European Journal of Ophthalmology / Vol. 15 no. 2, 2005 / pp. 196-201

Corneal thickness and functional damage in patients with ocular hypertension

M. ZEPPIERI[1,3], P. BRUSINI[1,], S. MIGLIOR[2]

[1]Department of Ophthalmology, S. Maria della Misericordia Hospital, Udine
[2]Department of Ophthalmology, University of Milano-Bicocca, Milano
[3]Department of Ophthalmology, University of Udine, Udine - Italy

PURPOSE. *To correlate functional damage over time detected by standard automated perimetry (SAP) and frequency doubling technology (FDT) with central corneal thickness (CCT) in patients with ocular hypertension (OHT).*
METHODS. *Seventy-eight OHT patients underwent CCT measurements, SAP, and FDT (the latter two also after 12 and 18 months). Patients were divided into three equally sized groups of 26 patients each: thin (< 540 µm), normal (540-580 µm), and thick cornea (> 580 µm). The frequency of abnormal FDT and SAP results was analyzed over time (Pearson χ^2 test).*
RESULTS. *Six of 26 patients with thin corneas (23.1%) presented an abnormal FDT test at baseline, compared to 1 of 26 (3.8%) in the normal thickness cornea group and 1 of 26 (3.8%) in the thick cornea group. After 12 months, the abnormal FDT tests were as follows, respectively: 9 of 26 (34.6%), 2 of 26 (7.7%), and 2 of 26 (7.7%). For SAP the abnormal results were as follows, respectively: 8 (30.1%), 5 (19.2%), and 2 (7.7%). After 18 months, the abnormal FDT tests were as follows, respectively: 16 (61.5%), 5 (19.2%), and 5 (19.2%). For SAP, the abnormal results were as follows, respectively: 10 (38.5%), 5 (19.2%), and 2 (7.7%).*
CONCLUSIONS. *OHT patients with thinner corneas have a greater risk of developing functional damage over time. (Eur J Ophthalmol 2005; 15: 196-201)*

KEY WORDS. *Central corneal thickness, Frequency doubling perimetry, Ocular hypertension, Primary open angle glaucoma, Visual field testing*

Accepted: November 4, 2004

INTRODUCTION

Primary open-angle glaucoma (POAG) is one of the most frequent causes of irreversible blindness. The World Health Organization attributes approximately 13.5% of cases of blindness in the world to this disease (1). The diagnosis of the disease is classically based on the presence of 1) progressive cupping of the optic nerve head due to a loss of nerve fibers, 2) typical visual field defects, and/or 3) elevated intraocular pressure (IOP), which is not always present.

The results of two recently published clinical trials (2, 3) indicate that the risk of developing POAG in patients with ocular hypertension (OHT) and that of developing progressive glaucoma changes in POAG patients is higher in patients with greater functional loss at baseline. Considering that a high IOP alone is not sufficient in discriminating between those patients who will actually develop POAG and those who will not (the vast majority), other parameters should thus be considered in the evaluation of OHT patients.

It has been clearly shown that corneal thickness may affect IOP measurements (4): a thicker cornea gives an overestimated IOP taken with Goldmann tonometry, whereas a thinner cornea has the opposite effect (5, 6). Moreover, numerous articles have shown that patients

1120-6721/196-06$15.00/0

with normal tension glaucoma have a lower mean corneal thickness (7, 8), and that OHT patients tend to have a higher mean corneal thickness (9, 10), as compared to glaucoma patients and normal controls. The OHT study has shown that a thin cornea represents a clinically relevant predictive factor for the development of POAG (11).

Although standard automated perimetry (SAP) is considered as the standard technique for measuring visual field loss in glaucoma (12), it has been shown that it is not able to detect early functional damage, due to the redundancy of the retinal ganglion cells (13, 14). Frequency doubling technology (FDT) selectively stimulates a subgroup of retinal ganglion cells which could selectively be damaged in early glaucoma and which are not functionally redundant, hence giving the possibility to identify early visual field loss (15-20).

The aim of this study was to evaluate the progression of functional damage detected by SAP and FDT in OHT patients, and to correlate the frequency of abnormal perimetric tests over time with corneal thickness.

METHODS

Seventy-eight consecutive patients with OHT were enrolled in this study (Tab. I). The specific inclusion criteria included an IOP > 21 mmHg on at least two occasions; no history of ocular diseases (besides having an initial cataract), past ocular surgeries, or laser treatments; best-corrected visual acuity of 7/10 or better; normal SAP (HFA 30-2 SITA standard test); normal ocular fundus; and informed consent to participate in the study. The following exclusion criteria were used: POAG in at least one eye; the use of more than two drugs to lower the ocular pressure; abnormal optic nerve head (cup/disc ratio > 0.6, any notching of neural rim area, disc hemorrhage, cup/disc asymmetry between both eyes > 0.2); non reliable visual field test (> 33% of false-positive and false-negative responses and/or > 20% of fixation losses); any other ocular pathologies that could explain the OHT (trauma, exfoliation).

The study abided by the principles of the Declaration of Helsinki, and informed consent was obtained from all the patients. Sixty-five of the 78 patients (83.3%) at baseline used either a beta-blocker or a prostanoid to lower the IOP. Many of them had some risk factors of developing glaucoma (IOP > 25 mmHg, positive history for glaucoma). One eye of each patient was randomly selected for study purposes. Each subject initially underwent a comprehensive ophthalmic examination, including best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination using a 78-diopter lens, central ultrasonic pachymetry (Altair pachymeter, Optikon 2000) in which a mean of five measurements was used, SAP (30-2 SITA standard test Humphrey Field Analyzer model 745, Humphrey Systems, Dublin, CA), and FDT (N-30 threshold test, FDT Visual Field Instrument, Welch Allyn-Zeiss-Humphrey Systems, Dublin, CA). All patients had previous experience of automated visual field testing. SAP was classified as abnormal if at least one of the Hodapp et al criteria (21) was met: 1) a glaucoma hemifield test (GHT) outside normal limits; 2) a cluster of three points (not corresponding to the blind spot) with a probability level (p) < 5 % on the pattern deviation map, with at least one of these having a p < 1%; or 3) PSD with a p < 5%. An FDT test was considered to be abnormal if at least two areas in the total deviation map had a probability level of p < 5% (22).

Each patient was re-evaluated after 12 and 18 months from the beginning of the study with both SAP and FDT. If an FDT test appeared to be abnormal for the first time or significantly worse than a previous test, the abnormality had to be confirmed by a second test. We considered as significantly worsened those FDT tests that showed a lowering in the p level at any location in the pattern deviation map in at least two previously abnormal points, or the presence of at least two new abnormal points. A SAP abnormality had to be confirmed by a second test.

The patients were divided in three groups of equal size (26 patients in each) based on their central corneal thickness: 1) thin cornea group (corneal thickness < 540 µm), 2) normal cornea group (corneal thickness ranging from 540 to 580 µm), and 3) thick cornea group (> 580 µm). The percent of abnormal SAP and FDT tests at each time period was calculated for each group and statistically evaluated with Pearson's χ^2 test. A p value of less than 0.05 was considered statistically significant.

RESULTS

The mean central corneal thickness in the studied population was 559.5 ± 38.4 µm, ranging from 478 to 638 µm. The demographic and ocular data at baseline of the patients, divided in the three separate groups based on central corneal thickness, are listed in Table I.

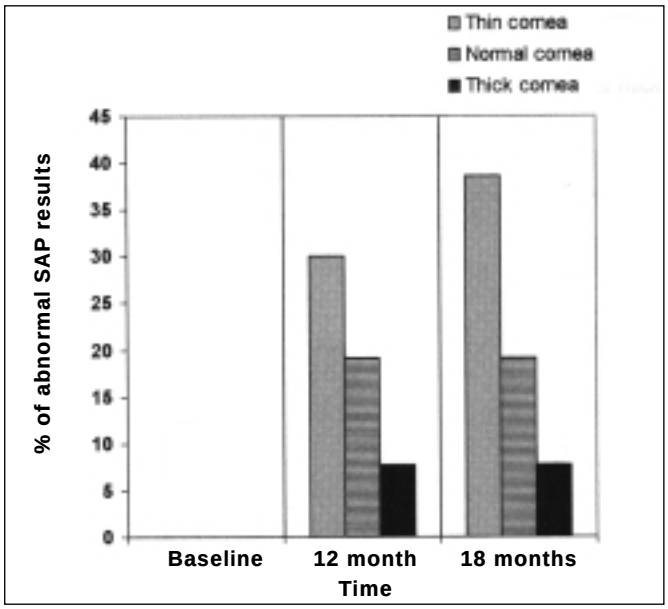

Fig. 1 - *The percentage of abnormal standard automated perimetry (SAP) results is shown for each corneal thickness group at baseline, where SAP was normal by definition, the first follow-up (12 months), and the second follow-up (18 months).*

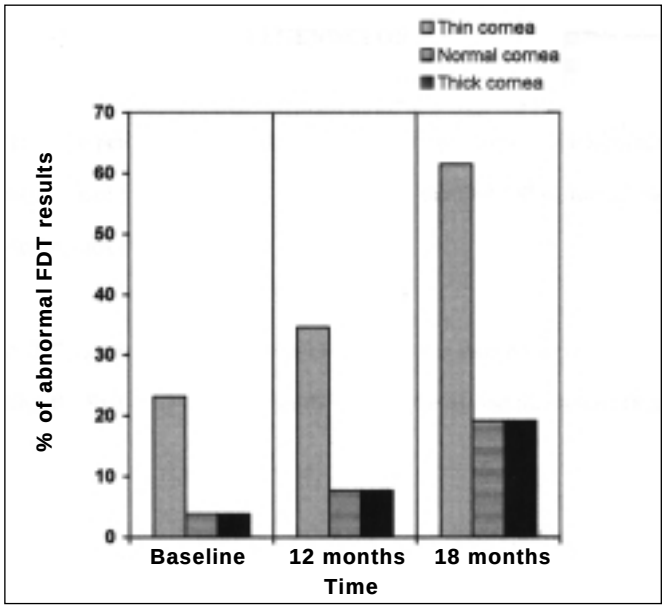

Fig. 2 - *The percentage of abnormal frequency doubling technology (FDT) results is shown for each corneal thickness group at baseline, the first follow-up (12 months), and the second follow-up (18 months).*

The proportion of subjects who developed either an abnormal SAP or FDT test at each time period for each corneal thickness group is shown in Figures 1 and 2, respectively.

Six of the 26 patients with thin corneas (23.1%) presented an abnormal FDT test at baseline, compared to 1 case of 26 in the normal thickness cornea group (3.8%) and 1 of 26 (3.8%) in the thick cornea group (statistically significant differences, p = 0.031). At the first follow-up (12 months), the frequency of abnormal SAP tests was 8 of 26 (30.1%) in the thin cornea group, 5 of 26 (19.2%) for the normal cornea group, and 2 of 26 (7.7%) in the thick cornea group (p = 0.108). The frequency of abnormal FDT results at the first follow-up was 9 of 26 (34.6%) for the thin cornea group, 2 of 26 (7.7%) for the normal group, and 2 of 26 (7.7%) in the thick cornea group (p = 0.006). At the second follow-up (18 months), the frequency of abnormal SAP tests was 10 of 26 (38.5%) for the thin corneal group, whereas no changes were observed in the other two groups (p = 0.025). The frequency of abnormal FDT tests was 16 of 26 (61.5%) for the thin cornea group, 5 of 26 (19.2%) for the normal cornea group, and 5 of 26 (19.2%) for the thick cornea group (p = 0.0001).

In analyzing the single groups, the only statistically significant difference that could be found in SAP was between the thin cornea group and the thick one after 18

TABLE I - DEMOGRAPHIC AND OCULAR DATA OF THE 79 PATIENTS AT BASELINE

Variable	Thin cornea (< 540 mm)	Normal cornea (540-580 µm)	Thick cornea (> 580 µm)	Total
No. of subjects	26	26	26	78
No. of females/males	16/10	11/15	13/13	40/38
Age range, yr	36-78	46-78	46-75	36-78
Mean age ± SD, yr	63.3±9.5	62.1±8.3	61.9±7.8	62.5±8.5
No. of patients in therapy (%)	22 (84.6)	22 (84.6)	21 (80.8)	65 (83.3)
Central corneal thickness range, µm	478-539	541-580	581-638	478-638
Corneal thickness mean ± SD, µm	516.7±18.2	559.6±13.1	602.3±15.0	559.5±38.4

months (p = 0.021). With regards to FDT, there was a statistically significant difference (p = 0.001) only between the thin and normal cornea groups and between the thin and thick cornea groups both after 12 months and after 18 months.

When analyzing the differences between SAP and FDT in identifying a functional loss, apart from at baseline in which SAP was normal by definition, the percentage of abnormals identified was either very similar (15 with SAP vs 13 with FDT after 12 months) or more frequent for FDT (17 with SAP vs 26 with FDT after 18 months). At baseline, 8 patients (10.3%) had an abnormal FDT, one of which became normal at the second follow-up. All but one of these patients gave an abnormal SAP by the end of the second follow-up. Five of the 17 patients (29.4%) with an abnormal SAP at the first and/or second follow-up had a normal FDT by the end of the study. Four patients with an abnormal SAP test at the first follow-up had a normal test by the end of the study. After 18 months, 26 patients (33.3%) developed glaucomatous damage according to FDT, vs 17 (21.8%) according to SAP.

DISCUSSION

In a clinical setting, the identification of predictive factors of POAG is clinically relevant in order to decide whether to treat or simply observe the OHT patients, especially considering that most of them have no evidence of structural or functional damage, which usually never develops in time. The results of this study confirm the clinical importance of central corneal thickness as a predictive factor to identify which patients are more likely to develop a field loss. Several studies have shown that, in general, the mean CCT tends to be higher in patients with OHT, when compared to both normal subjects and those with POAG (9, 11, 23, 24).

Doughty and Zaman (10) confirmed this observation in a meta-analysis of 600 articles in a 31-year time span, which showed that the average corneal thickness in normal patients was 534 µm, whereas OHT patients had a mean CCT of 563 µm and the normal tension glaucoma group had a mean of 505 µm. Considering the effect that corneal thickness has on the IOP measurements, numerous correction factors have been proposed (25-27), ranging from 0.19 to 0.7 mmHg for each 10 µm difference in CCT compared to the mean values. According to some authors (28-30), 30% to 65% of patients with OHT actually only have a thick cornea, giving rise to an overestimation of the IOP values. OHT patients could thus be composed of two groups: the “true” OHT subjects that have a normal or thin corneal thickness in which tonometric readings are accurate or underestimated, and “pseudo” OHT subjects having a thick cornea which gives an overestimated IOP reading. True OHT subjects in essence are those individuals that give rise to a corrected IOP of at least 21 mmHg or more. Pseudo OHT subjects, on the other hand, have IOP < 21 mmHg when the CCT correction is considered. The true OHT patients should thus be more at risk of developing an early POAG, showing more frequent functional and structural deficits, when compared to the pseudo OHT subjects.

In our study, except for the 12-month follow-up in the normal cornea thickness group, FDT identified more abnormal cases than SAP at any time. Moreover, FDT identified 8 of 78 OHT patients (10.3%) as abnormal at baseline (in which 6 had a thin cornea, 1 normal, and 1 thick cornea). The total number of abnormal FDT results showed an increase over time, which was statistically significant. These results are in agreement with other studies that show that FDT is similar to if not better than SAP in identifying early glaucomatous damage (12, 17-21, 31-34). This can be explained by the fact that, differently from SAP, FDT assesses a subgroup of neurons classified as My cells, which are scarcely redundant and may be selectively damaged in early subclinical phases of POAG (16, 20, 35). Various authors have reported that FDT has a sensitivity that ranges from 91% to 100% in identifying abnormal visual fields and a specificity of 90% to 95% (19-21). Many studies have shown that FDT has a good sensitivity in OHT patients (17, 19, 32, 36), in which it is difficult to distinguish the normal subjects from those with an initial damage. FDT seems to offer visual field testing that is rapid, simple to use, efficient, sensitive, not influenced by refractive errors or myosis, portable, and economic.

In agreement with other studies (37, 38), our study showed that OHT patients with thinner corneas presented more abnormal visual field results with both SAP and FDT, which became more evident with FDT over time. FDT always showed more functional damage than SAP, with exception to the normal corneal group at the first follow-up (5 of 26 abnormal SAP vs 2 of 26 abnormal FDT). Furthermore, only one of the eight patients with an abnormal FDT at baseline did not develop an abnormal SAP by the end of the study.

Inconsistencies in the SAP and FDT testing were found in a few cases. Some patients who originally had an abnormal FDT or SAP gave rise to a normal test by the end of the study. This may be due in part to physiologic fluctuation or to a persisting learning effect.

In the present study, a quite high percentage of OHT patients developed a functional damage over time: one third according to FDT testing, and approximately one fifth according to SAP by the end of the 18-month period. These numbers are higher than those reported in OHTS (2). This can partly reflect the fact that some of our patients may have had pre-perimetric glaucomatous defects that were not detected at the beginning of the study, thus being erroneously classified at baseline as OHT patients without any functional damage. It may be also explained by the more specific assessment of visual field change of the OHTS that was based on the agreement of three consecutive visual field tests. Keltner et al (39) reported that 85.9% of new visual field defects revert to normal on a subsequent test and that as many as half revert to normal on the third test. The fact that two consecutive visual field tests were used in our study as opposed to three in the confirmation of abnormality or progression can explain this discrepancy and may also partly explain the cases of confirmed abnormalities at the 12-month time point that reverted to normal at the 18-month follow-up.

In conclusion, a thin central cornea is an important predictive factor that should be considered in patients with OHT. From a theoretical point of view, it is not possible to exclude that a thin cornea can be associated with a thin sclera, with a congenital weakness of the collagen, which can lead to a progressive damage of optic nerve fibers due to shrinkage of the lamina cribrosa holes. Corneal thickness measurements, along with FDT, should be considered when dealing with patients with OHT. These two tests, taken together with other clinical information concerning round the clock IOP fluctuations, tests that analyze anatomic damage of the optic nerve head and/or nerve fiber layer, and other non-conventional visual field tests, all offer the ophthalmologist a clearer clinical picture of each patient, which is imperative in deciding the correct therapeutic approach.

ACKNOWLEDGEMENTS

The authors thank Lucia Parisi for help with collection of the patient data and Dr. Maria Letizia Salvetat for assistance in statistical analysis of the data.

Reprint requests to:
Paolo Brusini, MD
S.O.C di Oculistica
Azienda Ospedaliera S. Maria della Misericordia
P.le S. Maria della Misericordia 15
33100 Udine, Italy
brusini@libero.it

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