Original Article

Correlation between the pressure-to-cornea index and both structural and functional measures of glaucoma

Andrea M B V Franco, Niro Kasahara

Purpose: the pressure-to-cornea index (PCI) was proposed in order to integrate intraocular pressure and central cornea thickness as a single-risk factor for glaucoma. The purpose of this study was to correlate the PCI with a structural and two functional measures of glaucoma. **Setting:** University Hospital in South America. **Materials and Methods:** Pressure-to-cornea index was calculated for 70 eyes of 36 subjects (glaucoma and suspects). Cup-to-disc (C/D) ratio, mean deviation (MD) and pattern standard deviation (PSD) as recorded by Humphrey automated perimetry (SITA 24-2) were correlated with PCI (Pearson's correlation coefficient). **Results:** Pearson's correlation coefficient between PCI and C/D was 0.329 (95% confidence interval [95% CI], 0.09–0.526; $P = 0.006$); between PCI and MD was − 0.356 MD (95% CI, −0.549 to − 0.126; $P = 0.003$); and between PCI and PSD was − 0.215 (95% CI, −0.433 to 0.025; $P = 0.07$). **Conclusion:** In addition to serve as a single-risk factor, PCI can be used to stage glaucoma severity as well.

Keywords: Glaucoma, pressure-to-cornea index, visual field

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The association of central cornea thickness (CCT) and glaucoma has been reappraised recently in large population-based and clinical studies. The Los Angeles Latino Eye Study examined 5970 subjects and concluded that CCT was an important independent risk factor for the prevalence of glaucoma.[1] Wong *et al.* noted that CCT was a significant determinant of intraocular pressure (IOP) in Asian persons aged 40–80 years, especially in younger persons.[2] The ocular hypertension (OHT) treatment study concluded that CCT was an independent predictive factor for the development of glaucoma.[3,4] Several authors have recognized CCT as a risk factor for advanced glaucoma damage.[5-7]

Central cornea thickness can influence IOP measurement by Goldmann applanation tonometry resulting in an inaccurate reading. That is particularly true in thinner corneas in which applanation tomonetry readings are lower than true values. A meta-analysis of the possible association between CCT and IOP measures of 133 data sets revealed that a 10% difference in CCT would result in a 3.4 ± 0.9 mmHg difference in IOP.[8] The magnitude of the effect, however, is subject to much individual variation.[9]

A number of algorithms have been proposed to correct applanation tonometry readings according to CCT. However, there is wide disagreement among investigators as to if there is an adequately validated correction algorithm.[10] Corrections using only the CCT and curvature may not be sufficient in each individual case.[11]

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The pressure-to-cornea index (PCI) was proposed in order to integrate IOP and CCT as a single-risk factor for glaucoma.[12] Until date, no study has explored the possible use of PCI as a parameter for disease severity. The purpose of the study was to correlate the PCI with a structural and two functional measures of glaucoma.

Materials and Methods

Study population and inclusion criteria

This cross-sectional study included patients with OHT or primary open-angle glaucoma (POAG) older than 40 years of age of both genders, with 20/20 best corrected visual acuity, and any ethnicity. Subjects with cataracts or any other ocular disease, and previous incision or laser surgery for glaucoma were not included in the study. Data were collected from April to October 2010. Institution Board Review approved the study, and the procedures followed adhered to the principles for medical research involving human subjects of the Declaration of Helsinki in 1964 (amended by the 59th WMA General Assembly, Seoul, Korea, October 2008). In order to be included in the study, POAG patients had typical optic disc damage (diffuse or localized rim thinning, enlarged cupping, disc hemorrhage, asymmetry in cup-to disc (C/D) ratio, 0.2 or greater between eyes) with corresponding visual field loss on reliable automated perimetry (at least 3 adjacent points in the expected location of the central 24° - field that have $P < 5\%$ on the pattern deviation plot, one of which with $P < 1\%$; glaucoma hemifield test "outside normal limits"; pattern standard deviation [PSD] with a $P < 5\%$), and open angles on gonioscopy. A reliable perimetry was an exam with <20% fixation loss, and < 33% of both false negative and false positive. OHT was defined as any individual with IOP higher than 21 mmHg with no glaucoma medication, healthy appearing optic disks and no visual field defect on automated perimetry.

Seventy eyes of 36 patients with POAG or OHT enrolled this cross-sectional study. Fourteen patients were male (38.9%) and

22 female (61.1%). As to ethnicity, six were African-Brazilian, 10 patients were white, 19 were mixed, and one was Asian. Mean age was 65.9 ± 23.0 years.

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After explaining the procedures, all subjects signed an informed consent and underwent a complete eye examination with evaluation of the visual acuity, anterior segment biomicroscopy, tonometry with the Goldmann tonometer (Haag-Streit AG, Switzerland) after instillation of proparacaine and fluorescein drops, gonioscopy with a three mirror lens OG3M (Ocular Instruments, Bellevue, Washington, USA), and optic disk assessment with 78 D Volk lens (Volk Optical Inc., Mentor, OH, USA) on a tropicamide dilated pupil. The IOP was measured after discontinuation of all glaucoma medications for at least 21 days. The C/D ratio assessment was done by two observers, which in common agreement classified the optic disk according to a decimal system. Standard automated perimetry (SITA standard 24-2) was done with the HFA 730 (Carl-Zeiss Humphrey, Dublin, CA, USA) with appropriate refractive correction. Patients with unreliable exams were instructed to do the perimetry a second time in an attempt to get a reliable test, and those who remained with an unreliable test were not included in the study. CCT was measured with ultrasonic pachimeter (300P Pacscan, Sonomed-Escalon, Wayne, PA, USA); the probe was placed at the 5 mm central diameter of the cornea after instillation of proparacaine drops and three measurements where averaged to obtain one single value.

Statistical analysis

Pressure-to-cornea index was calculated as the ratio between untreated IOP and CCT to the power of three (in mm) for each subject as proposed by Iliev *et al*. (PCI = IOP/CCT^3).[12]

Pearson's product moment correlation coefficients with 95% confidence intervals (95% CI) were calculated to quantify the linear relationship between the PCI and a structural measure (C/D ratio) and the PCI with two functional measures mean deviation (MD and PSD values from automated perimetry). Statistical significance was set at $P < 0.05$, and all the analyses were done with MedCalc® software, version 9.3.7.0 (MedCalc Software bvba, Belgium).

Results

The mean values of the MD and PSD from automated perimetry of the 70 eyes were - 9.9 ± 7.6 dB and 5.4 ± 3.1 dB, respectively. The median C/D ratio was 0.8 (range, 0.3–1.0). The mean CCC was 533.0 ± 40.4 µ, mean IOP was 19.7 ± 5.1 mmHg, and mean PCI was 132.9 ± 51.4.

The PCI showed a statistically significant negative correlation with MD (r = −0.356, 95% CI, −0.549 to − 0.126; P = 0.003) [Fig. 1]; the correlation between PCI and PSD values of automated perimetry, however, failed to reach statistical significance (r = −0.215, 95% CI, −0.433 to 0.025; P = 0.07) [Fig. 2]. Good correlation was found between PCI and C/D ratio (r = 0.329, 95% CI, 0.09 to 0.526; P = 0.006) [Fig. 3].

Discussion

In an attempt to integrate IOP and CCT into a unified risk factor, rather than simply attempting to correct for IOP measurement inaccuracy, Iliev *et al*. have proposed a new glaucoma index, the PCI. The authors believed that PCI could better reflect the individual susceptibility to glaucomatous damage than either IOP alone or CCT by itself. In a group of 220 normal controls, 53 patients with normal-tension glaucoma (NTG), 76 with OHT, and 89 with POAG, the authors have assessed the ability of PCI to discriminate between glaucoma (NTG + POAG), and non-glaucoma (controls + OHT) and compared with that of three published formulae for correcting IOP for CCT. Mean PCI value for normal control was 92 ± 24.8 and for glaucoma patients 173.6 ± 40.9. PCI demonstrated a larger area under the receiver operating characteristic curve (area under the curve [AUC]) and significantly higher sensitivity at fixed 80% and 90% specificities compared with each of the correction formulas. The authors proposed the range of 120–140 as the upper limit of "normality," and concluded that PCI may reflect individual susceptibility to a given IOP level, and thus represent a glaucoma risk factor.[12] Eballe *et al*. analyzed CCT and IOP in the Cameroonian non-glaucomatous population and the PCI values for this population was close to the cutoff proposed by Iliev *et al*.[13]

Since its introduction, the PCI has not been studied by other authors. To the best of our knowledge, this is the second study that evaluated the usefulness of PCI in glaucoma patients. In our study, we have evaluated the utility of PCI as an index of glaucoma severity, and our results have shown a correlation between the index and the MD value of automated perimetry. Visual field sensitivity is expressed on a logarithmic (decibel) scale; hence, one might expect a curvilinear relationship between PCI and MD. The relationship between PCI and MD depends solely and directly from the formula that defines the relationship between them, and does not depend on the logarithmic nature of retinal sensitivity with respect to luminous magnitudes. Therefore, it is absolute and necessarily linear.

Patients with lower MD presented with higher PCI values. The MD value of automated perimetry is a weighted average decibel deviation from age normal database; the lower the MD value, the more damaged the visual function is. Nevertheless, the MD can be affected by media opacity such as cataract and uncorrected refractive error. In our study,

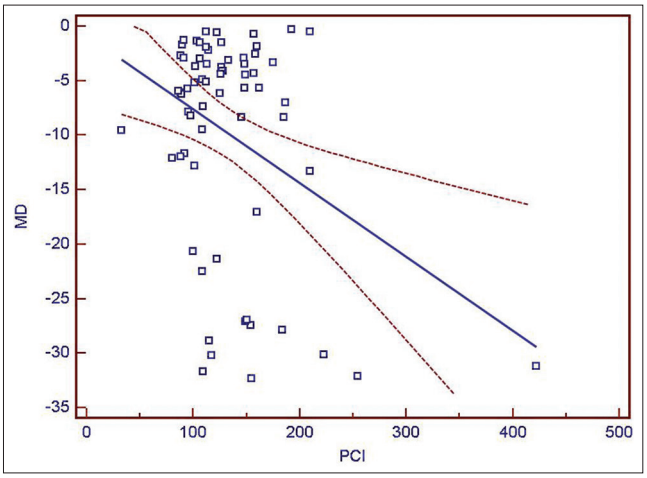

Figure 1: Correlation between the pressure-to-cornea index (PCI) and mean deviation (MD)

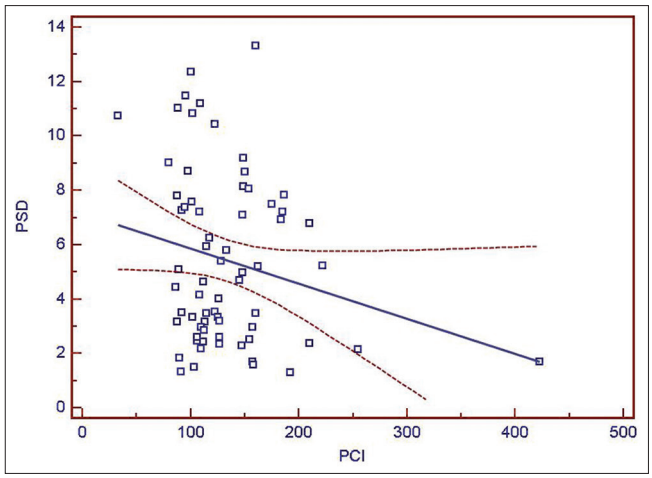

Figure 2: Correlation between the pressure-to-cornea index (PCI) and pattern standard deviation (PSD)

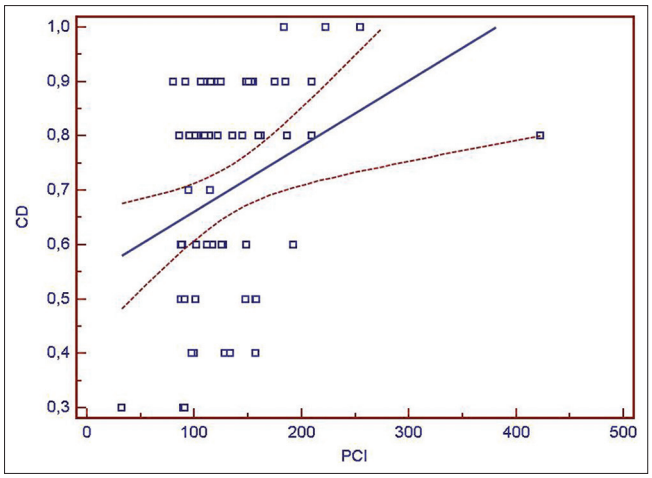

Figure 3: Correlation between the pressure-to-cornea index (PCI) and cup-to-disk ratio (CD)

only patients with 20/20 vision and no cataract were included, and the automated perimetry was done with the patient's appropriate refractive correction, so that MD values were very representative of glaucoma-related visual dysfunction.

The PSD value is the standard deviation of the difference between the threshold value at each test location and expected value and as an indicator of localized defects it reflects the roughness of the visual field. It is calculated by summing the absolute value of the difference between the threshold value for each point and the average visual field sensitivity at each point. As higher PSD indicates more damaged visual fields, and assuming that PSD has a positive correlation with PCI, one would expect that the higher the PCI value, the higher the PSD. In this study, however, the correlation between PCI and PSD revealed a trend toward a negative correlation, not statistical significant, though. We are unsure if these results are due to the sample size or any selection bias.

In general, automated perimetry, as a psychophysical test, is subject to patient cooperation and individual cognitive function causing imprecision of the measurements. These can degrade the relationship between functional measures and the PCI. We have tried to minimize this imprecision by selecting only automated perimetry exams with good reliable indices.

Our results revealed good linear correlation between the PCI and the C/D ratio. Patients with higher C/D ratios presented with higher PCI values. The C/D ratio is a subjective, qualitative method to assess the optic nerve head in glaucoma patients. It is widely used in clinical practice, and it gives an appraisal of the cup diameter in relation to the optic disk size; on a decimal scale, it ranges from zero (no cupping) to one (optic nerve head completely excavated). However, it does not take into account localized defects of the neural rim, disk hemorrhages or the posterior bowing of the lamina cribrosa. Besides, glaucoma patients with small optic discs will have proportionally small C/D ratios, giving a falsely impression of healthy looking optic disk. Conversely, normal subjects with macrodisks will present with large C/D ratios giving a false impression of damaged optic disk. Hence, the C/D ratio is not a precise surrogate of glaucomatous optic disc damage without consideration of the relative disc size, area, and the quantitative assessment of neural rim width and area. Using this structural measure is a major shortcoming and quantitative measures of the optic disk structure as provided by new technologies should have been a better choice for correlation studies.

Another shortcoming of the study is the use of both eyes of the same individual. Doing so for the measurement of an attribute or variable, rather than selecting one eye at random or the more severe affected eye for analysis tend to overestimate variability, artifactually influencing *P* value and decreasing chances of observing a significant effect, decreasing statistical power and increasing chances of type II error. Besides, we have not used any regression models to appropriately treat the eye as the unit of analysis, which tends to bias observations. However, incomplete data collection or selection of eyes for inclusion in a study on clinical grounds has the potential to introduce bias, and we decided to use both eyes of the same patient to avoid waste of data.

The results of the study seem to dependent on a single outlier case with a PCI value greater than 400, which is above the maximum range described in a much larger population in the paper by Iliev *et al*. This was a patient with untreated IOP of 38 mmHg and CCT of 0.46 mm. A *post-hoc* analysis eliminating this data point revealed that the value of *r* is reduced, but *P* still is significant (except for PCI and PSD). However, we have decided to keep this patient in the study because an estimate indicated that increasing the number of cases could result in statistical significance.

More recently, Leung *et al*. have proposed a new pressure-cornea-vascular index (PCVI). The index is derived from the PCI and extended with risk factors identified as associated with field-progression in a prospective cohort of 415 patients with NTG followed for 3 years. The authors concluded that PCVI might be useful for predicting progression in NTG with a satisfactory AUC comparable to established scoring systems in neurovascular medicine.[14] In our study, we had not assessed any vascular parameters and did not evaluate the PCVI.

In summary, the results of our study have revealed that PCI has a correlation with both the MD value of automated

perimetry and the C/D ratio. These observations concur with the hypothesis that PCI can be used to stage disease severity.

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