessary treatment, which also may drive patients into chronic disease stress. After proper diagnosis and classification, CCT also must be taken into account in treatment plans, as thin cornea may be a risk factor for glaucoma progression. Brandt et al<sup>25</sup> detected thinner CCT in African Americans and thought that the poor prognosis of glaucoma in these patients might be attributed to insufficient target IOP levels. Accordingly, CCT values should be taken into account in determination of target IOP levels.

In conclusion, our results indicate that NTG and OHT patients have significantly lower and higher CCT values, respectively. In addition to be an evidence of the relationship between CCT and glaucoma sub-groups, we also found some associations between age, systemic diseases and CCT in different types of glaucoma. This study demonstrates that the measurement of CCT is mandatory for monitoring the cases with glaucoma or glaucoma suspects for proper diagnosis and follow-up of the disease.

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