Novel pressure-to-cornea index in glaucoma

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Background: Several conversion tables and formulas have been suggested to correct applanation intraocular pressure (IOP) for central corneal thickness (CCT). CCT is also thought to represent an independent glaucoma risk factor. In an attempt to integrate IOP and CCT into a unified risk factor and avoid uncertain correction for tonometric inaccuracy, a new pressure-to-cornea index (PCI) is proposed.

Methods: PCI (IOP/CCT^3) was defined as the ratio between untreated IOP and CCT^3 in mm (ultrasound pachymetry). PCI distribution in 220 normal controls, 53 patients with normal-tension glaucoma (NTG), 76 with ocular hypertension (OHT), and 89 with primary open-angle glaucoma (POAG) was investigated. PCI's ability to discriminate between glaucoma (NTG+POAG) and non-glaucoma (controls+OHT) was compared with that of three published formulae for correcting IOP for CCT. Receiver operating characteristic (ROC) curves were built.

Results: Mean PCI values were: Controls 92.0 (SD 24.8), NTG 129.1 (SD 25.8), OHT 134.0 (SD 26.5), POAG 173.6 (SD 40.9). To minimise IOP bias, eyes within the same 2 mm Hg range between 16 and 29 mm Hg (16–17, 18–19, etc) were separately compared: control and NTG eyes as well as OHT and POAG eyes differed significantly. PCI demonstrated a larger area under the ROC curve (AUC) and significantly higher sensitivity at fixed 80% and 90% specificities compared with each of the correction formulas; optimum PCI cut-off value 133.8.

Conclusions: A PCI range of 120–140 is proposed as the upper limit of "normality", 120 being the cut-off value for eyes with untreated pressures ≤ 21 mm Hg, 140 when untreated pressure ≥ 22 mm Hg. PCI may reflect individual susceptibility to a given IOP level, and thus represent a glaucoma risk factor. Longitudinal studies are needed to prove its prognostic value.

The role of intraocular pressure (IOP) as a major causative risk factor in glaucoma has been confirmed in several large multicentre, randomised controlled clinical trials.^{1–3} In addition, many studies have also pointed out the importance of central corneal thickness (CCT) as a parameter influencing the accuracy of tonometric readings as well as our decision-making in the management of glaucoma.^{4–7} The influence of CCT has been demonstrated for various tonometers, and particularly the Goldmann applanation tonometer, with thin corneas leading to an underestimation and thick corneas to an overestimation of the true IOP.^{8–13} To correct for this variable, several conversion tables or formulae have been suggested in the literature. However, these various formulae deviate considerably from one another, and there is no formula with proven superiority at the present time.^{14–18} In addition, the relationship between applanation IOP and CCT may not be linear.⁷

Even if an appropriate correction formula for IOP, based on CCT, is determined, this may not fully address the significance of CCT in the glaucomatous process. There are reasons to assume that corneal thickness may represent an independent risk factor for the development and progression of glaucoma, although this has yet to be clarified.^{6, 19–21} In an attempt to integrate IOP and CCT into a unified risk factor, rather than simply attempting to correct for IOP measurement inaccuracy, we propose a new glaucoma index, called pressure-to-cornea index (PCI).

We hypothesise that PCI may better reflect the individual susceptibility to glaucomatous damage than either of the integrated parameters, IOP and CCT, alone. We report a cross-sectional study of PCI in patients with primary open-angle glaucoma, normal-tension glaucoma, ocular hypertension and in normal controls.

METHODS

This was a retrospective review of the records of patients and normal controls examined at the Department of Ophthalmology, University of Bern, Switzerland, divided into four groups: (1) primary open-angle glaucoma (POAG; established glaucomatous optic disc and visual field damage, untreated IOP ≥ 22 mm Hg); (2) normal-tension glaucoma (NTG; established glaucomatous disc and field damage, untreated IOP ≤ 21 mm Hg); (3) ocular hypertension (OHT; normal optic discs, visual fields and anterior chamber angle, untreated IOP ≥ 22 mm Hg, no family history of glaucoma); and (4) normal controls (IOP ≤ 21 mm Hg, normal discs, fields and anterior chamber angle, no history of ocular disease or surgery, no family history of glaucoma). The normal controls had been recruited and fully examined for earlier studies. In all groups, only one randomly selected eye per patient was included. Exclusion criteria were pseudoexfoliation, pigmentary glaucoma, narrow anterior chamber angle, secondary glaucoma; history of corneal disorder, corneal surgery or contact lens wear at the time of the CCT measurements; intraocular disorders, other than mild cataracts; myopia < -6.0 D, hyperopia > 4.0 D, astigmatism > 2 D, best corrected visual acuity $< 20/40$, or unreliable visual fields (reliability factor $> 20\%$). IOP was measured with Goldmann applanation tonometry (AT900, Haag-Streit International, Koeniz, Switzerland), CCT with ultrasound pachymetry (TOMEY Bio & Pachy Meter AL-1000), and visual field with standard automated perimetry (Octopus 101, threshold program G2, Haag-Streit International, Koeniz, Switzerland). For most participants, colour optic disc

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; NTG, normal-tension glaucoma; OHT, ocular hypertension; PCI, pressure-to-cornea index; POAG, primary open-angle glaucoma; ROC, receiver operating characteristic

Figure 1 Pressure-to-cornea index (PCI) in the four study groups. PCI is calculated as IOP/CCT^3 where CCT (central corneal thickness) is expressed in mm. POAG, primary open-angle glaucoma; OHT, ocular hypertension, NTG; normal-tension glaucoma; Controls, persons with normal IOP, normal ophthalmological status and negative family history of glaucoma. One eye per patient was included.

photographs, HRT images (Heidelberg Retina Tomograph, Heidelberg Engineering GmbH, Heidelberg, Germany; software version 1.7 of the HRT II), and GDx VCC images (Carl Zeiss Meditec, Dublin, California) were available.

The basic pressure-to-cornea index was defined as the highest recorded applanation IOP in mm Hg without treatment, divided by the CCT in mm [$PCI_{basic} = IOP/CCT$ in mm]. High IOP and thin corneas resulted in high PCI values and vice versa (eg IOP 22, CCT 0.525 mm, $PCI_{basic} = 41.9$; IOP 17, CCT 0.572 mm, $PCI_{basic} = 29.7$). In an attempt to reduce the relative role of IOP and accentuate the relative role of CCT in the formula, we also included “amplified” index versions: IOP/CCT^2 , IOP/CCT^3 and IOP/CCT^4 . Since IOP/CCT^3 differentiated between the groups best, we suggest it as “PCI amplified” or just “PCI”. In the above examples: IOP 22, CCT 0.525 mm, $PCI = 152$; IOP 17, CCT 0.572 mm, $PCI = 90.8$).

The aims of the study were to look at the distribution of PCI in the normal population, in ocular hypertension and in the subcategories of primary open-angle glaucoma; to investigate PCI’s ability to differentiate between glaucoma and non-glaucoma, and to compare its performance with known IOP correction formulae for CCT. For this purpose, the correction formulae of Ehlers *et al.* (1975), Doughty and Zaman (2000), and Shimmyo *et al.* (2003) were used.

Ehlers *et al.* (1975): The originally published Table III Additive correction (ΔP) for Goldmann applanation tonometer readings was used, ΔP varying according to the CCT and the level of

Table 1 Demographic characteristics of the study groups (mean $\pm$ SD)				
	Normal (n=220)	NTG (n=56)	OHT (n=73)	POAG (n=89)
Male/female	98/122	16/40	31/42	38/51
Age (years)	51.64 $\pm$ 14.22	63.4 $\pm$ 11.7	55.2 $\pm$ 11.1	65.0 $\pm$ 11.0
Visual acuity (decimal)	1.07 $\pm$ 0.17	0.93 $\pm$ 0.13	1.0 $\pm$ 0.08	0.92 $\pm$ 0.15
Refraction (SE)	-0.26 $\pm$ 1.04	-0.03 $\pm$ 1.73	-0.25 $\pm$ 1.6	-0.6 $\pm$ 2.1
MD (dB)	0.68 $\pm$ 0.97	5.0 $\pm$ 3.7	-0.7 $\pm$ 1.1	5.1 $\pm$ 4.5
LV (dB ²)	3.7 $\pm$ 1.34	26.9 $\pm$ 24.8	3.3 $\pm$ 1.3	22.0 $\pm$ 20.6

SE: spherical equivalent in diopters; MD: mean defect in the Octopus standard white-on-white automated perimetry, normal range -2.0 to +2.0 dB, abnormal values >2.0; LV: loss variance in the Octopus standard white-on-white automated perimetry, normal range 0.0 to +6.0 dB², abnormal values >6.0).

Table 2 Pressure-to-cornea index (PCI) (mean $\pm$ SD)				
	Normal	NTG	OHT	POAG
IOP (mm Hg)	14.9 $\pm$ 3.1 (7–21)	18.4 $\pm$ 2.2 (13–21)	24.7 $\pm$ 2.3 (22–31)	26.3 $\pm$ 4.3 (22–40)
CCT (μ m)	549.0 $\pm$ 36.5 (465–660)	525.7 $\pm$ 30.6 (469–600)	573.4 $\pm$ 34.5 (502–658)	536.9 $\pm$ 36.5 (457–630)
PCI_{basic} (IOP/CCT)*	27.3 $\pm$ 5.7 (12.9–41.0)	35.2 $\pm$ 4.5 (24.8–44.8)	43.3 $\pm$ 4.6 (33.4–53.8)	49.2 $\pm$ 8.2 (36.5–75.5)
PCI (IOP/CCT ³)*	92.0 $\pm$ 24.8 (42.0–185.4)	129.1 $\pm$ 25.8 (83.8–203.6)	134.0 $\pm$ 26.5 (77.2–197.6)	173.6 $\pm$ 40.9 (92.0–315.8)

* For the calculation of PCI_{basic} and PCI, the CCT is expressed in mm.

measured IOP.¹⁴ For our study, a difference of 20 μ m between optical (Ehlers) and ultrasound pachymetry (this study) was taken into account; in cases of high IOP or thick corneas not covered by the original table, correction values were extrapolated.

Doughty and Zaman (2000) suggested that “The correction for eyes with chronic disease should be 2 or 3 mm Hg for 0.05 mm difference in CCT from 0.535.”¹⁶ We used a 2 mm Hg correction for a 50 μ m difference in CCT from 0.535 mm.

Shimmyo *et al.* (2003): The originally published correction Table 11. GAT (A) Correction for Error (X) and 1/X in combination with Formula 3 from APPENDIX 2 ($P = A + (550 - T)/X$) was adopted.⁷

Statistical analysis was performed with StatsDirect software. The Mann–Whitney U test was used to test differences between two independent random samples. Statistical significance was considered if $p < 0.05$. To compare the differentiation ability

Table 3 Comparison of PCI values at the same level of IOP within the range 16 to 29 mm Hg					
IOP (mm Hg)	Normal		NTG		p
	n	PCI (mean $\pm$ SD)	n	PCI (mean $\pm$ SD)	
16–17	43	101.6 $\pm$ 22.6	13	115.0 $\pm$ 17.2	0.0071
18–19	34	109.6 $\pm$ 23.6	15	123.4 $\pm$ 26.6	0.069
20–21	19	117.9 $\pm$ 19.2	23	143.9 $\pm$ 23.8	0.0003

IOP (mmHg)	OHT		POAG		p
	n	PCI (mean $\pm$ SD)	n	PCI (mean $\pm$ SD)	
22–23	28	120.1 $\pm$ 19.1	30	157.8 $\pm$ 31.1	<0.001
24–25	18	138.4 $\pm$ 30.4	15	160.9 $\pm$ 37.7	0.0780
26–27	15	143.7 $\pm$ 28.1	17	175.3 $\pm$ 36.3	0.0109
28–29	11	146.2 $\pm$ 20.9	10	176.4 $\pm$ 22.4	0.0024

Figure 2 Distribution of PCI in % in the control group (n=220). For abbreviations see fig 1.

Figure 3 Differentiating between glaucoma (NTG+POAG) and non-glaucoma (controls+OHT), ROC. For abbreviations see fig 1. Formulae to correct applanation IOP for corneal thickness are explained in the text.

between glaucoma and non-glaucoma, ROC curves were constructed.

RESULTS

Four hundred and thirty-eight eyes of 438 subjects were included: 220 normal controls, 54 with NTG, 73 with OHT, and 89 with POAG. The demographic characteristics are given in table 1.

Distribution of PCI in the study groups

In the normal cohort, the distribution of the two basic parameters, IOP and CCT, followed a Gaussian distribution. Mean IOP, CCT, PCI_{basic} and PCI of the four study groups are shown in table 2 and fig 1.

Clinically, after the untreated pressure has been established, differential diagnosis is usually made between NTG and normality, and between POAG and OHT. Between the NTG study group and the controls, and between the POAG group and the OHT group, CCT, PCI_{basic} and PCI differed highly significantly ($p < 0.001$ for both comparisons). Mean IOP also differed significantly. To minimise this latter bias (IOP is included in the PCI formula and in the diagnosis definition), subgroups within the same pressure range were separately compared (table 3). At most IOP levels, PCI differed highly

significantly between controls and NTG, and between OHT and POAG groups; at two IOP levels it showed a strong trend.

In the control group, PCI peaked between 80 and 100 (fig 2). PCI of 120 or less was found in 89% of the controls, in 37.5% of the NTG eyes, in 31.5% in the OHT and in 6.7% of the POAG group. PCI of 140 or less was observed in 67.1% of the OHT, and in 15.7% of the POAG eyes. In other words, two-thirds of the NTG eyes had a PCI above 120, and two-thirds of the OHT eyes had a PCI below 140.

Discriminating between glaucoma and non-glaucoma (sensitivity and specificity)

To analyse the discrimination ability of the new index, we pooled all glaucoma eyes (NTG + POAG, $n = 145$) and all non-glaucoma eyes (controls + OHT, $n = 293$) together. ROC curves were built for IOP, CCT, PCI_{basic} and PCI. PCI demonstrated better sensitivity and specificity compared with its integrated parameters (fig 3A).

We further tested whether combining applanation IOP and CCT in an index offers any advantages over correcting applanation IOP for CCT. Three correction formulae described in the Methods section were applied (table 4).

Figure 3B,C,D present the ROC curves comparing PCI with each of the three correction formulas. A larger area under the

Table 4 IOP corrected for central corneal thickness

	Controls	NTG	OHT	POAG
IOP applanation	14.9±3.1	18.4±2.2	24.7±2.3	26.3±4.3
IOP corr. Ehlers	14.2±3.7	19.4±2.9	22.6±3.2	26.8±4.8
IOP corr. Doughty	14.4±3.2	18.8±2.4	23.2±2.6	26.2±4.3
IOP corr. Shimmyo	15.0±3.6	20.1±2.9	23.0±3.3	27.3±4.8

The formulae are explained in the Methods section in the text.

ROC curve (AUC) and a significantly higher sensitivity at fixed 80% and 90% specificity were found for PCI (table 5). The optimum PCI cut-off value was calculated to be 133.8 (sensitivity = 72%, specificity = 85%).

DISCUSSION

At the present time, corneal thickness is believed to influence the glaucoma diagnosis in two ways: as physical parameter influencing the accuracy of applanation tonometry^{10–12 14–16} and as independent risk factor for glaucoma.^{19–21} Evidence for both influences exists, but the specific effect of each is uncertain. Specifically, IOP correction formulae for CCT deviate significantly from one another (table 6A). Also, normal or average corneal thickness varies from author to author and according to the pachymetry method (table 6B).^{7 14–18}

In this study, we investigated a new parameter, the pressure-to-cornea index (PCI). The index is based on the raw measures of IOP (applanation) and CCT (ultrasound) and is thought to reflect a more precise glaucoma risk than either parameter alone. PCI was tested in 220 normal persons and 218 patients with OHT, POAG or NTG. With respect to the distribution of the two individual parameters, IOP and CCT, our results are in good concordance with those of larger, population-based studies published in the literature.^{22–24} IOP in the normal cohort followed a Gaussian distribution with a peak between 14 and 15 mm Hg. Ultrasound CCT in the normal population showed a mean value of 549 µm and formed a bell-curve in the range 460–660 µm with a peak between 521 and 540 µm. Although the mean CCT value of the POAG eyes was lower than in the normal eyes (536.3 µm), CCT distribution within the glaucoma group did not show substantial differences and followed a similarly shaped bell-curve with the same peak between 521 and 540 µm. NTG eyes had thinner than average, and OHT eyes thicker than average central corneas. PCI in the normal controls peaked between 80 and 100.

PCI (IOP/CCT³) was found to better differentiate glaucoma from non-glaucoma than each of the individual parameters alone and when compared with the corrected IOP according to three published correction formulae. PCI may thus offer some advantages, since it is easier to calculate, and does not replace the measured IOP, but rather adds a new component.

Table 5 Area under the ROC curve (AUC; Wilcoxon estimate) and comparison of sensitivity at fixed specificity (McNemar test)

Parameter	AUC (SE)	Sensitivity at 80% specificity (vs PCI)	Sensitivity at 90% specificity (vs PCI)
CCT	0.672 (0.044)	40% (p<0.001)	24% (p<0.001)
IOP	0.787 (0.021)	52% (p<0.001)	30% (p<0.001)
PCI _{basic}	0.832 (0.019)	66% (p<0.001)	45% (p<0.001)
PCI	0.861 (0.018)	78%	61%
IOP corr. Ehlers	0.851 (0.018)	72% (p=0.008)	52% (p=0.002)
IOP corr. Doughty	0.849 (0.018)	66% (p<0.001)	39% (p<0.001)
IOP corr. Shimmyo	0.831 (0.019)	73% (p=0.023)	54% (p=0.070)

Table 6 Correlation of applanation intraocular pressure (IOP) and central corneal thickness (CCT) in some major published reports

A. Correction of applanation IOP per 100 µm difference from “normal” CCT	
Whitacre <i>et al</i> , 1993	2.0 mm Hg/100 µm
Doughty and Zaman, 2000	2.0 mm Hg/100 µm (in healthy eyes) 4.6 mm Hg/100 µm (in eyes with chronic diseases)
Kohlhaas <i>et al</i> , 2005	4.0 mm Hg/100 µm
Ehlers <i>et al</i> , 1975	7.1 mm Hg/100 µm (5 mm Hg/70 µm)
B. “Normal” or “average” CCT	
Ehlers <i>et al</i> , 1975:	520 µm (optical pachymetry)
Doughty and Zaman, 2000:	535 µm (meta-analysis: all pachymetry methods) 544 µm (meta-analysis: ultrasound pachymetry) 530 µm (meta-analysis: slit-lamp pachymetry)
Shimmyo <i>et al</i> , 2003:	550 µm (ultrasound pachymetry)

IOP is a very strong glaucoma risk factor and is the major clinical parameter that can be modulated by the currently available treatment methods. The proposed PCI is IOP-dependent, and may be a useful additional parameter in the context of the other clinical findings. It is our assumption that PCI may reflect individual susceptibility to an IOP level in a given situation. The PCI value which best differentiated between glaucoma and non-glaucoma was 133.8. However, a PCI range of 120–140 may be considered the upper limit of “normality”, with a cut-off value of 120 in eyes with untreated applanation IOP in the normal range, and a cut-off value of 140 when IOP of 22 mm Hg and higher is measured. A low PCI indicates “low risk of pressure-related damage”, while a high PCI suggests “increased risk of pressure-related damage”.

The proposed PCI may prove to have value as an indicator of risk in the complex evaluation of glaucoma. For example, a person with IOP 20 mm Hg and CCT 510 µm (PCI 150.8) may be at a considerably higher risk of glaucoma than a person with IOP 26 mm Hg and CCT 600 µm (PCI 120.4), even though the CCT-corrected IOPs may be comparable. This may contribute to a better estimation of “treat-worthy” patients.²⁵ The PCI may also be useful in setting an IOP target range in the treatment of glaucoma. For example, since a PCI<100 was clearly the domain of normal controls, it may be speculated that a target IOP corresponding to a PCI value below 100 is appropriate. To reach such values in an eye with a CCT of 520 µm, an IOP of 14 mm Hg would be needed (PCI 99.6), while in an eye with CCT of 565 µm, an IOP of 18 mm Hg would be the minimum (PCI 99.8). Of course, the target range will also continue to depend primarily on the status of the optic nerve.

Further, longitudinal studies are needed to prove the prognostic value of PCI. Correlation of PCI with visual field or retinal nerve fibre layer damage may be intriguing.

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