Special Focus on Glaucoma

Chapter 5

The Role of Central Corneal Thickness in Ocular Hypertension and Primary Open Angle Glaucoma

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1. Introduction

Glaucoma denotes a broad and heterogeneous range of ocular diseases, all of them sharing a damage to the optic nerve which, on the long run, is able to cause irreversible visual field loss and vision impairment. According to a popular and authoritative study conducted in 2006 by Quigley and Braman [1], glaucoma is the second leading cause of blindness worldwide: the aforementioned study reports that the estimated number of persons affected by glaucoma is around 60 million in 2010 and such a number is expected to increase to 79.6 million by 2020. The same study estimated that bilateral blindness due to glaucoma is likely to occur in around 4 million people, rising to more than 5 million people in 2020. Among the different form of glaucoma, we pay a special attention to primary open-angle glaucoma (POAG) which is the most common form of glaucoma in the Western world [1] while another form of glaucoma is primary angle closure glaucoma (PACG) which mainly occurs in Asian populations. The etiology of POAG is still unclear but very recent studies [2,3] point out that that genetic variants, epigenetic modifications as well as environmental factors may contribute to glaucoma and they could explain the prevalence of one type of glaucoma in a specific area of the world.

The intraocular pressure (IOP) is universally considered as the most important risk factor for developing glaucoma: the well-known Ocular Hypertension Treatment Study (OHTS) proved that topical ocular hypotensive medication is effective in delaying or preventing the onset of POAG in those individuals affected by high IOP [4].

The IOP is the only treatable risk factor to prevent glaucoma progression: according to Gordon et al. [4], in fact, demographic and clinical factors that may influence POAG are older age, larger vertical or horizontal cup-disc ratio. To this end, the Ocular Hypertension Treatment Study revealed that the central corneal thickness (CCT) was an important factor influencing the progression from a condition of high ocular hypertension to primary open angle glaucoma. It is still unclear if the CCT is a factor risk for POAG because: (a) it is associated with biomechanical anomalies in ocular tissues or (b) it determines an increase in IOP or, finally, if facts (a) and (b) jointly occur.

This chapter seeks at answering the following questions:

1. What is the relationship between IOP and CCT? Do anomalies in CCT reflect on wrong IOP readings? Is there a clinical procedure to assess IOP which is more resilient to anomalies in CCT?

2. Can we improve IOP readings via corrective factors which incorporate CCT?

3. Do factors such as age, gender and genetic factors influence CCT? In addition, we conclude the chapter by illustrating the finding of a randomized clinical trial we conducted at the University of Messina (Italy) on patients with high IOP and CCT and patients with glaucoma and CCT.

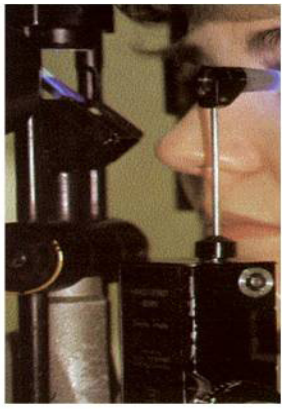

Figure 1: Goldmann tonometer

2. The Intraocular Pressure and Central Corneal Thickness

The standard procedure to measure IOP is the so-called Goldmann applanation tonometry (GAT), which was introduced by Goldman and Schmidt in 1957. The GAT performs IOP readings through a dedicated device called tonometer (see **Figure 1**).The GAT relies on the so-called *Imbert -Fick principle*: give a dry and thin-walled sphere,the pressure P inside the sphere is well approximated by the ratio of the force F applied to the sfere to the surface A of the sphere itself [4-6]. In practice, the tonometer is applied on the cornea contact surface with a measurable amount of force; in their derivation, Goldman and Schmidt assumed that the contact surface (applanation area) gets deformed in reaction of the external force application and, in addition, they assumed that the applanation area was a circle with a diameter of 3.06

millimeters. Applanation area show cases an innate resistance to flattending and such a resistance is balanced by the force produced by the capillary attraction of the tear meniscus. Consequently, Goldman and Schmidt proposed to measure the IOP by dividing the force applied to the cornea to the applanation area. In the IOP estimation, the average corneal thickness is assumed to be equal to 550 μm and a core assumption behind GAT is that corneal thickness is roughly uniform across population worldwide. The measurement of CCT is generally carried out by methods based on ultrasound, which are easy to administer and, simultaneously, provide quite accurate results. Specifically, ultrasonic pachymetry is now broadly accepted as the standard and it has been confirmed by extensive studies on large populations [7]. Large deviations from μ are likely to occur and this fact deeply affects the accuracy of the IOP measurement process [8,9]. In detail, if cornea thickness is greater than 550μm, an overestimation of IOP may occur, than the estimated one; in contrast, a cornea that is thinner than 550μm can be more easily flattened, and this fact leads to an underestimate of IOP. Abnormal development of corneal thickness may lead to a wrong estimation of IOP: for instance, Johnson and Kass [9] reported the clinical case of a 17-year-old girl who had IOP readings from of 30 to 40 mmHg in both eyes, with normal visual fields and optic nerve heads. In each eye, however, the central corneal thickness was 900μm and no corneal edema was observed. Subsequent cannulation of the left anterior chamber revealed an IOP of 11 mmHg, which was very different from IOP readings at tonometer but perfectly coherent with other clinical findings. A further drawback in the Goldman method is that the standard reference value for corneal thickness of 550μm was calculated on the basis of observations on white populations but such an approach may lead to wrong results if applied on non-white populations. To this end, an important randomized trial to cite is the so-called Barbados Eye Study [7], which was conducted about two decades ago on a population of 1142 persons, aged between 40 and 84. Patients under investigation lived in the Barbados, West Indies. The Barbados Study suggest that important corrections to the assumption of uniform corneal thickness has to be considered: specifically, black participants tended to have thinner corneas (with an average thickness of 529.8μm) than mixed black and white (537.8μm) and white participants (545.2μm), respectively. Among black participants, increasing values of corneal thickness were significantly related to younger age, diabetes history, and refractive error. Results above indicate that important differences in the distribution of CCT can be observed in practice and that anomalies in CCT can lead to wrong estimation of IOP. In the next section, we will explore studies devoted to investigate if a correlation between IOP readings and CCT exists in practice.

3. Correcting IOP Readings as Function of CCT

In 2000, Doughty and Zaman [10] were concerned with determining the normal value of CCT in corneas.In their meta-analysis, they reviewed studies carried out between 1968 and 1999: in this way, they were able to collect a set of 600 CCT data, 134 of which included IOP

measurements.

One of the main goals of Doughty and Zaman was to assess the impact of variables such as age, diurnal effects, contact lens wear, pharmaceuticals, ocular disease, and ophthalmic surgery on CCT. Their study highlighted an age-related decline in CCT for non-white individuals and only ocular diseases associated with collagen disorders (including keratoconus) or endothelial-based corneal dystrophies (such as Fuchs) were likely to produce a decrease (resp. increase) of CCT. A broad range of intraocular surgeries (in detail, cataract operations and penetrating keratoplasty) produced a marked increases in CCT; in contrast, photorefractive surgery generated a sensitive decrease in CCT.

Secondly, Doughty and Zaman were concerned with assessing whether a statistically significant association between CCT and IOP readings performed by GAT exists. As expected, thicker (resp., thinner) corneas were associated with higher (resp., lower) readings of IOP: in detail, they found that a variation of roughly 10μm in corneal thickness was associated with a variation of 0.2 mmHg in IOP reading. An important update to the results of Doughty and Zaman is due to Tonnu et al. [11] who analyzed how CCT influences IOP measurements provided that different devices are used.Here, the authors focused on the following devices, namely: the aforementioned GAT, the Tono-Pen XL, the ocular blood flow tonograph (OBF), and Canon TX-10 non-contact tonometer (NCT).In their study, Tonnu et al. considered a random sample of 105 untreated patients with IOP and glaucoma and, for each patient, they measured IOP with the GAT (two observers),Tono-Pen, OBF, and NCT in a randomized order. The relation of measured IOP and of inter-tonometer difference with CCT and subject age was explored by linear regression analysis.

The analysis revealed that IOP recordings is affected by CCT in all four methods but, interestingly enough, the NCT is affected by CCT significantly more than the GAT. Studies above suggest to introduce correction factors on IOP readings which take CCT into account. According to Brandt et al., a possible “arithmetic correction” of IOP reading by a factor of some mmHg would be an oversimplification which would fail to catch the complex (and non-linear) relationship between CCT and IOP. For the sake of completeness, however,we report some of the most popular corrections (we denote as IOP_c the corrected value as function of CCT and as IOP the GAT reading):

More advanced studies (see, for instance, [15]) prove that differences in corneal biomechanics across individuals have, in many cases, a bigger influence on IOP readings than corneal thickness or curvature and, therefore, more advanced mathematical models to derive dependency of IOP to CCT are available on the literature [16,17]. The correction methods briefly reviewed in this section are able to adjust IOP reading to get more accurate estimation but they cannot be classified as reliable screening tool for early detection of glaucoma in

1. Ehleres *et al.* [8]:

$$IOP_c = IOP - \left[\frac{5 \times (\frac{CCT}{1000} - 0.520)}{0.07}\right] \quad (1)$$

2. Whitacre *et al.* [13]:

$$IOP_c = IOP - \left[\frac{2 \times (\frac{CCT}{1000} - 0.520)}{0.1}\right] \quad (2)$$

3. Doughty and Zaman [10]

$$IOP_c = IOP - \left[\frac{2.5 \times (\frac{CCT}{1000} - 0.535)}{0.05}\right] \quad (3)$$

4. Kohlhaas *et al.* [14]

$$IOP_c = IOP + (23.28 - 0.0423 \times CCT) \quad (4)$$

population at risk, as de Saint Sardos et al. [18] reports: in short,there is no concrete benefit in trying to adjust IOP reading if our goal is to assess and treat patients who are affected by glaucoma or who are suspected to have glaucoma.

4. Factors Influencing CCT

The CCT is a key factor in the global assessment of a potential glaucoma patient: in previous sections, in fact, we showed that anomalies in CCT may influence a correct measurement and prognosis of IOP and, according to the Ocular Hypertension Study a CCT thinner than 555µm increases the risk of primary open angle glaucoma (POAG) due to ocular hypertension [4]. Unfortunately, in glaucomatous patients, the true diagnostic power of CCT as predictor of glaucoma progression is less certain and only few results are known: for instance, as Kniestedt et al. [19] reports, patients with advanced damages showcase, in general, a very thin CCT. A promising research avenue consist of identifying those genetic, biological, environmental causes which determine a thinner CCT and the main goal is to check if the above mentioned factor are also capable of influencing the onset and progression of glaucoma. As for genetic factors, Lu et al. [20] performed a meta-analysis on 20.000 individuals from European and Asian populations. Their analysis identified 16 loci associated with CCT, with high statistical significance. Two out 16 of these loci, namely FOXO1 and FNDC3B increased the risk of keratoconus and, in addition, FNDC3B was also associated with POAG. A recent study Toth et al. [21] investigated on the hereditability of the anterior chamber volume (ACV) as well as on the correlation between the ACV and the CCT. In their study, Toth et al. considered 220 eyes from 110 Hungarian twins (41 monozygotic and 14 same-sex dizygotic pairs with an average age of 48.6 and standard deviation equal to 15.5 years) for which anterior segment measurement were available. They found a negative (and statistically significant correlation) between ACV and CCT and genetic factors significantly accounted to explain covariance.

The role of gender on CCT is more controversial: few studies, in fact, agree on the fact that females have thicker CCT than males [12] while many other studies indicate that males have thicker CCT than females [22,23] and, finally, a study carried out on Korean population [24] do not report significant differences between males and females. Another factor to consider

is age: many studies, in fact, highlight, a negative (and statistically significant correlation) between age and CCT and it is possible to estimate that CCT decreases by 2 μm to 10 μm per decade [12,23,25,26]. Finally, drugs may have a variable impact on CCT: for instance, Bafa et al. [27] analyzed the effects of prostaglandin analogues on the CCT of patients with chronic open angle glaucoma (COAG). Such a study include 129 eyes, 108 of which were treated with three prostaglandin analogue, namely latanoprost, travoprost and bimatoprost; 21 eyes were treated with ß - blockers and they were used as controls. The CCT was measured before treatment and at three month intervals. Bafa et al. reports a moderate (but statistical significant) increase in those eyes which received bimatoprost and latanoprost and, more in detail, treatment with bimatoprost produced a constant increase (from 1.85 to 8.83 μm) in CCT at every point of the study. Latanoprost increased CCT only for the first year of study while travoprost did not produced any change in CCT. Grued and Rohrbach [28] investigated the impact of timolol on CCT. They tested a sample of 20 healthy individuals in a double-blind, prospective, and randomized study. Individuals who received timolol 0.5% eye drops for a period of 28 days. The administration of timolol yielded an average reduction of IOP from 16.2 mmHg to 13.0 mmHg, an average increase of CCT from 555.11 μm to 567.9 μm and an increase of stromal thickness from 494.4 μm to 498.9 μm after 9 days each. From day 10 on, a decrease in CCT, epithelial thickness, and stromal thickness was observed. At the end, CCT, epithelia thickness and stromal thickness had returned toward the values initially measured, while endothelial thickness did not vary.

5. An Experimental Study

We conclude our contribution by illustrating the outcome of a trial conducted at the Glaucoma Unit of the University Of Messina, Italy.We studied 52 POAG patients and 48 patients with high IOP (OHT group).

The control group consisted of 80 persons. We excluded from our study contact lens wearers, patients affected by corneal pathologies, patients who underwent surgical interventions or were subject to a trauma and, finally, patients with refractive impairment greater than 3.50D. At the gonioscopy (open angle), all POAG patients showcased typical damage to the optic nerve; the average IOP reading was 16.88(with a standard deviation equal to 3.76) subjects in the OHT group displayed an average IOP of 23.92 (with a standard deviation equal to 1.62) and a normal optical disk.

All patients were subjected to biomicroscopic examination (slit lamp), IOP was measured by means of the Goldmann applanation tonometer. To measure CCT we used the Sonomed pachymeter applied (see **Figure 2**) to the center of the cornea; patients were sitting and, before measurement, they received topical anesthetic.

All the statistical tests were conducted at a significance level of 5%. **Table 1** reports the

Figure 2: Sonomed pachymeter used in our experimental

main features of our dataset. We found that CCT in the OHT group were significantly higher than those measured in the POAG group (p-values was less than 0.05). We then applied linear regression to investigate correlation between CCT and IOP inthe OHT group. The fitted model was quite good with an R2 coefficient equal to 0.86; in contrast, no significant correlation was found between CCT and IOP in the POAG group.

Table 1: Main statistics of patients involved in our study. We have three groups, namely a POAG group (patients with Primary Open Angle Glaucoma), a OHT group (patients with a large IOP) and a Control Group. For each group we report the CCT, IOP, the number of male and female individuals and the age.

Parameter	Control Group	OHT Group	POAG Group
CCT (μm)	528.76 ± 24.22	588.64 ± 23.52	534.71 ± 20.38
Number of subjects	80	48	52
Male	43	30	31
Female	37	18	21
Age (years)	50,88 ± 15.81	51.29 ± 12.67	59.48 ± 8.75

6. Conclusion

In this manuscript, we aim at illustrating the role of CCT as predictor for both IOP and glaucoma onset/progression. Extensive literature shows that significant deviation in CCT may yield important alterations in IOP readings, independently of the method we apply to take IOP. As such, measures of CCT (which are generally taken through ultrasound pachimetry an easy and reliable fashion) are important clinical findings that any ophthalmologist should take into account to gain a better understanding of eyes health status.Analogously, CCT is an important predictor in those patients for whom we suspect the onset of glaucoma and, as such, a regular screening appears useful to early detect glaucoma. In contrast, CCT does not play any role in predicting the progression of glaucoma in established patients. Previous recommendations can be summarized as follows:

1. If IOP is less than 21 mmHg and visual field is normal we do not recommend pachymetry; in contrast, if visual field showcases alterations or the patient has a glaucoma we recommend pachymetry.

2. If IOP is greater than or equal to 21 mmHg, pachimetry is required for those e patients, for non-glaucomatous patients (independently of the outcome of visual field) and it is optional for glaucomatous patients. Recent studies tell us that many factors may, in principle, influence CCT but the actual role of some of these parameters is still unknown: for instance, CCT significantly depends on age but available studies on the role of gender as well as on some drugs are less conclusive. An important research avenue is on the role of genetic factors influencing CCT: there are only few studies and we think large patient samples need to be screened to discover genes regulating CCT.

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