ABSTRACT

Scope: to evaluate the association between corneal pachymetry and visual field progression in patients with primary open-angle glaucoma (POAG).

Basic procedures: retrospective, comparative case series. The Glaucoma Staging System (GSS) and pachymetric data from the right eyes of 168 patients with POAG and medically controlled intraocular pressure (IOP < 20 mmHg) were retrospectively analyzed. Exclusion criteria were laser or surgical ocular treatments and a follow-up period inferior to 4 years. Central corneal thickness (CCT) was determined by ultrasound pachymetry. The patients were split in two groups (group 1 < 540 micron; group 2 > or =540 micron). For each eye the stage of defect at baseline and at final follow-up were assessed using GSS. Statistical test of $\chi^2$ was used to analyze data.

Results: 89 females (52.3%) and 79 males (47.7%) were included in our study. The mean age was 58.8 ± 8.7 years (range 42-79). Considering the total number of patients, mean follow-up period was 4.6± 0.5 years. Mean CCT was 526.7± 10.4 microns in group 1 (84 patients) and 576.2 ± 32.7 microns in group 2 (84 patients).
In group 1 baseline glaucoma stage was the following: 66 patients (78.5%) at GSS 1 and 18 patients (21.5%) at GSS 2. In group 2, 70 patients (83.3%) were at GSS 1 and 14 patients (16.7%) at GSS 2. There was no significant difference for initial glaucoma stage between the two groups (p=0.3). At the final follow-up 39 patients (46.4%) of group 1 were stable while GSS worsened in 45 patients (53.6%); in group 2 GSS had no progression in 64 patients (76.1%), while it progressed in 20 patients (23.9%). There was a statistically significant difference for final GSS stage which was worse in group 1 than in group 2 (p<0.001).

Considering all eyes, at the final follow-up, 103 patients (61.3%) had stable GSS parameters, 65 patients (38.7%) progressed. Among these 65 patients, 45 cases (69.2%) belonged to group 1 and only 20 (30.8%) to group 2. Eyes with a final GSS3 were 7/84 (8.4%) in group 1 and 5/84 (6.1%) in group 2 (p=0.6).

Conclusions: in our study CCT did not significantly correlate with glaucomatous damage at presentation. In medically controlled primary open-angle glaucoma, visual field progression evaluated with GSS was significantly associated with thinner CCT. In more advanced glaucoma stages CCT might not play a role.

INTRODUCTION
Central corneal thickness (CCT) assessment is important in glaucoma management for several reasons. CCT is a proven strong risk factor for conversion from ocular hypertension (OHT) to primary open-angle glaucoma (POAG)\(^1\). CCT can have a significant effect on intraocular pressure (IOP) measured with Goldmann’s applanation tonometry\(^2,3,4\), and
is also useful to define glaucoma therapy. Many studies have reported that progression of the visual field in patients with POAG was significantly associated with a thinner CCT\textsuperscript{5,6,7,8}. Standard automated perimetry (SAP) is still the accepted technique to quantify glaucoma-related damage. The Glaucoma Staging System (GSS) was introduced in 1996 to provide standardised classification of perimeter results. It is based on two main global perimeter indices (Mean Deviation [MD] and Corrected Pattern Standard Deviation [CPSD], or Corrected Loss Variance [CLV]) that are placed in a Cartesian graph with intervals decreasing from left to right and from top to bottom\textsuperscript{9} (Fig. 1). The scope of our study was to assess the association between corneal pachymetry and visual field progression in patients with pharmacologically compensated POAG.

METHOD
Clinical records of patients reporting to our clinic in the period 2008-2010 were subjected to retrospective analysis. 168 patients met the inclusion criteria of POAG with target IOP <20

misurazione della pressione intraoculare (IOP) ottenuta mediante tonometria ad applanazione di Goldmann\textsuperscript{2,3,4}, ed è anche utile per stabilire la terapia del glaucoma. In molti studi la progressione del campo visivo in pazienti con POAG era significativamente associata con una CCT più sottile\textsuperscript{5,6,7,8}. La perimetria standard automatizzata (SAP) è ancora la tecnica accettata per quantificare il danno glaucomatoso. Nel 1996, il Glaucoma Staging System (GSS) è stato introdotto con l’intento di fornire una classificazione standardizzata dei risultati perimetrici. Si basa su due principali indici perimetrici globali (Deviazione media [MD] e Deviazione Standard Pattern Corretta [CPSD], o Perdita di Varianza Corretta [CLV]), disposti su di un grafico cartesiano, in cui gli intervalli diminuiscono andando da sinistra a destra e dall’alto verso il basso\textsuperscript{9}. (Fig. 1) Lo scopo del nostro studio è stato quello di valutare l’associazione tra pachimetria corneale e progressione del campo visivo nei pazienti con POAG in compenso farmacologico.

METODOLOGIA
Le cartelle cliniche dei pazienti affetti al nostro ambulatorio tra il 2008 e il 2010 sono state analizzate retrospettivamente.
168 patients met the inclusion criteria: POAG with IOP target <20 mmHg obtained pharmacologically, 4 to 5-year follow-up and negative history of past ocular surgical or parasurgical treatments. Glaucoma Staging System (GSS) data and CCT values were only recorded for the right eye of each patient. In fact, for pathological conditions, whose onset is equally probable in both eyes, analyses based on the selection of only one eye or on randomised selection are statistically equivalent. CCT was measured with ultrasound pachymetry. Patients were divided into 2 groups with 84 eyes with pachymetry <540 micron (group 1) and 84 eyes with pachymetry >0 = 540 micron (Group 2). GSS stage at baseline and at the final follow-up visit was assessed for every eye. Differences in GSS stage at the first and at the final visit were assessed using the Chi square test ($\chi^2$). Statistical significance was set at $p < 0.05$.

RESULTS

Epidemiological data is illustrated in Table 1. The study enrolled 89 females (52.3%) and 79 males with mean age 58.8 ± 8.7 years (range 42-79). Considering the total number of patients, the mean follow-up period was 4.6 ± 0.5 years. The mean CCT was 526.7 ± 10.4 micron for group 1 (84 patients) and 576.2 ± 32.7 micron for group 2 (84 patients). In group 1, glaucoma staging recorded 66 patients (78.5%) at GSS 1 and 18 patients (21.5%) at GSS 2. In group 2, 70 patients (83.3%) were at GSS 1 and 14 patients (16.7%) at GSS 2. There was no statistical significance in the difference in glaucoma staging at baseline between the two groups ($p = 0.3$). The results are schematically presented in Table 1. At the final follow-up visit, 39 patients (46.4%) in group 1 were stable, whereas the GSS stage
had worsened in 45 patients (53.6%); in group 2, the GSS stage presented no progression in 64 patients (76.1%), whereas it had progressed in 20 patients (23.9%). The final follow-up visit found a statistically significant difference in GSS stage progression between group 1 and group 2 (p <0.001). Considering all the eyes, at the final follow-up visit, 103 patients (61.3%) had stable GSS parameters, and 65 patients (38.7%) presented a worsened GSS stage. Of these 65 patients, 45 cases (69.2%) belonged to group 1 and only 20 (30.8%) to group 2. Eyes with final GSS3 were 7/84 (8.4%) in group 1 and 5/84 (6.1%) in group 2 (p=0.6) (Fig. 2).

**DISCUSSION**

CCT is widely accepted as a key parameter for the assessment of patients with POAG. Many authors have described the correlation between CCT and glaucoma-related

schematicamente nella tabella 1: al follow-up finale 39 pazienti (46.4%) del gruppo 1 erano rimasti stabili, mentre lo stadio GSS era peggiorato in 45 pazienti (53.6%); nel gruppo 2 lo stadio GSS non aveva evidenziato progressione in 64 pazienti (76.1%), mentre era progredito in 20 pazienti (23.9%). Al follow-up finale c'era una differenza statisticamente significativa per la progressione dello stadio GSS tra il gruppo 1 e gruppo 2 (p <0.001). Considerando tutti gli occhi, al follow-up finale, 103 pazienti (61,3%) avevano parametri GSS stazionari, 65 pazienti (38,7%) mostravano un peggioramento della stadiazione GSS. Tra questi 65 pazienti, 45 casi (69,2%) appartenevano al gruppo 1 e solo 20 (30,8%) al gruppo 2. Gli occhi con un GSS 3 finale erano 7/84 (8,4%) nel gruppo 1 e 5/84 (6,1%) nel gruppo 2 (p=0.6) (Fig. 2).

**DISCUSSIONE**

La CCT è universalmente accettata come un parametro importante per la valutazione
damage or progression both in POAG and in ocular hypertension. The major part of the studies measured CCT with ultrasound pachymetry, as in our case. Mean IOP is the only currently consolidated modifiable risk factor for the progression of glaucoma-related damage, and multiple randomised clinical trials have provided evidence that the reduction in intraocular pressure slows down visual field deterioration in glaucoma patients. In the Early Manifest Glaucoma Trial, which analysed the effect of immediately reducing IOP on the progression of open-angle glaucoma, progression velocity in treated patients was 45%. Our progression rate was 38.7%, though we considered a smaller patient population. All patients in our study had pharmacologically controlled IOP for the entire follow-up period; hence, the probability of visual field progression was independent from this factor. Several randomised multicentre clinical trials have identified IOP-independent risk factors for glaucoma progression. They include elderly age, high cup-disc ratio, peripapillary atrophy of the beta zone, low corneal hysteresis, and pseudoxefoliation syndrome. A thin central cornea is a risk factor for conversion to glaucoma.

Fig. 2
Comparison of patients assessed by GSS stage at time 0 and after 4 years, differentiated by CCT.

Confronto tra pazienti valutati secondo lo stadio GSS al tempo 0 e dopo 4 anni, differenziati secondo CCT.

GROUP 1 (CCT < 540 micron)

GROUP 2 (CCT > 540 micron)
in patients with ocular hypertension, but the ratio between central corneal thickness and glaucoma progression remains uncertain\textsuperscript{11-19}. In a prospective observational study involving 861 eyes of normal patients, patients with ocular hypertension and patients with POAG, Jonas et al\textsuperscript{19} reported that the development or progression of visual field defects was statistically independent from central corneal thickness. Conversely, in a retrospective multicentre study of a cohort of 230 patients presenting ocular hypertension with 5 year follow-up, Konstas\textsuperscript{21} observed that patients with thin corneas most often progressed to full-blown glaucoma. In a retrospective study, Hong et al\textsuperscript{12} evaluated the association of central corneal thickness (CCT) and visual field progression in patients with chronic primary closed-angle glaucoma (CPACG) with low intraocular pressure (IOP). A total number of 163 eyes with IOP <18 mmHg were included in the study. The patient population was divided into two groups based on the CCT value. The authors describe that patients with CPACG with a thinner cornea present a higher risk of visual field progression, though they maintain a low IOP after therapy. Viswanathan et al\textsuperscript{5} examined 163 eyes of 163 glaucoma patients who were treated with medical therapy and monitored for 6.8 ± 1.8 years. At the initial follow-up visit a thinner CCT was associated with more advanced damages, and the eyes that progressed had a lower CCT than the eyes that showed no progression. In a case-controlled retrospective study, Kim et al\textsuperscript{6} included 88 patients with primary open-angle glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma, or normal-zone beta peripapillare, diminuzione dell’isteresi corneale, e la sindrome da pseudoesfoliazione. Una cornea centrale sottile è un fattore di rischio per la conversione a glaucoma di pazienti con ipertensione oculare, ma il rapporto tra spessore corneale centrale e progressione glaucomatosa rimane incerto\textsuperscript{11-19}. In uno studio osservazionale prospettico su 861 occhi di pazienti normali, ipertesi oculari e affetti da POAG, Jonas et al\textsuperscript{19} hanno dimostrato che lo sviluppo o la progressione di difetti del campo visivo era statisticamente indipendente dallo spessore corneale centrale. Al contrario, in un’analisi retrospettiva, multicentrica, di una coorte di 230 pazienti ipertesi oculari con 5 anni di follow-up, Konstas\textsuperscript{21} ha trovato che i pazienti con cornee sottili più spesso progredivano a glaucoma conclamato. In uno studio retrospettivo Hong et al\textsuperscript{12} hanno valutato l’associazione di spessore centrale della cornea (CCT) e progressione del campo visivo in pazienti con glaucoma ad angolo chiuso primario cronico (CPACG) con bassa pressione intraoculare (IOP); un totale di 163 occhi e IOP <18 mmHg sono stati inclusi nello studio; sulla base del valore CCT, il campione è stato suddiviso in due gruppi; gli autori descrivono che i pazienti con CPACG con una cornea più sottile sono a maggior rischio di progressione del campo visivo, anche se mantengono una IOP bassa dopo terapia. Viswanathan et al\textsuperscript{5} hanno esaminato 163 occhi di 163 pazienti glaucomatosi trattati con terapia medica e seguiti per 6,8 ± 1,8 anni; al follow-up iniziale una più sottile CCT era associata a danni più avanzati e gli occhi che progredivano avevano una CCT inferiore rispetto agli occhi che non mostravano progressione. Kim et al\textsuperscript{6} in uno studio retrospettivo caso-controllo hanno incluso 88 pazienti con glaucoma primario ad angolo aperto, glaucoma pseudoesfoliativo,
tension glaucoma who were monitored for a mean period of 8 years. Cases presenting progression were compared by race, diagnosis, age and pachymetry against progression-free controls. Patients with thin corneas had a greater probability of aggravation than those with thicker CCT, and the CCT was the only identified risk factor that was significantly associated with visual field progression. In a retrospective study conducted in 2012 on both eyes of 794 glaucoma patients concluded that more severe damage was associated with the eye presenting thinner CCT than the contralateral one. There is no formula to calculate the risk of glaucoma progression starting from a set of initial data. GSS is currently the only method that provides an immediate and reliable classification both of the gravity and type of visual field defects, using 30-2 / 24-2 Zeiss-Humphrey tests or G1 / G1X / G2 Octopus programmes. Several studies have proven that it is useful both in clinical practice and in research, and it can help to monitor defect progression in the course of time. We also appreciated that GGS was useful to classify glaucoma-related damage, using the 24-2 Zeiss-Humphrey test. All our patients included in the baseline follow-up were within GSS 2, though the major part of them was at GSS 1. Cases with a lower initial pachymetric value had a significantly higher probability of progression of their initial GSS stage, as indicated by the above authors. In the analysis of the final GSS subgroups, it was interesting to note that the number of eyes that had reached GSS 3 was identical in the two groups compared (p=0.6), underscoring the fact that a lower baseline pachymetric value

glaucoma pigmentario, o glaucoma a tensione normale, seguiti per una media di 8 anni; i casi con progressione sono stati confrontati per razza, diagnosi, età e pachimetria con i controlli che non avevano avuto progressione. I pazienti con cornee sottili avevano una maggiore probabilità di peggiorare rispetto a quelli con CCT più spessa e la CCT è stato l’unico fattore di rischio identificato che era significativamente associato con la progressione del campo visivo. Anche Lester in uno studio retrospettivo del 2012 condotto su entrambi gli occhi di 794 pazienti glaucomatosi concludeva che un danno più severo era associato all’occhio con CCT più sottile rispetto a quello controlaterale. Non esiste una formula con cui calcolare il rischio di progressione glaucomatosa a partire da una serie di dati iniziali. Il GSS è attualmente l’unico metodo che fornisce all’utente una classificazione immediata e affidabile sia della gravità che del tipo di difetti del campo visivo, utilizzando i test 30-2 / 24-2 Zeiss-Humphrey o i programmi G1 / G1X / G2 Octopus. Vari studi hanno dimostrato che è utile sia nella pratica clinica che nella ricerca e può aiutare a monitorare la progressione difetto nel corso del tempo. Abbiamo anche apprezzato l’utilità del GGS per classificare i danni del glaucoma, utilizzando il 24-2 Zeiss-Humphrey test. Tutti i nostri pazienti inclusi al follow-up basale si trovavano entro il GSS 2, anche se la maggior parte di loro era al GSS 1. I casi con un valore pachimetrico iniziale inferiore avevano una probabilità significativamente più alta di una progressione del loro stadio GSS di partenza come indicato dagli altri autori di cui sopra. Nell’analisi dei sottogruppi GGS finali è stato interessante notare che il numero degli occhi che avevano raggiunto un GSS 3 era sovrapponibile tra i due gruppi a confronto (p=0.6), evidenziando che nel glaucoma in stadi più avanzati un
was not a negative prognostic factor anymore for progression in the more advanced stages of glaucoma. Our hypothesis was that, in late glaucoma, CCT would not play an important role anymore but other systemic or local risk factors might contribute to the final clinical picture. According to Lester, the clinical trials at our disposal do not prove that CCT is a risk factor for the development of glaucoma; hence, in glaucoma eyes, IOP must be treated regardless of baseline CCT. Further studies, perhaps prospective, multicentre and randomised, should be conducted to finally clarify the role of corneal pachymetry in glaucoma progression.

CONCLUSIONS

In pharmacologically compensated primary open-angle glaucoma, the visual field progression assessed with GSS seems to be significantly associated with a lower CCT. CCT might not play a role in most advanced glaucoma damage, while other risk factors might contribute to the final clinical picture.

REFERENCES