European Journal of Ophthalmology / Vol. 15 no. 5, 2005 / pp. 550-555

Ocular hypertension and corneal thickness: A long-term prospective study. Results after two years

P. BRUSINI[1], C. TOSONI[1], L. PARISI[1], L. RIZZI[2]

[1]Department of Ophthalmology, S. Maria della Misericordia Hospital, Udine
[2]Department of Statistical Sciences, University of Udine, Udine - Italy

PURPOSE. To study the importance of the central corneal thickness (CCT) in patients with ocular hypertension in a 2-year follow-up.
METHODS. A total of 110 subjects with ocular hypertension (intraocular pressure [IOP] >21 mmHg and normal automated visual field test) were admitted to the study. All patients periodically underwent the following tests: 1) circadian IOP curve; 2) standard automated perimetry (SAP, Humphrey 30-2 SITA test); 3) short wavelength automated perimetry (SWAP); 4) frequency doubling technology perimetry (FDT, N-30 threshold test); 5) nerve fiber layer analysis with GDx; 6) ibopamine test; 7) ultrasonic pachymetry. Patients were divided into three groups, based on corneal thickness. The frequency of abnormal tests within these groups was evaluated with the Pearson's χ^2 test. Baseline IOP was corrected using the Doughty and Zaman formula. CCT was also considered as a continuous variable. A control group of 48 normal subjects was also considered.
RESULTS. The mean CCT was 562.8 µm ± 37.7. The difference with respect to normal subjects was statistically significant ($p<0.01$). Using the correction formula, 43 eyes (39.1%) had an IOP <21 mmHg. Abnormal test results were more frequently found with FDT. The percentage of abnormal results was found to be inversely proportional to CCT. The other tests gave inconsistent or conflicting results. Using the values of CCT as a continuous variable, no significant association was found with the GDx number and the visual field indices.
CONCLUSIONS. The results of our 2-year study confirm the importance of CCT measurement in the evaluation of the risk of developing glaucomatous damage. (Eur J Ophthalmol 2005; 15: 550-5)

KEY WORDS. Central corneal thickness, Frequency doubling technology, Non-conventional visual field examination, Ocular hypertension

Accepted: March 1, 2005

INTRODUCTION

Ocular hypertension is frequently observed in people over the age of 40. The management of patients with an intraocular pressure (IOP) greater than 21 mmHg but without any detectable damage is debatable, and there is no general consensus on medical treatment, if any. Many studies have demonstrated that IOP measurement may be significantly influenced by corneal thickness (1-7). According to some authors (4, 5, 8), 30% to 65% of patients with ocular hypertension actually only have a thick cornea, giving rise to an overestimation of the IOP values. Structural and functional damage should thus be minimally observed or absent in these patients having an overestimated IOP.

We began this long-term prospective study in the autumn of 2000, with the aim of evaluating the importance of corneal thickness when dealing with pa-

1120-6721/550-06$15.00/0

Presented at the 2nd meeting of the Italian-Greek Glaucoma Societies; March 19, 2003; Barcelona

tients with ocular hypertension and to establish the diagnostic tools most useful in detecting those subjects who were more prone to develop the disease. The results after 2 years of this ongoing study, which is planned to last more than 5 years, are presented in this article.

MATERIALS AND METHODS

A total of 110 subjects with ocular hypertension (IOP>21 mmHg on more than two occasions), normal optic disc at slit lamp biomicroscopic examination, and a normal standard automated visual field (Humphrey 30-2 threshold test) were admitted in the study (56 male and 54 female; mean age 64.4 years ± 13.2; range 29 to 86 years). Only the right eye was taken into consideration in the statistical analysis of the results.

At baseline, 75 patients (68.2%) were under medical treatment with either b-blockers or prostaglandins. Patients with any of the following listed conditions were excluded from this study: 1) other ocular disease apart from mild cataract, 2) best-corrected visual acuity lower than 8/10, 3) previous ocular surgery, 4) a serious systemic disease, 5) bad reliability, 6) a refractive defect higher than 4 diopters. Only reliable tests (fixation losses <20% and a false positive and negative rate <33%) were considered.

All patients periodically underwent the following tests:

1) A circadian IOP curve at the beginning of the study: four IOP measures were taken at 8, 12, 16, and 20 o'clock; the mean and the highest value were taken into account; patients with either an IOP mean value lower than 19 or a maximum IOP value lower than 22 were excluded from the study.
2) Standard automated perimetry (SAP) every 6 months. SAP testing was performed using the Humphrey Field Analyzer (HFA) II 745 (Carl Zeiss Meditec Inc., Dublin, CA) 30-2 test, with Swedish Interactive Threshold Algorithm (SITA) standard strategy.
3) Short wavelength automated perimetry (SWAP) every 12 months (HFA 24-2 threshold test). SWAP uses blue-on-yellow stimuli on a yellow background for specifically assessing S-cones and small bistratificate ganglion cells.
4) Frequency doubling technology perimetry (FDT) every 6 months. FDT perimetry was performed with the N-30 full-threshold test of the FDT Visual Field Instrument (Welch-Allyn, Skaneateles Falls, NY, and Zeiss-Humphrey System, Dublin, CA). FDT selectively analyzes the My ganglion cells, which have a very low redundancy. A pattern of sinusoid gratings with a low spatial frequency and a high temporal frequency counterphase flicker stimulus is displayed on a small CRT monitor. The threshold is considered as the amount of contrast needed to perceive the stimulus and is measured in 17 locations within the central 20 degrees plus two locations in the nasal area.
5) Nerve fiber layer analysis with GDx (Laser Diagnostic Technologies, Inc., San Diego, CA, software version 2.0.09) every 12 months. Scanning laser polarimetry (SLP) with GDx is a noninvasive, objective, and reproducible method, designed to evaluate the retinal nerve fiber layer (RNFL) thickness in vivo. The technique involves measuring the phase shift, otherwise known as retardation, of a polarized light passing though a birefringent medium, such as the RNFL. The retardation appears to be linearly correlated to the RNFL thickness.
6) Ibopamine test at the beginning of the study (IOP measurement before and 45' after instillation of a drop of ibopamine; the test was considered positive if the IOP increase was greater than 2 mmHg).
7) Central ultrasonic pachymetry (Altair pachymeter, Optikon 2000, Italy) taken at the beginning of the study: a mean of five measurements was taken into consideration.

The study abided by the principles of the Declaration of Helsinki, and informed consent was obtained for all the patients. As this research was an observational study, and no sensible data were used, approval from ethical committee was not required.

Abnormality criteria

SAP was classified as abnormal if at least one of the Hodapp et al criteria (9) was met: 1) a glaucoma hemifield test (GHT) outside normal limits; 2) a cluster of three or more points (not corresponding to the blind spot) worse than 5% probability level on the pattern deviation map with at least one of those points worse than 1% probability level; and 3) PSD with p<5%.

A SWAP test was defined as abnormal when one of the following was observed: 1) a GHT outside normal limits; 2) either a cluster of four or more points worse

than 5% probability level or a cluster of three or more points worse than 1% probability level (not corresponding to the blind spot and not located along the periphery) on the pattern deviation map; and 3) PSD with p<5%.

The Quigley criteria (10) were used to define an FDT test, in which a test was considered abnormal if at least two points on the total deviation map had a probability level of p<5%.

Using the GDx, a mean of three images per eye was taken for the analysis. Those images that were obtained during eye movement or were unfocused or poorly centered were excluded. As the old GDx model with a fixed correction of corneal birefringence was used in this study, a macular image was always taken in advance to calculate the residual anterior segment birefringence (ASB) magnitude and axis, following the method described by Zhou and Weinreb (11). An inadequate GDx ASB compensation is indicated by the presence of a "double hump-like" pattern in the macular scans (12). This pattern limits the use of GDx results for diagnostic purposes. Since the reproducibility of results has proven to be good (13, 14), these data can be used for follow-up purposes.

A GDx test was considered to be abnormal when one or more of the following conditions was met:

1) more than two GDx indices statistically abnormal (p<5%);
2) a significant loss in the deviation map (p<2%);
3) "the number" >35. Those tests having an inadequate ASB compensation were considered only for the assessment of modifications over time.

Functional tests resulting outside normal limits were repeated within a 2-week period, and results were considered as abnormal only when the defect was reproducible.

Baseline pretreatment IOP values (an average of three measurements) were corrected on the basis of the corneal thickness, using the Doughty and Zaman formula (a decrease of 0.46 mmHg for every 10 µm of corneal thickness over 545 µm and vice versa) (15). A control group of 48 normal subjects, ranging in age from 21 to 90 years (mean 61.2 ± 19.3), was also taken into consideration. Patients were arbitrarily divided into three groups, according to the corneal thickness: A) <541 µm; B) 541 to 590 µm; C) > 590 µm. The frequency of abnormal tests within these three groups was evaluated with the Pearson χ^2 test.

Corneal thickness was also considered as a continuous variable and its association with the GDx number and with both the MD and PSD, resulting from SAP, SWAP, and FDT, was evaluated with bivariate correlation coefficients.

RESULTS

The following test results were observed at baseline:

1) SAP, as previously stated, was normal in all eyes.
2) Corneal thickness: mean: 562.8 µm ± 37.7. A corneal thickness <541 µm (Group A) was found in 37 eyes (33.6%); from 541 to 590 µm (Group B) in 44 eyes (40%); and >590 µm (Group C) in 29 eyes (26.4%). Using the Doughty and Zaman correction formula, 43 eyes (39.1%) had an IOP <21 mmHg, while in 67 cases (60.9%) the IOP was ≥21 mmHg.
3) SWAP: abnormal in 15 eyes (13.6%), with the following distribution: Group A: 7 eyes (18.9%); Group B: 7 eyes (15.9%); Group C: 1 eye (3.5%) (differences not statistically significant).
4) FDT: abnormal in 30 eyes (27.3%); with the following distribution: Group A: 15 eyes (40.5%); Group B: 10 eyes (23.3%); Group C: 5 eyes (17.2%) (statistically significant difference between Groups A and B, p<0.05, χ^2 test).
5) GDx: abnormal in 35 eyes (31.8%), with the following distribution: Group A: 11 eyes (29.7%); Group B: 11 eyes (25%); Group C: 13 eyes (44.8%) (differences not statistically significant). An inadequate GDx ASB compensation was found in 13 eyes (37.1%).
6) Ibopamine test: the test was positive in 70 eyes (65.5 %), with the following distribution: Group A: 21 eyes (56.8%); Group B: 27 eyes (61.4%); Group C: 22 eyes (75.9%) (differences not statistically significant).

In the control group, the mean corneal thickness was 542.6µm±36.0 (difference statistically significant, p<0.01). SAP was normal in all but two cases, with a specificity of 95.8%. SWAP was normal in 47 cases (specificity of 97.9%), while with FDT, three false positive results were observed (specificity of 93.8%). GDx gave normal results in 39 cases (specificity of 81.3%). Ibopamine test was normal in all cases (100% specificity).

At the end of the 2-year period, 85 patients com-

pleted all of the tests. The total number of patients in each group was as follows: 33 eyes (38.8%) with a corneal thickness <541 µm (Group A); 29 eyes (34.1%) from 541 to 590 µm (Group B); and 23 eyes (27.1%) with a corneal thickness >590 µm (Group C).

The following test results were observed after 2 years:

1) SAP: abnormal in 6 eyes (7.1%), with the following distribution: Group A: 3 eyes (9.1%); Group B: 3 eyes (10.3%); Group C: 0 eyes (0%) (differences not statistically significant).
2) SWAP: abnormal in 8 eyes (9.4%), with the following distribution: Group A: 3 eyes (9.1%); Group B: 4 eyes (13.8%); Group C: 1 eye (4.3%) (differences not statistically significant). Of the total of 15 abnormals at baseline, the following was observed after 2 years: 4 dropped out; 7 remained abnormal; 4 (all from Group A) converted to normal. Of the total of 8 abnormals at 2 years: 1 eye was normal at baseline; 7 were already abnormal at baseline.
3) FDT: abnormal in 31 eyes (36.5%), with the following distribution: Group A: 14 eyes (42.4%); Group B: 11 eyes (37.9%); Group C: 6 eyes (26.1%) (differences not statistically significant). Of the total of 30 abnormals at baseline, the following was observed after 2 years: 7 dropped out; 22 remained abnormal; 1 converted to normal. Of the total of 31 abnormals at 2 years: 9 eyes were normal at baseline; 22 were already abnormal at baseline.
4) GDx: abnormal in 26 eyes (29.4%), with the following distribution: Group A: 10 eyes (30.3%); Group B: 7 eyes (24.1%); Group C: 9 eyes (39.1%) (differences not statistically significant). Of the total of 35 abnormals at baseline, the following was observed after 2 years: 7 dropped out; 21 remained abnormal; 7 converted to normal. Of the total of 26 abnormals at 2 years: 5 eyes were normal at baseline; 21 were already abnormal at baseline.

Using the values of corneal thickness as a continuous variable, no significant association was found when evaluating bivariate correlation coefficients with both the GDx number and the visual field indices of SAP, FDT, and SWAP.

DISCUSSION

It has been established that corneal thickness plays an important role when dealing with patients with ocular hypertension. When different correction factors are taken into consideration, a significant percentage of eyes with ocular hypertension have, in essence, only a thick cornea and an IOP that is statistically normal (pseudo-hypertension). The use of a reliable correction factor based on the central corneal thickness is, however, difficult due to several problems (such as the nonlinear relationship between these two parameters, the influence of scleral rigidity). In our sample, in applying a correction factor that was of the medium range, a significant percentage of eyes with ocular hypertension (39.1%) actually only had a thick cornea and a statistically normal IOP, after correction. In this study, patients with either a thin or normal corneal thickness gave rise to a greater percentage of abnormal tests with non-conventional visual field testing after 2 years, especially with FDT, even if the differences were not statistically significant. These patients had an IOP that was either truly elevated, or at times, underestimated.

Functional defects, on the other hand, were less frequent in eyes with a corneal thickness greater than 590 µm. The results of our study are in accordance with other recent reports (16, 17) and further support the hypothesis that a thin cornea with an underestimated IOP is an important risk factor in the genesis of glaucomatous damage.

The possibility of false positive results must of course be taken into consideration and only reproducible defects should be accepted (18). Short wavelength automated perimetry, differently from other studies (19, 20), did not provide any useful information.

This may in part be due to the high interindividual variability of this technique, which can contaminate the results, thus lowering its sensitivity. Moreover, a consistent learning effect was observed during the study, even if all patients had previous experience in visual field examination. This learning effect can explain the lower percentage of abnormal SWAP results after 2 years in comparison with the baseline.

SWAP showed a large variability over time. An abnormal result could be confirmed at the end of the follow-up only in 64% of cases. These results suggest prudence before defining a patient as having glaucoma-related functional damage on the basis of only one test. Patients with an abnormal baseline SWAP who became normal after 2 years could be explained by the learning effect and long-term fluctuation.

The analysis of the nerve fiber layer with GDx gave conflicting results. This is probably due to the corneal birefringence, which at times is not adequately corrected by the integrated compensation system (37% of cases in our sample).

The fact that 25% of abnormal GDx results at baseline were not confirmed after 2 years can be explained by occasional erroneous corneal compensation, which can occur in the former GDx FCC. The new GDx VVC, which is able to individually compensate the corneal birefringence, however, seems to be able to prevent these drawbacks and have an improved diagnostic ability.

The ibopamine provocative test aims at evaluating the trabecular meshwork functionality by means of causing an increase in aqueous humor production (21). The test can reveal early alterations in the outflow system, even if the IOP is still in the normal ranges, due to autoregulation mechanisms, as can be seen in patients' relatives with chronic glaucoma. In these cases, the increase of aqueous production produces a clear IOP increase.

This test has proven to be highly sensitive and specific and thus allows glaucoma subjects to be differentiated from normal controls (22). In the present study, however, it did not show any statistical correlation with other tests. Its predictive value is to be further assessed at the end of the follow-up period.

Upon full completion of this study at the end of the 5-year period, further useful information pertaining to the management of patients with ocular hypertension can be obtained, which can thus provide valuable information and aid in the therapeutic approach to these patients.

CONCLUSIONS

This is an observational ongoing study, and thus its power is due to increase in time owing to the additional data provided by the ongoing follow-ups. The 2-year results confirm what was found in the Ocular Hypertension Treatment Study and in other studies (6, 23, 24) in that a reduced corneal thickness, which gives rise to an underestimated IOP, is an important risk factor in the genesis of functional glaucomatous damage. The FDT seems to be a useful technique in detecting an early functional loss. Of course, data from any psychophysical test must be considered with caution, owing to the subjectivity of these methods, physiologic fluctuation, artifacts, and false positive results. At times, a test defined as abnormal at the baseline was observed to be normal by the end of the follow-up. This can make it difficult to assess the results of the study. The specificity of functional tests shown in our control sample, however, was good, as a low rate of false positive results was observed. New diagnostic devices, such as the GDx VCC, HRT 2, and RTA, could help in detecting the structural loss in the early phases of the disease; however, further studies are needed to establish their predictive value and clinical usefulness in patients with ocular hypertension.

No author has any commercial or proprietary interest in any product or company cited in the article.

Reprint requests to:
Paolo Brusini, MD
Department of Ophthalmology
Santa Maria della Misericordia Hospital
33100 Udine, Italy
brusini@libero.it

REFERENCES

1. Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. Acta Ophthalmol 1975; 53: 34-43.
2. Wolfs RCW, Klaver CCW, Vingerling JR, Grobbees DE, Hofman A, de Jong PT. Distribution of central corneal thickness and its association with intraocular pressure: The Rotterdam Study. Am J Ophthalmol 1997; 123: 767-72.
3. Herndon LW, Choudhri SA, Cox T, Damij KF, Shields MB, Allingham RR. Central corneal thickness in normal, glaucomatous, and ocular hypertensive eyes. Arch Ophthalmol 1997; 115: 1137-41.
4. Bron AM, Creuzot-Garcher C, Goudeau-Boutillon S, d'Athis P. Falsely elevated intraocular pressure due to increased central corneal thickness. Graefes Arch Clin Exp Ophthalmol 1999; 3: 220-4.
5. Brusini P, Miani F, Tosoni C. Corneal thickness in glaucoma: an important parameter? Acta Ophthalmol Scand 2000; 78 (Suppl): S41-2.
6. Brandt JD, Beiser JA, Kass MA, Gordon MA. Corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology 2001; 108: 1779-88.
7. Damji KF, Muni RH, Munger RM. Influence of corneal

variables on accuracy of intraocular pressure measurement. J Glaucoma 2003; 12: 69-80.
8. Copt R-P, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma. Arch Ophthalmol 1999; 117: 14-6.
9. Hodapp E, Parrish II RK, Anderson DR. Clinical Decisions in Glaucoma. St. Louis: Mosby, 1993; 46-7.
10. Quigley HA. Identification of glaucomatous visual field abnormality with the screening protocol of frequency-doubling perimetry. Am J Ophthalmol 1998; 125: 819-29.
11. Zhou Q, Weinreb RN. Individualized compensation of anterior segment birefringence during scanning laser polarimetry. Invest Ophthalmol Vis Sci 2002; 43: 2221-8.
12. Garway-Heath DF, Greaney MJ, Caprioli J. Correction for the erroneous compensation of anterior segment birefringence with the scanning laser polarimeter for glaucoma diagnosis. Invest Ophthalmol Vis Sci 2002; 43: 1465-74.
13. Zangwill L, Berry CA, Garden VS, Weinreb RN. Reproducibility of retardation measurements with the nerve fiber analyzer II. J Glaucoma 1997; 6: 384-9.
14. Waldock A, Potts MJ, Sparrow JM, Karwatowski SS. Clinical evaluation of scanning laser polarimetry: I. Intraoperator reproducibility and design of a blood vessel removal algorithm. Br J Ophthalmol 1998; 82: 252-9.
15. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol 2000; 44: 367-408.
16. Medeiros FA, Sample PA, Weinreb RN. Corneal thickness measurements and visual function abnormalities in ocular hypertensive patients. Am J Ophthalmol 2003; 136: 805-13.
17. Medeiros FA, Sample PA, Weinreb RN. Corneal thickness measurements and frequency doubling technology perimetry abnormalities in ocular hypertensive eyes. Ophthalmology 2003; 110: 1902-7.
18. Keltner JL, Johnson CA, Quigg JM, Cello KE, Kass MA, Gordon MO. Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study. Arch Ophthalmol 2000; 118: 1187-94.
19. Demirel S, Johnson CA. Incidence and prevalence of short wavelength automated perimetry deficits in ocular hypertensive patients. Am J Ophthalmol 2001; 131: 709-15.
20. Polo V, Larrosa JM, Pinilla I, Perez S, Gonzalvo F, Honrubia FM. Predictive value of short wavelength automated perimetry. A 3-year follow-up study. Ophthalmology 2002; 109: 761-5.
21. Virno M, Pecori Giraldi J, Taverniti L, Taloni M, Pannarale L. Intraocular hypertensive effects of topically administered ibopamine in eyes with hydrodynamic disorders: a new provocative test for glaucoma. Glaucoma 1990; 12: 88-92.
22. Virno M, Pecori-Girardi, Taverniti L, De Gregorio F, Sedran L. Ibopamine. D-1 Dopaminergic Agonist in the Physiopathology of Intraocular Pressure. Rome: I.N.C. Innovation-New-Communications Publ; 2003.
23. Gordon MO, Beiser JA, Brandt JD, et al, for the Ocular Hypertension Study Group. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open angle glaucoma. Arch Ophthalmol 2002; 120: 714-20.
24. Medeiros FA, Sample PA, Zangwill LM, Bowd C, Aihara M, Weinreb RN. Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. Am J Ophthalmol 2003; 135: 131-7.