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Diurnal intraocular pressure variation in pseudoexfoliation syndrome

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PURPOSE. *To describe and compare the diurnal intraocular pressure (IOP) variation in patients with pseudoexfoliation syndrome (PXS) and normal subjects.*
METHODS. *The authors prospectively investigated 19 PXS patients (10 bilateral and 9 unilateral) and 25 age- and sex-matched normal subjects. One eye of each control subject and bilateral PXS patient was selected randomly, and pseudoexfoliative eyes of unilateral cases were enrolled in this study. All patients were admitted to the authors' ophthalmology department and underwent diurnal IOP testing (six measurements over 24 hours).*
RESULTS. *The mean IOP of PXS patients at all time intervals was significantly higher than the control group ($p<0.05$). Likewise, a significant difference in the maximum IOP, range of IOP, and minimum IOP, as well as the standard deviation of the pressure at each time point, existed between groups ($p<0.05$). Normal individuals did not show diurnal variation greater than 5 mmHg. Of patients with PXS, 55.6% showed diurnal variation greater than 5 mm Hg. In addition, in 10% of patients with PXS, the diurnal variations were equal to or higher than 10 mmHg.*
CONCLUSIONS. *Variations in IOP during the daily 24-hour cycle in patients with PXS were higher than control groups. Significant fluctuations in the diurnal curve of IOP in PXS may be an important factor in predicting eyes that may develop pseudoexfoliative glaucoma. IOP fluctuation could influence the diagnostic and prognostic evaluation of PXS. (Eur J Ophthalmol 2004; 14: 495-500)*

KEY WORDS. *Intraocular pressure, Diurnal variation, Pseudoexfoliation syndrome*

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INTRODUCTION

Intraocular pressure (IOP) is generated by the balance between secretion and reabsorption or outflow of aqueous and level of episcleral venous pressure. IOP is a dynamic physiologic parameter varying with posture, cardiac and respiratory cycles, systemic blood pressure, age, sex, race, method of measurement, season, and within time of day (1-3). Sidler-Huguenin (4) recognized diurnal variation in human IOP a century ago. Although the word diurnal is defined as occurring in a 24-hour period daily, diurnal IOP has been used rather loosely in medical literature. Diurnal IOP was defined as the IOP during the daily 24-hour cycle in the round-table discussion moderated by Wax (5).

Subsequently, a number of studies have addressed this issue in normal, glaucomatous, and ocular hypertensive eyes. The diurnal IOP fluctuation is larger

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in patients with glaucoma, ocular hypertension, and normal tension glaucoma than in healthy individuals (6-12). Large diurnal IOP fluctuations were reported to be an independent risk factor for the progression of glaucoma (13). The recognition of a diurnal variation is important for diagnostic and therapeutic reasons (14). Pseudoexfoliation syndrome (PXS) is an age-related disease characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues (15). PXS is a generally accepted risk factor for glaucoma. In several previous studies, IOP of exfoliative eyes has been shown to be significantly higher than IOP of nonexfoliative eyes (16-20). The previous studies reported that ocular hypertension is more frequent in PXS eyes than non-PXS eyes and IOP is 2 mmHg higher in PXS eyes than non-PXS fellow eyes in unilateral PXS patients (21). Klemetti et al (18) reported that IOP in PXS eyes has a tendency to increase with time.

Pseudoexfoliation glaucoma (PXG) patients are found to have higher IOPs that are more difficult to control, more advanced optic nerve head damage, and more frequent need for filtration surgery than primary open-angle glaucoma (POAG) patients (22). Recently, Konstas et al (23) reported that the peak range of IOPs in PXG throughout the day is greater than in POAG.

In the current study we aimed to evaluate variations in IOP during the daily 24-hour cycle in patients with PXS and compare the results with those in a control group.

MATERIALS AND METHODS

The prospective study was comprised of 19 patients who were consecutively diagnosed with PXS (10 bilateral and 9 unilateral) and 25 age-matched control subjects examined between August 2001 and September 2002 at the Department of Ophthalmology at the University Hospital of Kocaeli, Turkey. One eye of each control subject and bilateral PXS patient was selected randomly, and pseudoexfoliative eyes of unilateral cases were enrolled in this study. All subjects gave their informed consent in accordance with the principles of the Declaration of Helsinki II. Subjects with glaucoma; a history of ocular surgery/trauma; ocular infection/inflammation, contact lens use, corneal abnormality, or any condition that prevented reliable applanation tonometry; a history of renal or hepatic impairment; diabetes mellitus; or severe cardiovascular disease were excluded from this study. Healthy control subjects were required to meet the following criteria: visual acuity >20/32; IOP always lower than 21 mmHg on repeated measurements with a Goldmann applanation tonometer; no abnormality of the anterior chamber on examination with a slit lamp; normal ophthalmoscopy with a cup/disc ratio <0.4; normal open angle (grade 3-4) confirmed gonioscopically; and normal visual field examined with the Octopus 101 perimeter.

The diagnosis of PXS had been made on the basis of typical signs such as deposits of grayish white material on the anterior lens surface, at the pupillary border, and on the anterior surface of iris; pigment dispersion from iris epithelium, particularly at the iris sphincter, and pigment deposition on the anterior iris surface, lens capsule, corneal endothelium, and anterior chamber angle detected gonioscopically; and transillumination defect of the iris especially at the pupillary ruff and margin. The PXS patients were also required to meet the following criteria: visual acuity >20/32; IOP always lower than 21 mmHg on repeated measurements with a Goldmann applanation tonometer; normal ophthalmoscopy with a cup/disc ratio <0.4; normal open angle (grade 3-4) confirmed gonioscopically; and normal visual field examined with the Octopus 101 perimeter.

Patients were admitted to the hospital in the morning to evaluate the variations in IOP during the daily 24-hour cycle. IOP measurements were recorded at 10:00, 14:00, 18:00, 22:00, 02:00, and 06:00. All measurements were performed by the same Goldmann applanation tonometer with both eyes open, and in primary sitting position, always measuring the right eye first. All subjects slept 8 hours at night. At the 22:00 measurement patients were awake at bed rest. At 02:00 and 06:00 hour measurements, they were awakened 10 minutes before the IOP measurement and were instructed to sit in primary position for 5 minutes before measurement.

During the day of diurnal measurement patients were forbidden to drink alcohol and caffeine-containing beverages. Meals were standardized. Patients were encouraged to lead as normal a life as possible within hospital boundaries.

Statistical analysis was performed using SPSS 10.0. Results are displayed as mean ± SD. Differences be-

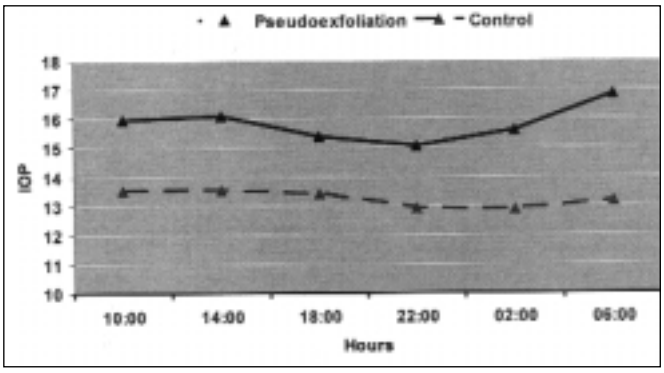

Fig. 1 - *The 24-hour cycle of mean intraocular pressure (IOP) (mmHg) in pseudoexfoliation syndrome and control eyes.*

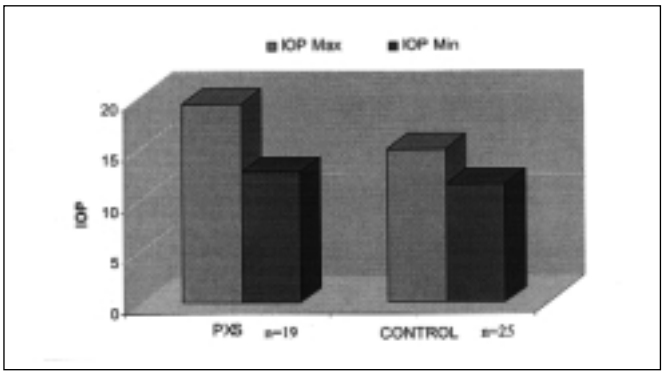

Fig. 2 - *The mean maximum and minimum intraocular pressure (IOP) (mmHg) in pseudoexfoliation syndrome and control eyes.*

tween the groups of patients and controls were analyzed by unpaired Student *t*-test. The significance level was set as $p<0.05$.

RESULTS

Clinical comparisons were carried out in 44 patients (10 bilateral PXS, 9 unilateral PXS, and 25 control subjects). The PXS group had a mean age of 67.55 ± 7.53 years and control group had a mean age of 64.00 ± 8.76 years. There were no statistically significant differences in age or sex between groups. Demographic data of PXS and control groups are shown in Table I. Mean IOP measurements at each time point in PXS patients and control subjects are shown in Table II. Significant differences existed at each time point between PXS and control subjects for the IOP ($p<0.05$) (Fig. 1). Likewise, a significant difference in the maximum IOP, range of IOP, and minimum IOP, as well as

TABLE I - DEMOGRAPHIC DATA OF GROUPS

Characteristics	PXS	Control	p Value
Age, yr	67.55 ± 7.53	64.00 ± 8.76	0.115
Sex			0.543
Male	10	9	
Female	10	15	

PXS = Pseudoexfoliation syndrome

TABLE II - MEAN (± SD) IOP MEASUREMENTS, MMHG

Time	PXS (n=29)	Control (n=25)	p Value
10:00	15.95 ± 2.72	13.52 ± 2.12	0.002
14:00	16.11 ± 2.85	13.52 ± 2.38	0.002
18:00	15.37 ± 3.24	13.40 ± 2.16	0.008
22:00	15.05 ± 2.80	12.92 ± 2.27	0.002
02:00	15.58 ± 3.15	12.84 ± 1.93	0.002
06:00	16.84 ± 4.40	13.16 ± 1.72	0.000
Maximum	19.47 ± 3.34	15.04 ± 1.97	0.000
Minimum	12.84 ± 1.98	11.60 ± 1.50	0.022
Range	6.63 ± 2.96	3.44 ± 1.08	0.000

IOP = Intraocular pressure; PXS = Pseudoexfoliation syndrome

the standard deviation of the pressure at each time point, existed between groups ($p<0.05$) (Fig. 2).
No subject in the control group showed diurnal variation higher than 5 mmHg. However, 55.63% of eyes with PXS showed diurnal variation larger than 5 mmHg. Also, in 10% of eyes with PXS, the diurnal variations were greater than 10 mmHg. The minimum mean IOPs of PXS patients were increased 53.03 ± 5.93% SE and 28.37 ± 9.37% SD in control group. This difference was statistically significant ($p=0.001$). In 45% of eyes with PXS, the peak level of IOP was found outside office hours.

DISCUSSION

This study found that the variations in IOP during the daily 24-hour cycle in patients with PXS were higher than control groups. Of eyes with PXS, 55.6% showed diurnal variation greater than 5 mmHg. In addition, patients with PXS had higher IOP measurements at each time point. To our knowledge, no attempt has been made to document the variations of IOP during a 24-hour cycle in patients with PXS, although earlier works evaluating diurnal curves generally may have included patients with PXS who were not analyzed separately (11, 12).
Lowering IOP is believed to be beneficial in slowing down glaucomatous changes of optic nerve and visual field. However, in a significant proportion of patients, the visual fields continue to deteriorate in spite of office pressures within the range of normal values. It has been suggested that the progressive damage in some cases could be because of peaks of IOP or a variability of diurnal IOP not detected by tonometry during office hours (24-26). The realization that IOP varies during the day has led a number of investigators to monitor the pressure over the day in order to study its relationship with the concurrent glaucomatous damage (27, 28). The diurnal IOP fluctuation is larger in patients with glaucoma, ocular hypertension, and normal tension glaucoma than in healthy individuals (8-12). Konstas et al (23) reported that the significant fluctuation in the diurnal curve of IOP distinguishes PXG from POAG. In both POAG and secondary glaucomas, the diurnal range of IOP has been significantly correlated with visual field loss (29-32). Presence of pseudoexfoliation is a definitive risk factor for the development of glaucoma independent of IOP level (15, 33). When clinically detected, PXS occurs unilaterally, but within 5 years, 14% to 41% of the cases may develop the bilateral form (18, 34, 35). No prognostic factors for conversion to bilateral PXS were found. A total of 24.7% to 34.5% of eyes with PXS developed ocular hypertension or glaucoma during the 10-year follow-up period (36). Mitchell et al (37) noticed a fivefold increase in the risk of glaucoma in PXS eyes, and the risk was independent of other known glaucoma risk factors. Puska (36) reported the factors associated with conversion to PXG as initial IOP, pupillary dilatation value, and the IOP difference between the fellow eyes and suggested that the unmeasured IOP peaks could be a risk factor. In this study, we observed that the mean IOP, as well as the maximum and minimum IOP, were higher in the PXS group compared with the control group. Our study confirms previous impressions that PXS is associated with higher IOP than in non-PXS subjects (16-20). We also found that the variations in IOP during a daily 24-hour cycle in patients with PXS were higher than in a control group. These variations in IOP during the daily 24-hour cycle and high mean maximum IOP level may be risk factors that contribute to conversion to glaucoma. Further prospective studies are required in patients with PXS associated with large diurnal curve. Most IOP assessments will inevitably take place during office hours, between 9:00 and 18:00. The question arises as to whether any clinically significant pressure variation will be evident over the course of this 9-hour time interval. The results of several studies suggested that this period is sufficient to reveal a definite IOP fluctuation. High IOP measurements were found to be more numerous in the morning hours (8, 9). Our study confirms previous impressions that single office measurements provide limited information on the range and the maximum value of IOP (38-40). For example, Drance (38) reported that 60% of his patients with untreated POAG exhibited peak IOP outside office hours. Also, Konstas et al (23) reported that exfoliation glaucoma patients frequently demonstrate a peak IOP outside normal office hours. In this study we observed that in 45% of eyes with PXS, the peak level of IOP was found outside office hours. Twenty-four–hour cycle IOP measurements may add more information in patients with PXS during follow-up.
It was recommended to perform the first measure-

ment while the patient was in bed and in a darkened room during assessment of the diurnal IOP curve (41). The nocturnal supine IOP was found to be higher than the sitting IOP during the daytime and evening in healthy young and aging adults (42, 43). A valid criticism of this study is that making a diurnal curve and measurements only in sitting position can allow some pressure peaks to escape from investigation. These influences, however, would apply equally to both controls and patients with PXS. This question may best be answered with studies of 24-hour IOP cycle with measurements of IOP in supine during night.

This study suggests that large fluctuations of IOP in PXS patients may be an important factor in predicting which patients are likely to develop PXG and a single IOP measurement is not sufficient for estimating the IOP level, especially in exfoliation syndrome. Further progressive long-term studies are required to elucidate the significance of the various IOP features of patients with PXS at presentation (maximum IOP, minimum IOP, and range of 24-hour IOP cycle) on the rate of conversion to PXG.

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