Central Corneal Thickness and Glaucoma Treatment: An Italian Multicenter Cross-Sectional Study

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Abstract

Purpose: Supposedly, prostaglandin analogs (PGA) could reduce the central corneal thickness (CCT), while topical carbonic anhydrase inhibitors (TCAI) could increase CCT. The aim of the study was to evaluate clinically significant CCT effects in patients treated with PGA or TCAI.

Methods: At least 50 glaucomatous patients were saved on the Italian Glaucoma Register from 16 different glaucoma centers. About 816 glaucomatous patients were found in the register; of these, 316 were recruited in this study because they were treated with PGA or TCAI. The diagnosis of glaucoma was based on visual field examination, optic nerve head analysis, intraocular pressure (IOP) measurements, and gonioscopy. Two agematched subgroups were created: one treated with PGA and the other with TCAI. CCT, ophthalmoscopic cup/ disc ratio (CDR), mean deviation (MD), pattern standard deviation (PSD), and IOP were considered for both eves of each patient. Student *t*-test was used to compare the 2 subgroups.

Results: The mean age of the PGA group was 66.35±12.17 years, while 65.17±12.52 years was for the TCAI group. No significant difference was found for CCT (543.75±35 µm and 544±35 µm, respectively), CDR $(0.55\pm0.2 \text{ and } 0.53\pm0.2, \text{ respectively})$, MD $(-4.5\pm4.9 \text{ dB} \text{ and } -5.4\pm6.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ and } -5.4\pm0.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ dB}, \text{ respectively})$, PSD $(4.6\pm3.4 \text{ dB}, \text{ respectively})$, PS 4.6 ± 4.9 , respectively), and IOP (15.9 ± 3.3 mmHg and 15.7 ± 2.9 mmHg, respectively) between the 2 subgroups. A significant (P < 0.001) correlation was found between CCT and CDR and between CCT and IOP.

Conclusion: No significant difference in CCT was found between patients treated with PGA and TCAI, suggesting that these topical medications did not statistically and clinically change the CCT.

Introduction

LAUCOMA IS A progressive neurodegenerative disease. GIt has been shown that a decrease in intraocular pressure (IOP) could lower the progression of the damage. Topical application of anti-glaucoma medications has been the primary mode of glaucoma treatment for the last century.

Central corneal thickness (CCT) has been shown to be an independent risk factor for glaucoma,¹ and the relationship between CCT and the risk of glaucoma damage is still controversial. No correlation among the thickness of the central cornea of the peripapillary retinal nerve fibers² and of the lamina cribrosa³ was found in nonglaucomatous human eyes, while in glaucomatous eyes, no data showed a relationship between corneal thickness and hystomorphometry of the lamina cribrosa or peripapillary nerve fiber layer thickness. There is no consensus on the influence of CCT values on the likelihood of progression of glaucomatous damage in established glaucoma.

Several medications could be used but 2 of them, prostaglandin analogs (PGA) and topical carbonic anhydrase inhibitors (TCAI), could display secondary effect on corneal structure.^{4,5} Although the prostaglandins are isopropyl ester

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⁸See Appendix.

prodrugs and bimatoprost is a prostamide, because they have a similar action, we grouped them together for this analysis.⁴

The IOP reduction obtained with PGA might be related to the activation of matrix metalloproteinases (MMPs).^{6–8} Because the cornea is mainly composed of collagen fibers, it was reasonable to hypothesize a possible influence of topical PGA on CCT. On the other hand, the TCAI medications could have a negative effect on the cornea due to their inhibition of the carbonic anhydrase II (CA-II), with a secondary effect on the CCT.^{4,9,10} The aim of the study was to evaluate whether patients treated with PGA and TCAI would have a difference in CCT values.

Patients and Methods

This was a retrospective, cross-sectional, multicenter study. Institutional review boards and ethics committees at the institutions gave their approval of this study. This study followed the principles of the Declaration of Helsinki.

From 16 different glaucoma centers, at least 50 glaucomatous patients for each center were saved on the Italian Glaucoma Register (IGR).¹¹ From the database, only patients treated with prostaglandins or TCAI in mono-therapy were included in the study.

Glaucomatous eyes were diagnosed based upon having a reproducible and characteristic visual field (VF) defect on 3 nonedge points all of which were depressed on the pattern deviation plot at P < 5%, along with an asymmetrical cupping greater than 0.2, the presence of a notch on the rim, and/or an increased cupping greater than 0.6 when measured as Cup/Disc Ratio (CDR) and an open angle at gonioscopy.¹²

All subjects underwent at least 2 Swedish Interactive Thresholding Algorithm (SITA) Standard 24–2 perimetry. Reliable tests had fewer than 30% fixation losses, false-negative and false-positive responses. In this study, the included patients had a best-corrected visual acuity of 20/60 or better and their refractive error ranged from +6.00 to -6.00 diopters. Subjects were excluded for a history of diabetes or posterior pole pathology other than glaucoma. Additionally, subjects were excluded for use of systemic steroids, any other systemic medication known to affect the retina, and any neurological condition known to affect the VF. Furthermore, eyes that underwent any intraocular surgery, including cataract extraction during the period of follow-up, were excluded.

In each center the same observer always performed an ultrasonic contact pachymetry. Patients were instructed to look straight ahead at a fixation target located at 3 m. After having pushed the button to initiate corneal thickness measurements, the probe tip was gently positioned to touch the patient's cornea at its center. The pachymeter probe had to be perpendicular to the apex of the cornea. If the measurement was valid, a value appeared on the digital display. The mean value of 3 consecutive measurements was used for the statistical analysis.

CCT, ophthalmoscopic CDR, mean deviation (MD), pattern standard deviation (PSD), and IOP were considered in this study.

From the entire IGR database, first we excluded the patients who did not have all the data, and then we selected those patients who were on PGA monotherapy or TCAI monotherapy, and 2 age-, CDR-, MD-, and PSD-matched groups were created. The data were analyzed by descriptive analysis and when the distribution of the data was normal, a *t*-test and Pearson's r coefficient were used when the distribution of the data was non-normal, a Mann–Whitney test and Spearman coefficient were used.

Results

Eight hundred sixteen patients were included in the IGR. Twenty-two patients were excluded: in particular 15 because the CCT measurement was present for only one eye (5 patients had only right measurements and 10 only left measurements), and 7 because patients did not have the VF data for both eyes. All the patients were Caucasian. A descriptive analysis of the included patients is described in Table 1. Three hundred sixteen patients were recruited in this study, and then 2 age-, CDR-, MD-, and PSD-matched groups were recreated after excluding PGA patients, who were the majority. Table 2 lists the details of the 2 groups. No significant difference was found for CCT between the 2 groups (Table 2).

A significant (P<0.001) negative correlation was found between CCT and CDR, while a significant (P<0.001) positive correlation was found between CCT and IOP; both correlations had a low r coefficient value. Furthermore, a significant (P<0.05) but weak correlation was found between CCT and MD (Table 3).

Discussion

It has been supposed that PGA could reduce CCT,^{13–16} while TCAI could increase CCT.⁵ Long-term local treatment is always associated with adverse effects, some of which affect the corneal tissue.^{12,17–19} The cornea is mainly composed of collagen fibers; PGA seems to affect the corneal stromal structure by decreasing the extracellular matrices.²⁰

The MMP family includes several types of enzymes that may be found in the anterior segment of the eye, including corneal epithelium, stroma and endothelium, conjunctiva, lacrimal film, aqueous humor, trabecular meshwork, ciliary muscle cells, and lens.^{6–8,16,21} In the eye, MMPs are responsible for the degradation of extracellular matrix compounds and basal membrane, including collagen types I, II, III, IV, fibronectin, and laminin.^{22,23} Previous studies showed that MMPs played an important role in the healing process of corneal epithelium and stroma. Maeda et al. reported that MMP-2 and MMP-9 activities were enhanced in the stromal tissue after refractive surgeries (both photorefractive keratectomy and laser *in situ* keratomileusis).²⁴ In rabbits, the use of MMP inhibitor was effective in reducing the subepithelial opacity after photorefractive keratectomy.25 Garrana et al. demonstrated that MMP-2 expression was increased in corneal epithelial cells in patients with recurrent corneal erosion.²⁶ Abnormal expression of MMP active forms was found in thinner and ulcerated corneas after thermal and alkalis burns.²⁷ After stromal healing, it was possible that the opacity reduction of the new scar tissue occurred because of the remodeling of collagen fibers, which, in turn, might result from the activity of MMP-2 and MMP-3 from the stromal fibroblasts.²⁸

PGAs have proved to be effective ocular hypotensive drugs that reduced IOP by enhancing aqueous humor through the uveoscleral pathway to the suprachoroidal space and to the episcleral veins. Although the exact cellular

TABLE 1. DESCRIPTIVE ANALYSIS

	Mean	SD
Age (years)	65.88	12.77
IOP (mmHg)	16.14	3.54
CDR	0.56	0.21
MD (dB)	-5.23	6.46
PSD	4.79	10.61
CCT (µm)	545.48	36.50

SD, standard deviation; IOP, intraocular pressure; CDR, cup/disc area ratio; CCT, central cornea thickness; MD, mean deviation; PSD, pattern standard deviation.

mechanism for this effect was not clarified, it was well known that these drugs could reduce collagens in the tissues of the uveoscleral outflow pathway and increase the production of MMPs.^{6,7}

Most of the recent studies have shown that PGA could decrease the CCT values.^{13–16} PGA (latanoprost 0.005% and bimatoprost 0.03%) were found to increase the CCT value slightly.⁴ Zhong *et al.* have shown in a longitudinal study based on 69 patients that topical therapy with PGA was associated with CCT reduction, and in particular latanoprost $(14.95\pm5.04\,\mu\text{m})$, travoprost $(15.73\pm3.25\,\mu\text{m})$, and bimatoprost (17.00 \pm 6.23 µm) had a similar effect on CCT.²⁹ Besides in the results they found no significant difference in the CCT reduction among the 3 groups (P > 0.05) and no significant difference in the CCT reduction between the patients with less than or equal to 6 months treatment and the patients with more than 6 months treatment among the 3 groups (P > 0.05). However, in these studies, the change in CCT found could not significantly change the IOP values measured.

On the other hand, in the corneal endothelium CA-II played a role in the pumping mechanism, which helped to maintain the relatively dehydrated state of the corneal stroma. Inhibition of this mechanism might lead to the development of corneal decompensation and edema with secondary impaired vision.⁵ In a randomized, double-blind clinical trial, 372 glaucomatous and ocular hypertension patients received brinzolamide 1% or timolol 0.5%. After 18 months of treatment, no significant change was found in corneal thickness and corneal endothelium cell density.³⁰ However, in their study only subjects with healthy corneas were included, although there remained some concern in patients with compromised corneas in those treated with dorzolamide, supporting case reports that have been published suggesting a possible corneal decompensation.^{31,32} Zhou and colleagues have reported 2

TABLE 2. COMPARISON BETWEEN PROSTAGLANDIN AND TOPICAL CARBONIC ANHYDRASIS INHIBITOR SUBGROUPS

	<i>PG</i> (n=123)	<i>TCAI</i> (n=74)	P value
Age (years) CCT (μm) CDR MD(dB) PSD	$66.35 \pm 12.17 543.75 \pm 35 0.55 \pm 0.2 -4.5 \pm 4.9 4.6 \pm 3.4$	$\begin{array}{c} 65.17 \pm 12.52 \\ 544 \pm 35 \\ 0.53 \pm 0.2 \\ -5.4 \pm 6.4 \\ 4.6 \pm 4.9 \end{array}$	0.379 0.545 0.124 0.371 0.665

PGA, prostaglandin analog group; TCAI, topical carbonic anhydrasis inhibitor group, Mean±standard deviation.

 TABLE 3.
 CENTRAL CORNEA THICKNESS CORRELATION

	r^2	P value
CCT vs. IOP	0.2	< 0.001
CCT vs. CDR	-0.2	< 0.001
CCT vs. MD	0.1	0.049
CCT vs. PSD	-0.02	0.621

cases of corneal decompensation following brinzolamide therapy that reversed with discontinuation; causation was difficult to assess, however, as the onset of corneal edema occurred 15 months and 2 years after initiating brinzolamide therapy, respectively, and neither patient was rechallenged after recovery.⁹ No significant CCT change was found.¹⁰

In this study we did not divide the PGA and TCAI in subgroups based on the brands, because we evaluated a possible effect of PGA and TCAI on CCT and we did not consider the duration of the topical treatment. Besides, this was not a longitudinal study, but it was a cross-sectional study, and in so large a cohort of patients we did not find any difference between the 2 groups. From a statistical point of view, if we applied the binomial (sign) test to the pattern of the mean changes across the points and the test assumed that point data were mutually independent, under the hypothesis of zero difference, the positive and negative point data were likely equal.

Furthermore, in this study the correlation we found outlined the previous published studies³³ showing that lower CCT patients had a worse CDR and MD with lower IOP values (Table 3).

The reliability of CCT measurement has been much less controversial than that of IOP measurements.³³ Techniques to measure CCT included optical (mean CCT 530 mm) and ultrasound (mean CCT 544 mm), with the latter being easier to perform. In addition, corneal hysteresis might also interfere with IOP measurements; it appeared as though this corneal variable described the response of the cornea to rapid deformation. Congdon *et al.* suggested that the relationship between glaucoma and corneal features was more complex than simple anatomic thickness.³⁴

In conclusion, from these data no significant clinical CCT difference was found between PGA and TCAI patients. We do not exclude a possible effect of both medications on the cornea, but it cannot be a significant and clinical bias in the IOP measurements.

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Author Disclosure Statement

None of the authors has proprietary interest in the development and marketing of any products mentioned in the article.

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Appendix

The Italian Glaucoma Register:

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