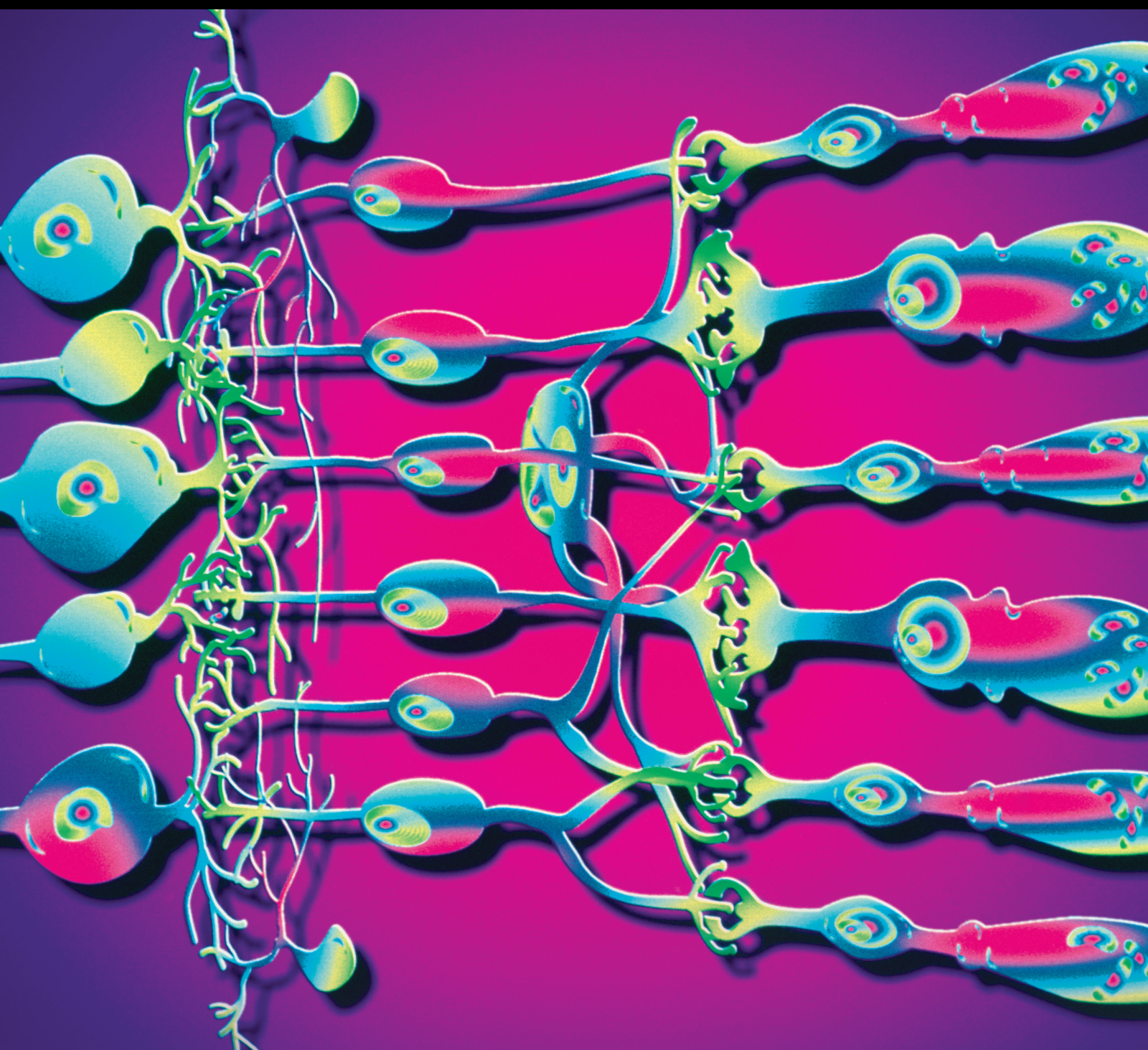
Journal of Ophthalmology

Glaucoma Quality of Life

Lead Guest Editor: Antonio M. Fea
Guest Editors: Fritz Hengerer and Leon Au



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Editorial Board

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Editorial

Glaucoma Quality of Life

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Growing attention has been given to the quality of life in several fields of medicine. The concept of quality of life is not unknown to the glaucoma culture if we recall that the European Glaucoma Society Guidelines state "the goal of glaucoma treatment is to maintain the patient's visual function and related quality of life (QoL), at a sustainable cost."

Nevertheless in the past, more attention has been given to quantitative matters as IOP, visual field, and optic nerve because those were the ones that can be directly modified and physicians were less interested in qualitative and subjective measures as the QoL. Measurements of QoL, on the other hand, tend to be time consuming and can be strongly influenced by other factors (general physical health, psychological state, personality, relationships, wealth, etc.), which are not necessarily related to the disease itself.

However, there is no doubt that when the physician pays attention to the claims of the patients, he will realize that most of their questions are related to everyday issues such as "will I be able to drive my car? Will I be able to be independent in my daily tasks within my home? And will I be able to go the supermarket two blocks from my house? Will I have problems reading?"

The same questions are relevant for insurances and governments because the disability caused by any disease will help determine the level at which the benefits of screening outweigh costs and decide which patient should be treated and how aggressive treatment should be. Furthermore, knowing the degree of disability can potentially help to increase patient safety with appropriate guidelines, to recognize patients who can benefit from rehabilitation and evaluate the efficacy of those measures.

Since the first studies on quality of life in glaucoma, several areas of interest have been identified and explored: (1) determining the symptoms that are more bothersome for the patients and correlating them with the stage of disease; (2) testing and building better methods to investigate the impact of glaucoma on the QoL; (3) assessing the impact of glaucoma on mental status; and (4) analyzing the impact of different therapies on the QoL of glaucoma patients.

(1) Thanks to recent investigations, we are now aware that vision defects in glaucoma patients are not as simple as the traditional view of peripheral vision loss, but they affect several aspects related to a generally decreased image quality including glare, letters appearing faded when reading, and needing more light. Glaucoma patients gave the higher importance to tasks involving central and near vision (reading) and to mobility outside the home, whereas the most frequent complaints were difficulties related to lighting and in particular adapting to different levels of light. Common complaints also included difficulty in walking, stair climbing, face recognition, and driving. The relative importance of these problems is correlated to the degree of visual function and to the age of the patient. The correlation coefficients for the lower paracentral and lower peripheral VF of the better eye were the highest for several sub-

scales, such as general vision, near vision, distance vision, social function, mental health, role limitation, and driving. Although the best correlations were generally found in the visual field of the better eye, the best metric to relate disease severity to disability is still a matter of debate and further work is needed in the field.

(2) QoL assessment traditionally used patient-reported-outcome (PRO) questionnaires. More than 30 vision-specific PRO measures have been developed in the context of glaucoma and can be classified in three categories: PROs addressing functional status related to vision, PROs addressing overall QoL, and PROs assessing other factors related to disease and treatment (i.e., symptoms, side effects, adherence, satisfaction, and self-efficacy). Several studies failed to demonstrate a correlation between QoL and glaucoma severity especially when PROs were not specifically designed. Research on the most appropriate type of PRO has been very active. The information gathered with questionnaires are subjective and influenced by many factors other than the disease, including emotions, concentration, personality, and desire to please or to mislead. Furthermore, data from the SEE project showed that 10% of the subjects have differences between their perception on their ability to perform activities and their actual performance. Nevertheless, responses to questions about visual ability seem to correlate with clinical objective measures, which suggests that in the future, it may be possible to use them to define subgroups in the overall population. An active area of research in the last few years was the development and testing of standardized, performance-based measures of function performed in a clinical setting. Potential implications of the disagreement between subjective and objective testing will be to investigate why some patients have discrepancies between self-reported and performance-based tests. The knowledge of what an individual with a specific vision problem can actually do opens the way to develop tools to improve his performance, lessen his problems, and actively improve his quality of life. Another potential and poorly explored area is to follow prospectively the patients to understand how attitudes and QoL modify as the disease progresses, as the patient ages, or as other subjective or objective factors (wealth, social relationships, activities, etc.) change.

(3) Glaucoma doctors always had the clinical impression that some psychological traits are typical of the glaucoma patients, but several papers demonstrated that glaucoma is a significant predictor of depression after adjustment for demographic factors and multiple comorbidities with a prevalence estimated around 10%. The finding that objective measures are not correlated to depression should alert clinicians that a high prevalence of depression may be present even among patients without clinically significant visual disabilities. Counseling regarding the generally slow progression rate of the disease may result in a decreased burden from depression.

(4) The impact of new therapies, minimally invasive surgical procedures, and slow drug-releasing implants on the patient's QoL will certainly be a rapid growing field of investigation. The research in this field may potentially guide the researchers to select new therapies that have minimal effect on the quality of life and the agencies to evaluate the general and economic impacts of these new therapies on the glaucoma patients.

We decided to dedicate this special issue to QoL with the aim to shed light on the quality of life of glaucoma patients and attract attention of the scientific community to pursue further investigations leading to a rapid development of this field.

A better understanding of patient-reported QoL can improve the relationship between the patient and the physician and enhance adherence in choosing the treatment options on the basis of the patient profile.

Acknowledgments

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Research Article

Self-Monitoring Symptoms in Glaucoma: A Feasibility Study of a Web-Based Diary Tool

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Purpose. Glaucoma patients annually spend only a few hours in an eye clinic but spend more than 5000 waking hours engaged in everything else. We propose that patients could self-monitor changes in visual symptoms providing valuable between clinic information; we test the hypothesis that this is feasible using a web-based diary tool. *Methods*. Ten glaucoma patients with a range of visual field loss took part in an eight-week pilot study. After completing a series of baseline tests, volunteers were prompted to monitor symptoms every three days and complete a diary about their vision during daily life using a bespoke web-based diary tool. Response to an end of a study questionnaire about the usefulness of the exercise was a main outcome measure. *Results*. Eight of the 10 patients rated the monitoring scheme to be "valuable" or "very valuable." Completion rate to items was excellent (96%). Themes from a qualitative synthesis of the diary entries related to behavioural aspects of glaucoma. One patient concluded that a constant focus on monitoring symptoms led to negative feelings. *Conclusions*. A web-based diary tool for monitoring self-reported glaucoma symptoms is practically feasible. The tool must be carefully designed to ensure participants are benefitting, and it is not increasing anxiety.

1. Introduction

Whilst the clinical and biological mechanisms of glaucoma are well explored, the impact of glaucoma on an individual's well-being has been relatively understudied [1, 2]. Patient-reported outcome measures (PROMs) estimate perceived health status, functional status, or health-related quality of life. PROMs, often administered as questionnaires, have been used to assess the effect of glaucoma on the quality of life in research studies for some time [3, 4]. PROMs are starting to be used as end points in clinical trials of treatments for glaucoma [5]. Such use of PROMs is a positive step because they directly assess the impact of symptoms of disease on a patient, certainly as they perceive it themselves. To date, PROMs are not used in regular clinical management of patients with glaucoma. Yet the benefits for this idea have been speculated upon, and PROMs are being increasingly used in the clinical management of other conditions [6, 7].

In the United Kingdom (UK), there are more than one million hospital visits a year for glaucoma [8]; clinicians likely have inadequate time and resources to cope with these visits. Moreover, patients likely do not get the opportunity to discuss their psychological well-being or the functional impact of their glaucoma at these visits. This is a pity because better between clinic visit information and time for patient/clinician interaction may lead to better glaucoma management [9]. At the same time, patients spend only a few hours a year in the eye clinic having their glaucoma monitored but they spend more than 5000 waking hours each year engaged in everything else [10]. This statistic suggests that there should be time for patients to potentially self-monitor their symptoms in between clinic visits. Self-monitoring approaches have proved effective in other chronic conditions such as type 2 diabetes [11]; these methods might be useful for people with glaucoma, and this is the main idea explored in this study.

In this work, we explore how people with glaucoma might self-monitor changes in visual symptoms with the aim of making them more engaged in their "glaucoma journey." We also examine how self-monitoring may be influenced by personality traits. We specifically test the hypothesis that a group of

volunteer patients will be sufficiently motivated to regularly self-report on their symptoms; we examine the feasibility of this using a web-based diary tool.

2. Materials and Methods

Participants responded to an invitation to take part in the study from a patient-based charitable organisation (International Glaucoma Association—http://www.glaucoma-association.com). The study was a prospective mixed-method feasibility study which took place over eight weeks in 2015.

Ten participants were recruited from different glaucoma clinics across England; all had a clinical diagnosis of primary open-angle glaucoma (POAG) with at least a five-year treatment history. Participants were asked to respond if they had glaucoma alone and no other ocular disease other than prior uncomplicated cataract surgery.

The study was approved by a Research and Ethics Committee (City, University of London, School of Health Sciences) and adhered to the tenets of the Declaration of Helsinki. Data was anonymised and stored in a secure location. All participants gave their informed written consent prior to taking part.

2.1. Pretesting. Participants were asked to attend the university to complete a series of pretest measures to confirm their eligibility for the study. A Mini-Mental State Examination was used to exclude people with any measureable cognitive impairment. Participants then underwent an examination of their vision by a qualified optometrist (DJT). This examination included refraction, measurement of contrast sensitivity (CS), visual acuity (VA), and slit-lamp examination on both eyes. An examination of the visual field (VF) confirmed that all participants had measureable VF loss in at least one eye. VFs were measured (Swedish Interactive Threshold Algorithm Standard 24-2) using a Humphrey Field Analyser (HFA) [Carl Zeiss Meditec, Dublin, CA]. The best sensitivity values at each location of the monocular VFs were merged to construct an integrated visual field (IVF) [12, 13].

Participants completed the EuroQol-5 dimension (EQ-5D) questionnaire and the Ten-Item Personality Inventory (TIPI) at the start of the study in a face-to-face interview. EQ-5D [14] is a five-item measure designed to measure general health. The items are scored either 1 (no problems), 2 (some problems), or 3 (severe problems) on the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The individual 1-digit item scores are combined into a 5-digit number which describes health state. For example, a score of 12112 indicates a participant has some problems with self-care and anxiety but no other perceived problems. The TIPI [15] estimates levels of extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience. The scale consists of 10 items, each scored on a 7-point Likert scale from 1 (disagree strongly) to 7 (agree strongly).

2.2. Web-Based Monitoring and Diary Tool. The participants were introduced to the web platform at a face-to-face baseline visit and were provided with a unique login. The web platform was designed to be user friendly and easy to navigate (Figure 1). The participants were provided with a guidebook, which gave instructions about using the web tool.

The participants were asked to complete a set of bespoke "symptom monitoring" questions every three days. We asked how much driving, walking, searching for objects, using a computer, watching television, and eating and drinking were affected by glaucoma. These questions were scored on a 5-point Likert scale from "not at all" to "very much." A summary score at each time point was generated (5 (no symptoms) and 45 (maximum symptoms)). The participants were sent automatic email prompts every three days as a reminder to complete the questions.

The participants were also invited to complete a written diary documenting any aspect of their glaucoma that they felt would be helpful to record. They could do this by typing directly into the web-based tool as frequently as they wanted to and could even upload photographs. This would be recorded by time and date. Again, they were prompted by an automatic email every three days.

2.3. Study Evaluation. The participants were asked to complete a series of questions (see Figure 2) about the usefulness of the exercise at the end of the eight-week study period.

2.4. Analysis. The composite symptom scores for each time point were used to plot change in symptom awareness over the course of the study. Individual personality traits for each participant were compared to the mean scores on the TIPI in a cross-sectional sample of the UK population (Table 1) [16]. The frequency of words written was used as a proxy for the level of diary usage. Univariate association between diary use and scores on personality traits was explored using Spearman's rho. The results from the evaluation questionnaire were assessed with simple summary statistics.

The information from the online diary tool was analysed using thematic analysis [17]. The lead researcher (LM) collated raw diary responses from each participant. The research team manually worked through each data set and highlighted sections of text that applied to the patients' glaucoma symptoms. These sections of text were grouped into themes.

3. Results

The participants (50% male) had a median age of 70 years (interquartile range (IQR) 66 to 76). The participants were from different regions of the UK and were educated to a minimum of high school level. All participants were married or living with a long-term partner.

A summary of patients' vision and baseline data is given in Table 2. Humphrey mean deviation (MD) in the better eye (BEMD) was used as a proxy measure for glaucoma disease severity. BEMD ranged from early to advanced, with median (IQR) BEMD −9.1 dB (−6.1, −13.4). Five participants had BEMD worse than −12 dB, and this level is sometimes described as advanced VF loss [18].

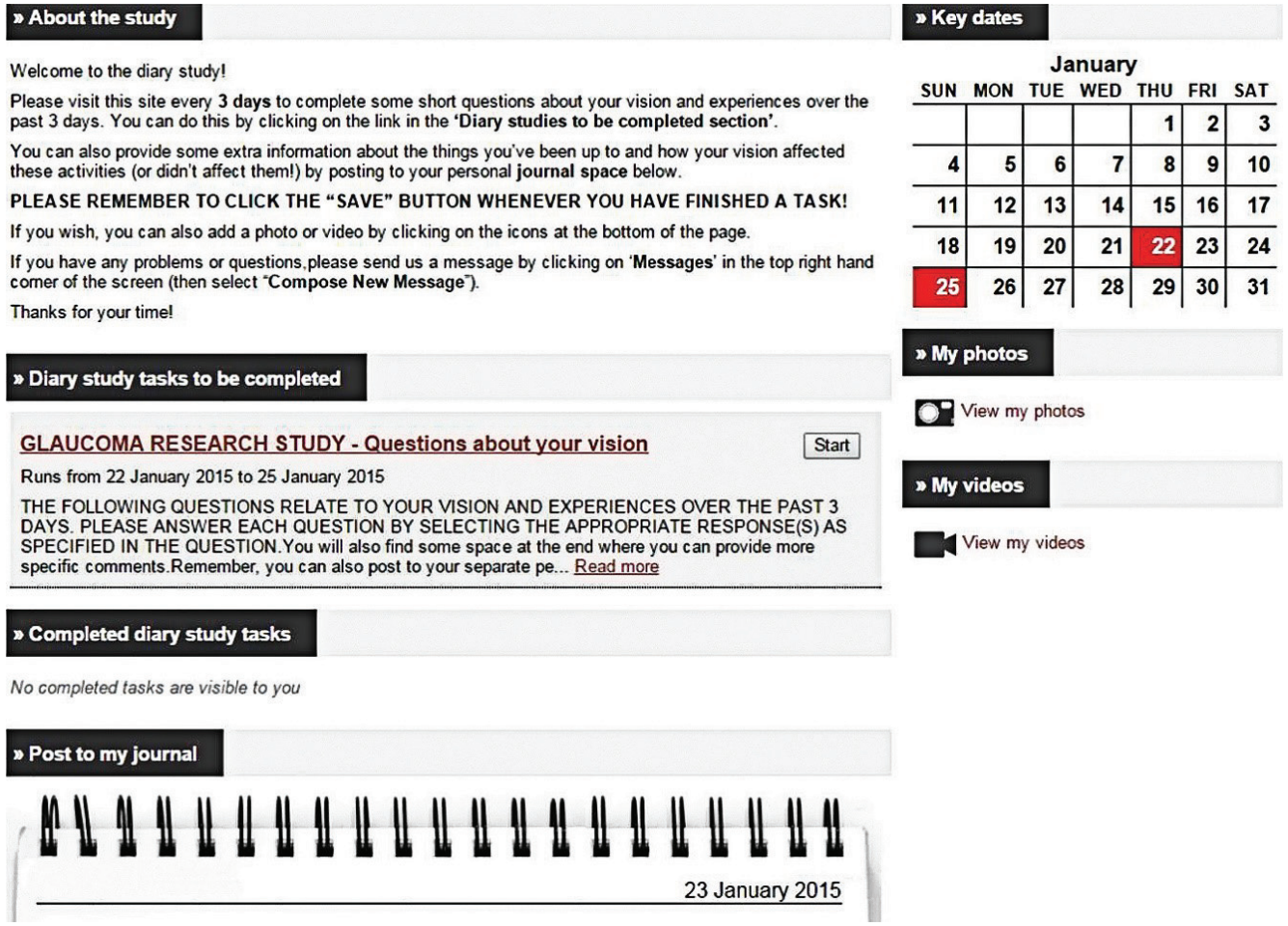

Figure 1: A screenshot of the web-based diary tool used by the participants. The page is split into "to be completed" and "completed" tasks.

1) How valuable did you find keeping a diary about your vision and experiences? 1 "not valuable" to 5 "very valuable"
2) To what extent has your view of your glaucoma and/or vision changed since beginning the diary study?
   "I am more aware of my vision loss since the beginning of the study"
   "Since beginning the study, I notice the effects of my vision loss more during my everyday activities"
   "I have found new ways of dealing with my glaucoma since beginning the study"
   "I have been better at remembering to take my drops since beginning the study"
3) Did you ever keep a journal or write down information about your vision and glaucoma care before this study? Yes/no
4) Will you ever keep a diary or write down information about your vision and glaucoma care after the study? Yes/no
5) What methods would you consider using to help keep a diary or log of your vision and glaucoma care? Website, computer documents, paper journal, smartphone app, other, none.

Figure 2: Study evaluation questions given to the participants at the end of the study.

3.1. Symptom Monitoring. The completion rate of the symptom-monitoring questions (96% over the eight-week period) was remarkably good. Composite symptom scores (from 5 to 45) for each time point were used to plot individual change in symptom awareness over the study period. Loess curves were fitted to the data points in order to

Table 1

	Extr.	Agre.	Consc.	Emo stab.	Open.
Population mean	9.11	10.12	10.44	9.05	10.11
M1	8	*12*	*11*	6	10
M2	5	8	9	9	*11*
M3	*11*	8	10	7	8
M4	8	3	7	*12*	9
M6	*13*	*14*	*13*	7	*12*
F1	7	8	*11*	7	*13*
F2	8	8	*12*	*11*	9
F3	*10*	*11*	*11*	7	6
F4	*11*	9	6	*10*	6
F5	8	10	8	4	10

The table demonstrates the raw Ten-Item Personality Inventory data for the study sample. Scores from left to right: extraversion, agreeableness, conscientiousness, emotional stability, and openness. Items in italic denote that the score is above reference population mean [16].

Table 2: A summary of patients' vision and baseline data.

	Years since diagnosis	Binocular visual acuity (LogMAR)	Binocular contrast sensitivity	Best eye HFA mean deviation (dB)	EQ-5D general health
M1	21	−0.2	1.95	−13.7	11111
M2	5	0	1.5	−7.9	11111
M3	26	−0.02	1.65	−5.5	11211
M4	23	−0.1	0.9	−17.4	21111
M6	25	0	1.95	−11.4	11111
F1	29	−0.1	1.2	−9.2	11111
F2	11	−0.1	1.35	−19.4	11211
F3	6	0	1.95	−2.2	11121
F4	15	0.1	1.35	−13.6	21211
F5	15	0	1.35	−9.0	11221

illustrate any "trend" in symptom awareness during the study period [19] (see Figure 3). These trends are purely illustrative given the short follow-up period.

The participants were remarkably well engaged with the diary entry tool. The median (IQR) number of diary words recorded per patient was 1858 (703, 4094) over the 8-week period.

Six participants reported higher levels of extraversion and openness to experience than the UK sample. Emotional stability was weakly correlated (rho = 0.39; $p = 0.05$) with the uptake of the diary exercise (number of words written in the diary exercise). There were no other statistically significant associations, but the sample size was very small.

3.2. Qualitative Analysis. Four main themes emerged from the thematic analysis at a semantic (explicit) level.

3.2.1. Frustration. The participants often reported a feeling of frustration regarding their impaired ability to complete tasks because of their vision.

It is very difficult to describe what it's like except that I know that my vision is not the same as it was a few years ago, it's not good and it's not right. (F2)

Some participants felt frustration at themselves, describing that they should be able to complete certain tasks such as reading.

As reading has become less pleasant, the piles of items waiting to be read tend to build up. Must try harder! (F3)

Not driving - wouldn't feel safe. Extremely difficult to read & shop. Getting very bad tempered & frustrated after almost 2 weeks of this. (F5)

3.2.2. Anxiety and Cessation of Activities. Some participants reported that they had stopped performing certain activities due to fears associated with their vision loss. Some of the instances of avoidance behaviour were preplanned.

I find it difficult to see in the dark these days as I struggle where there is very little contrast. I have stopped driving at night but live in an urban area that is reasonably well served by public transport. (F2)

There were also instances that appeared to be triggered by situational anxiety.

During the night I started worrying about coping with trains and planes on my own and where I'd be able to find somewhere to rest up during Monday, as the only flight was very early. I felt so awful by Sunday morning that I decided I'd have to stay at home. So much for thinking I am back to normal.... (F3)

3.2.3. Social Support. The participants in this sample discussed social support networks mostly in a positive light but sometimes reported feeling guilty at having to rely on a partner for social support and feared becoming a burden.

[Name omitted] drove me there but didn't come on the walk herself – I always feel a bit guilty about this.... (M6)

I don't like to rely on my partner for lifts but he often obliges. I will go out on foot with my trusty torch where necessary. (F2)

The participants reported strong social support networks, including partners and friends, and emphasised the importance of professional support groups.

IGA AGM was very much worthwhile attending. Loop system was working well so I could hear clearly. Particularly interested in all the research going on, DVLA [Driver and Vehicle Licensing Agency] aspect most relevant. (F4)

Social support networks seemed to consist of different people for different participants; one reported a lot of activity involving friends, but some only talked about their partners. Regardless of who the network consisted of, participants spoke about the importance of their social support network understanding their glaucoma-related issues.

I wouldn't have recognized him if he hadn't spoken – that sort of non-acknowledgement can probably seem rude to anyone who doesn't know about your glaucoma (I did apologize to him using the glaucoma excuse). (M2)

Some also identified social activities as an important "distraction" factor.

I'm not one for staying in bed but would prefer to keep active. Not up to my usual standard but still enjoyed the

session. Didn't have time to ponder on how I felt and how my eyes were affected. (M6)

3.2.4. Clinician Trust. The participants described different aspects of their glaucoma care in their diary entries. Most participants indicated that they had high levels of trust and a helpful dialogue with at least some of their care team.

Just glad my glaucoma was picked up when it was. If this is the sight I have 'for ever' whatever that means for me - then I am very grateful to have been looked after in the way I have been. (F1)

There were very few participants who reported negative aspects of care, although some participants reported concern regarding interactions with professionals during their glaucoma care which led to mistrust.

Opticians, new varifocals on order, titanium, bit pricey @ 640. But prefer to stick with local independent opticians. As one of larger chains, in my view, "missed" evidence of Glaucoma in its early stages when I complained that right eye vision through their new specs/lens provide was slightly inferior to left. This goes back some 8 years. (M2)

Overall, the participants in this study reported having very positive relationships with their clinicians.

3.3. Evaluation of Study. Overall, the participants reported that they found the diary exercise valuable, with eight out of ten participants rating the exercise "valuable" or "very valuable." One participant did not engage with the diary exercise and rated it not valuable at all. One participant rated the exercise neutral.

Interestingly, eight participants said they felt more aware of their vision loss and its effects since the beginning of the study. Only two of the ten participants felt that the intervention improved their medication adherence. Three participants felt that they had developed new ways of dealing with their vision loss.

Four participants said that they were more likely to keep an independent diary about their vision after completing the eight-week diary exercise. From the options given in the evaluation questions (see Figure 3), five participants said they were most likely to use a web-based or computer-based diary tool.

The participants' experiences of the diary exercise were mostly positive. The participants generally felt that they received benefit from the diary exercise and that they would continue to benefit from using the process in the future.

Thank you for asking me to take part in this research. No-one else knows the hassles I have mentioned, many others have bigger daily problems to cope with, so mine are trivial in comparison. (F4)

Although the majority of comments were positive, one participant reported negative feelings.

I don't think my sight is any worse than it was a few weeks ago, only that I am more focused on it. I am not sure that this is a good thing because it makes me more aware of problems when I would normally just deal with them or ignore them. (F2)

4. Discussion

A group of self-selected volunteer patients, with a range of disease severity and personality types, adhered remarkably well to using a web-based diary tool to monitor their glaucoma symptoms. The participants were able to report their own symptoms with remarkable regularity, yielding plots of how their symptoms were potentially changing over time. Most participants felt more aware of their vision loss after taking part in the exercise. Themes emerging from the qualitative synthesis of the diary entries were related to behavioural aspects that might be overlooked in typical patient-clinician consultations. We speculate that aspects of a patient's quality of life affected by glaucoma (frustration and anxiety) could be flagged by an online monitoring tool and then assessed in clinical consultations.

An investigation of the feasibility of self-monitoring symptoms of glaucoma has not been done before. Our study therefore represents new knowledge as it has at least demonstrated how this might be feasible in a group of volunteer patients. Research into surveillance of glaucoma away from the clinic has, for example, focused on monitoring intraocular pressure and aids for improving adherence to treatment [20–23]. Here, we have shown that this approach might be useful in recording between clinic visit PROMs. Self-monitoring techniques have been shown to play a useful role in patient care in other chronic conditions [11, 24, 25]. The volunteers in our study were remarkably positive about the idea of self-monitoring. This may be related to the volunteer's personalities. For example, six participants reported higher levels of extraversion and openness to experience than a reference standard.

A number of patients in our study reported feeling anxious about their glaucoma. A higher prevalence of anxiety disorders has been demonstrated in other chronic conditions [26, 27]. Patients also reported frustration at losing their normal functional abilities. Evidence from other eye diseases has found links between loss of functional abilities and frustration [28]. Negative feelings likely have an impact on a patient's self-efficacy, and if they are not identified and addressed, patients may be more likely to develop depression [29]. An online monitoring tool may allow some patients to articulate these anxieties, and this could be clinically useful in the management of glaucoma.

The results from this study hint at important clinical applications, and we speculate on these briefly now. Evidence suggests that PROMs such as the ones used in this study, as well as self-monitoring exercises, provide important clinical information about patients which act as part of a collaborative management plan in chronic illness [30]. Many patients may not get an opportunity to discuss their condition during clinic appointments [31, 32]. A diary tool allows patients to use reflective thinking in order to pinpoint difficulties with their condition. For example, one participant in the study reported that she felt her problems were "trivial" compared to others and chose not to share them. Plotting self-reported symptoms, using an appropriate tool, could have the same motivational behavioural effect as measuring daily steps as a measure of exercise [33]. This might be useful in terms of engagement and adherence with treatment.

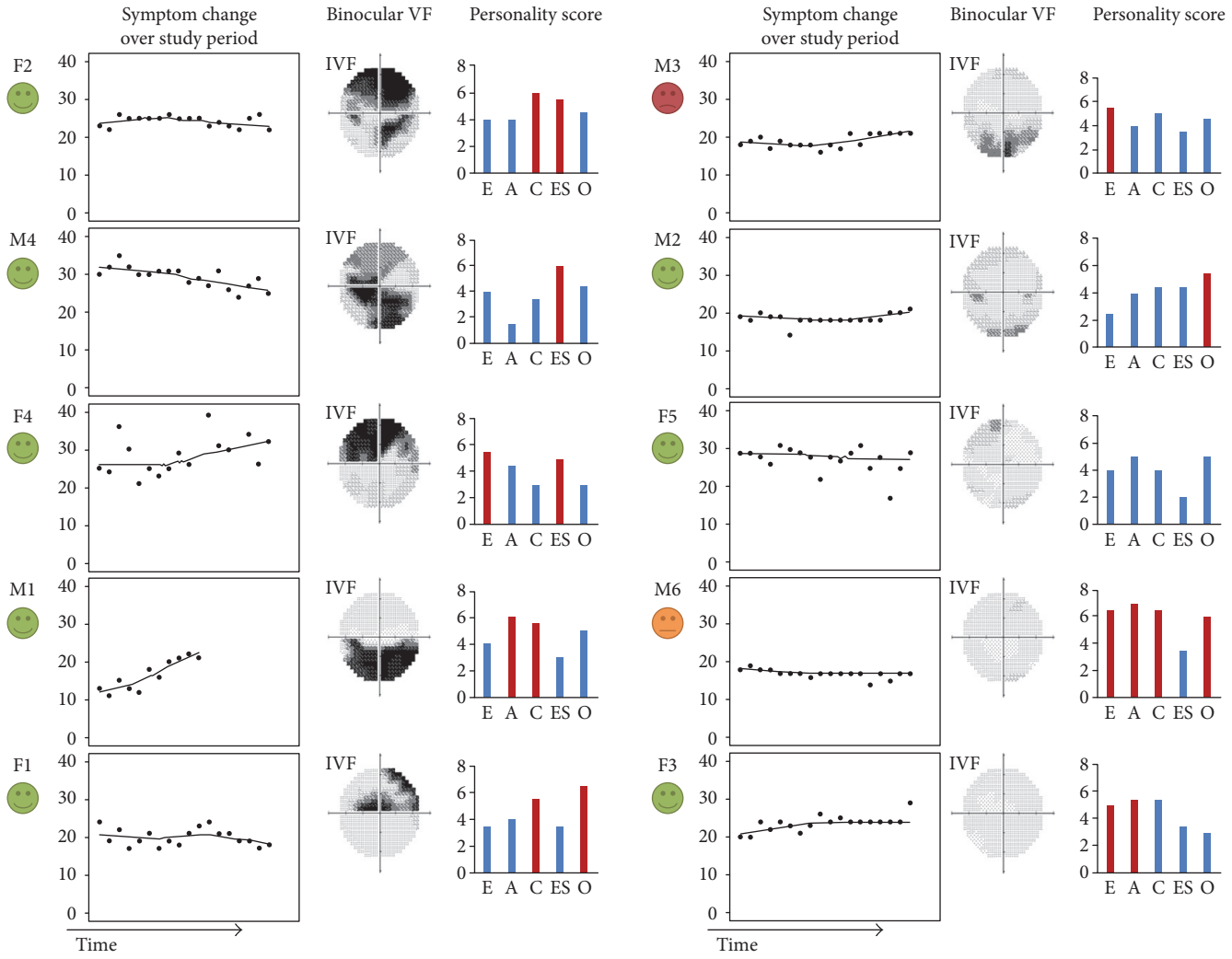

Figure 3: Shows results from 10 participants ordered according to the severity of binocular visual field loss. *From left to right*: face indicates self-response to review question about the value of the self-monitoring exercise; time series plot shows a composite visual symptom score recorded over a study period of 8 weeks. Binocular visual field is shown as grey scale of integrated visual field [5]. Individual bar chart indicates response to Big Five Inventory (BFI) personality questionnaire (E: extraversion, A: agreeableness, C: conscientiousness, ES: emotional stability, and O: openness). Red bars indicate that trait is significantly different from a reference population. For example, volunteer M6 had four significant personality traits.

Participants in this study provided a substantial amount of written information about their psychological well-being which may not previously have been shared with clinicians. Patients may be less likely to disclose psychological distress with clinicians due to fear of stigmatisation or involvement of mental health services [34, 35]. Interestingly, some evidence suggests patients are more likely to disclose information of a sensitive nature if they are able to do so using technologically advanced methodology, such as through a web-based tool [36, 37]. An online diary may therefore yield more information about a patient's psychological well-being when compared to a hospital consultation, and this should be investigated further.

One patient concluded that a constant focus on monitoring symptoms led to negative feelings and experiences. This is very noteworthy. Previous research has suggested that private self-focus and rumination are associated with depression and generalised anxiety in some people [38]. This observation would be important to consider in the development of the idea of self-monitoring symptoms. Moreover, the diary tool may have been making patients more aware of problems with their vision and this has significant implications that need to be considered in a future study. It would, for example, be interesting to integrate an exercise such as the one we have carried out with measures of adherence to treatment, which is a serious issue in glaucoma management. Interestingly, only two of the ten participants in our study felt that the intervention improved their medication adherence.

The experimental design of our study had several strengths, such as the combination of use of personality testing and symptom-monitoring questions. Of the ten participants, only one chose not to use the qualitative diary tool throughout the course of the study; however, this participant did complete the symptom-monitoring questions. The study

used a multifaceted approach which allowed participants to engage only with the parts of the exercise that they were comfortable with. The web pages were well designed, and all data was safely and securely captured.

There are also several limitations to our study. The study sample was small, and the glaucoma profile of the patients was very varied; this prevents us from drawing real conclusion other than proving the practical feasibility of the approach. Volunteers were self-selected and motivated. Volunteers had good levels of education and were sufficiently engaged with their glaucoma because, for example, they belong to a patient organisation. We do not know if adherence to the exercise would be so good in another population.

In conclusion, volunteer patients, with a range of disease severity and personality types, adhered remarkably well to using a web-based diary tool to monitor their self-reported glaucoma symptoms. A web-based diary intervention for the self-monitoring of glaucoma may therefore be practical. Future work should examine the feasibility of this approach in larger groups of patients with broader methods of recruitment and examine if it can change behaviour or be clinically useful. The monitoring tool must be carefully designed in order to ensure that the participants are benefitting, and it is not increasing anxiety.

Disclosure

This work was presented as a poster at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting 2016 in Seattle, Washington.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Research Article

Twenty-Four-Hour Variation of Intraocular Pressure in Primary Open-Angle Glaucoma Treated with Triple Eye Drops

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Objectives. To evaluate 24-hour intraocular pressure (IOP) variation in patients with primary open-angle glaucoma (POAG) treated with triple eye drops. *Subjects and Methods.* The IOP was measured in 74 eyes in 74 POAG patients (seated) on triple therapy (PG analogue, β-blocker, carbonic anhydrase inhibitor) at about every 3 hours. *Results.* The peak IOP was 13.5 ± 3.1 at 1:00, and the trough IOP was at 12.6 ± 2.4 mmHg at 7:00. The IOP at 7:00 was significantly lower than that at 10:00, 1:00, and 3:00 ($p < 0.05$). Based on the time of the peak IOP, we classified the patients into two groups: diurnal (28 eyes) and nocturnal types (37 eyes). There was significant difference at the spherical equivalent between diurnal and nocturnal types ($p = 0.014$). To assess the influence of reflective error, we conducted subanalysis for two groups: high myopic (26 eyes, ≤ -6D) and low/nonmyopic (24 eyes, ≥ -2D) groups. In the low/nonmyopia group, the IOP was significantly higher at 1:00 and 3:00 than at 13:00, 16:00, and 7:00 ($p < 0.05$). *Conclusion.* The mean of IOP elevated outside of clinic hour in the POAG patients on triple therapy. The low/nonmyopia patient should be carefully treated because the IOP of the patients at night elevated significantly.

1. Introduction

The intraocular pressure (IOP) reduction is the only evidence-based treatment for glaucoma [1–4]. The IOP in glaucoma patients is generally evaluated in single IOP measurement during clinic hours, although IOP varies over the course of 24 hours. Hence, it is obvious that understanding 24-hour IOP variation is important in glaucoma treatment.

Approximately 100 years ago, Maslenikow reported that IOP was generally higher during daytime than nighttime [5]. The biological clock in the suprachiasmatic nucleus, the central clock that regulates the circadian rhythm, controls aqueous humor production via sympathetic nervous system. Therefore, the IOP variation due to aqueous humor production is less at night than during daytime [6–9]. In general, the IOP variation pattern in the sitting position peaks in the morning and decreases toward midnight [10]. However, the IOP variation is affected by various factors such as posture and spherical equivalent [11].

In primary open-angle glaucoma (POAG), generally, the first-line treatment to reduce IOP is an instillation of eye drops. Daytime peak IOP is clinically important in predicting long-term glaucomatous progress in the patients treated with one or two kinds of eye drops because the IOP peaks at night in only 20% of cases [12]. In some cases, however, visual field defects progress quickly in spite of adequate reduction of IOP measured during clinic hours. The next step of treatment is usually to add eye drops up to three or four different types.

Table 1: Combinations of eye drops used by the patients in this study. Data is expressed as number of patients. All patients were treated with three different types of eye drops; PG, CAI, and β-blocker, in different combinations.

Prostaglandin	Latanoprost		Travoprost	Tafluprost	Bimatoprost
β-blocker	Carteolol hydrochloride 2% 2 times/1 time	Timolol maleate 0.5% 2 times/1 time	Carteolol hydrochloride 2% 1 time	Carteolol hydrochloride 2% 2 times/1 time	Carteolol hydrochloride 2% 2 times/1 time
CAI					
Dorzolamide 1%	4/1	5/10	1	1/0	1/0
Brinzolamide 1%	11/4	7/22	3	0/1	2/1

Importantly, combinations of eye drop treatment affect the pattern of the IOP variation. In many cases, the IOP during eye drop treatment peaks outside clinic hours [13, 14]. Moreover, the effective IOP-lowering durations vary among eye drops, which may also lead to the IOP variation. Unlike β-blockers, prostaglandin analogs (PG) and carbonic anhydrase inhibitor (CAI) lower the IOP significantly throughout 24 hours. During β-blocker treatment, the IOP is higher during daytime than at night [15–17].

When treated with multiple eye drops, combinations of drops generally flatten the IOP variation [18, 19]. Nakakura et al. found that the 24-hour IOP in patients treated with multiple eye drops tended to peak at night and that it was impossible to estimate the peak IOP based only on an IOP measured during daytime because there was no relationship between daytime and nighttime IOP [20]. In the present study, we measured 24-hour IOP variation in patients with POAG treated with triple eye drops and investigated the relationship with patient background factors including spherical equivalent.

2. Methods

Seventy-four outpatients (aged 54.6 ± 12.4 years, 37 males and 37 females) with POAG at the Department of Ophthalmology, Tokyo Metropolitan Police Hospital, Japan were studied. We randomly chose the right or left eye in the patients who had glaucoma in the both eyes. The subjects gave consent to be hospitalized for 24-hour IOP measurement. All patients were treated with three different types of eye drops: PG (latanoprost, travoprost, tafluprost, or bimatoprost), β-blocker (0.5% timolol maleate or 2% carteolol hydrochloride), and CAI (1% dorzolamide or 1% brinzolamide). The combinations of eye drops used by the patients are shown in Table 1.

The diagnostic criteria of POAG were as follows: normal open-angle; characteristic glaucomatous optic neuropathy with diffuse or focal optic rim thinning, cupping, or nerve fiber layer defects indicative of glaucoma and corresponding visual field changes according to Anderson and Patella criteria [21]; and presence of no other ocular, rhinological, neurological, or systemic disorders potentially causing optic nerve damage. Exclusion criteria were a history of cardiac or respiratory disorders; severe corneal disease, uveitis, or previous eye surgery; and concomitant use of any systemic medication that might affect the IOP.

We used the data of the patient that did not conflict with the above-mentioned exclusion criteria among the patients which have measured the IOP of 24-hour of treated with triple eye drops. Patients were hospitalized for 24-hour IOP measurement. In all patients, the IOP was measured in the sitting position by one ophthalmologist using a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) averages of 3 times at the following hours: 10:00, 13:00, 16:00, 19:00, 22:00, 1:00, 3:00, and 7:00. Five glaucoma specialists were involved in this study to measure the IOP of 74 eyes. During hospitalization, patients self-administered eye drops. For nighttime IOP measurements, patients were waken gently and walked 10–20 meters to the tonometer. The patients returned to bed immediately after the IOP measurement.

To facilitate assessment of the relationship between 24-hour IOP variation and demographic and clinical characteristics (age, difference between peak and trough IOP, baseline IOP at 10:00, and spherical equivalent refraction), we classified the patients into two groups: diurnal and nocturnal types. In diurnal type, daytime IOP (averaged IOP for 7:00, 10:00, and 13:00) was higher than the nighttime IOP (averaged IOP for 22:00, 1:00, and 3:00). Whereas nocturnal type, the nighttime IOP was higher than daytime IOP (Figure 1).

A Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) was used with program 30-2 for evaluating visual field in the patients. The mean deviation averaged across all eyes was -11.3 dB. We measured objective spherical equivalent refraction with an auto refractometer (Nidek ARK-530-A®). For statistical analysis, the repeated measures ANOVA, the Mann-Whitney U test, and two-way repeated measures ANOVA were used at a significance level of $p < 0.05$ (two-sided test). Statistical analysis was conducted using SPSS (SAS Institute, Cary, NC) and Matlab® (The MathWorks Inc Natick, MA).

3. Results

Figure 2 shows the variation of mean IOP at all time points of measurement for 74 eyes of 74 subjects treated with triple eye drops. The peak IOP was 13.5 ± 3.1 (mean $\pm$ SD) mmHg measured at 1:00, and the trough IOP was 12.6 ± 2.4 mmHg measured at 7 : 00. The trough IOP was significantly lower than the IOP at 1:00, 3:00, and 10:00 ($p = 0.0066$, 0.035, and 0.049, resp., repeated measures ANOVA).

Figure 3 shows the histograms of 24-hour IOP fluctuation defined as the difference between peak and trough IOP. The

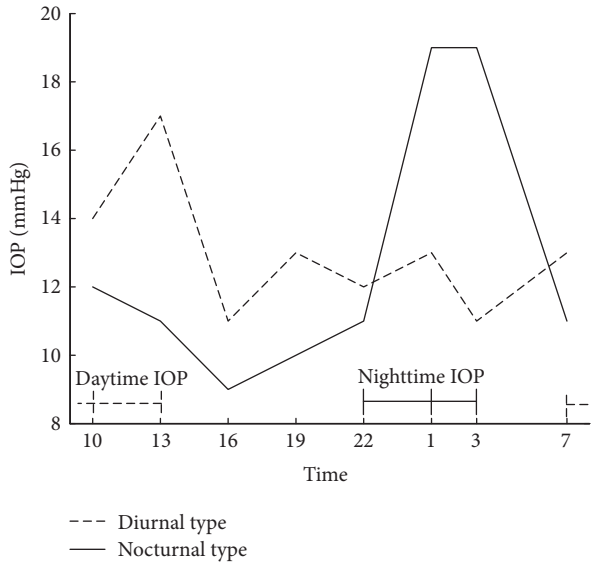

Figure 1: Typical examples of diurnal type and nocturnal type IOP profiles. Dashed line shows 24-hour IOP in a representative subject of diurnal type. In this patient, the averaged IOP for 7:00, 10:00, and 13:00 (daytime IOP) was higher than the averaged IOP for 22:00, 1:00, and 3:00 (nighttime IOP). Solid line shows 24-hour IOP of a representative subject of nocturnal type, in whom nighttime IOP was higher than daytime IOP.

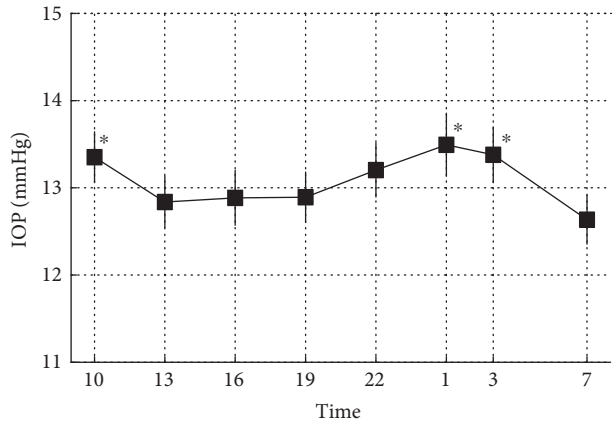

Figure 2: Mean 24-hour IOP at all time points of measurement in 74 eyes of 74 patients. Square indicates mean IOP of all eyes. The IOP at 7:00 was significantly lower than that at 10:00, 1:00, and 3:00. Error bar indicates standard deviation. *Higher than 7:00 ($p < 0.05$).

IOP fluctuation was within 10 mmHg in all subjects. Mean (± SD) 24-hour IOP variation was 3.3 ± 1.5 mmHg (95% confidence interval: 3.16–3.96 mmHg). The majority of 24-hour IOP fluctuation ranged from 2 to 6 mmHg. The 24-hour IOP fluctuation was 3 mmHg or more in 55 eyes even though all patients adhered to treatment with triple eye drops.

The histogram in Figure 4 shows the time when the peak IOP was measured in 55 eyes with IOP fluctuation of

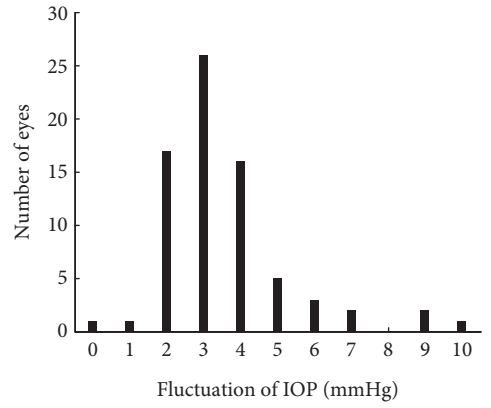

Figure 3: Distribution of 24-hour IOP variation among 74 eyes. Histogram shows the number of eyes with each variation.

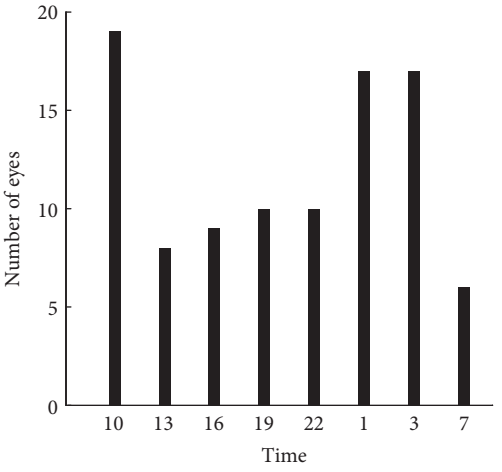

Figure 4: Time when peak IOP was measured. Histogram shows the number of eyes with each peak IOP time.

3 mmHg or more allowing repetition in one eye that showed two or more peaks (Figure 4). The peak IOP was measured in 19 eyes at 10:00 (19.8%), 17 eyes at 1:00 (17.7%), and 17 eyes (17.7%) at 3:00. Sixty eyes (62.5%) did not have peak IOP during office hours. Note that the time of peak IOP was outside clinic hours in many eyes.

We compared diurnal type to nocturnal type to assess the relationship between 24-hour IOP variation and demographic and clinical characteristics. Eyes with 24-hour IOP fluctuation of 2 mmHg or less ($n = 9$) were excluded in subsequent analyses because the aim of the subanalysis is to assess causes of the 24-hour IOP variation in the patients. Eventually, 65 eyes were analyzed; 28 and 37 eyes belonged to diurnal type and nocturnal type, respectively (Table 2).

Based on the classification, the average IOP at 10:00 in diurnal type was significantly higher than that in nocturnal type. Moreover, the spherical equivalent and IOP variation in nocturnal type were significantly greater than those in

Table 2: Comparison of background factors between diurnal and nocturnal types of IOP profile. Data are expressed as mean ± SD. Significant differences in spherical equivalent, variation of IOP and IOP at 10:00 were observed between diurnal and nocturnal types.

	Diurnal type ($n = 28$)	Nocturnal type ($n = 37$)	p value
Age (y)	51.9 ± 10.5	56.1 ± 14.1	0.18
Spherical equivalent (D)	−5.7 ± 4.0	−4.0 ± 4.0	0.014
Mean deviation (dB)	−10.8 ± 8.6	−11.7 ± 9.3	0.81
24-hour fluctuations of IOP (mmHg)	3.1 ± 1.1	4.2 ± 2.0	0.01
IOP at 10:00 (mmHg)	14.1 ± 2.4	12.7 ± 2.4	0.01

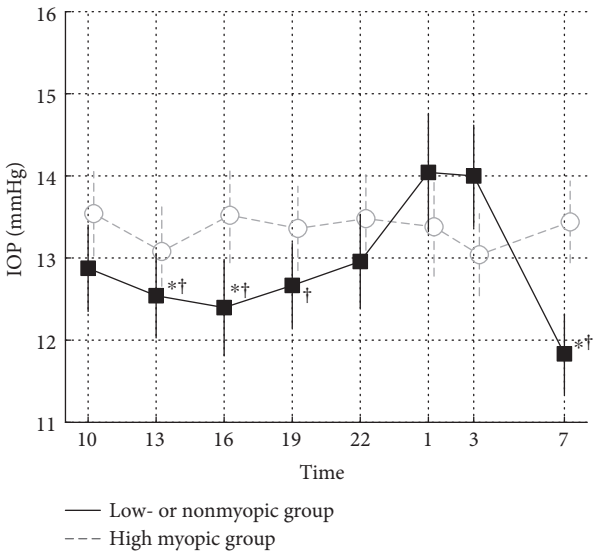

Figure 5: Comparison of 24-hour IOP variation in two groups with different spherical equivalent refraction. Gray dashed line and circles indicate mean IOP in high myopic group (HM). Black solid line and squares indicate mean IOP in low- or nonmyopic group (LNM). Error bar indicates standard deviation. *Lower than 3:00 ($p < 0.05$). †Lower than 1:00 ($p < 0.05$).

diurnal type ($p < 0.05$). There were no significant differences in age and mean deviation of HFA between diurnal and nocturnal types.

To perform a subanalysis according to spherical equivalent, we classified into three groups: high myopic, moderate myopic, and low or nonmyopic groups. We compared the 24-hour IOP variation between the high myopic (HM: less than −6D, 26 eyes) and low or nonmyopic groups (LNM: more than −2D, 24 eyes).

Figure 5 shows the mean 24-hour IOP of HM and LNM. The 24-hour IOP variation in HM was relatively small. On the other hand, the 24-hour IOP in LNM tended to increase at nighttime. There were no significant differences between two groups at all time points. Only in LNM, however, mean IOP at 13:00, 16:00, 19:00, and 7:00 was significantly lower than that at 1:00 and/or 3:00 ($p < 0.05$, two-way repeated measures ANOVA). The IOP at 3:00 was significantly higher than the IOP at 13:00, 16:00, and 07:00. Additionally, the LNM IOP at 3:00 was significantly higher than the IOP at 13:00, 16:00, 19:00, and 7:00, whereas there was no significant difference in HM group.

4. Discussion

This study determined the 24-hour IOP variation in patients treated with triple eye drops. The IOP measured in the sitting position normally peaks in the morning and declines toward the evening [10]. In patients on triple eye drop treatment, although the IOP level was higher at 10:00. Compared with other time points during the day, the peak was at 1:00 (13.5 ± 3.1 mmHg) and IOP remained at a significantly higher level at 3:00 compared to other time points.

Similar to our study, Nakakura et al. examined the 24-hour IOP variation in patients on triple eye drop treatment and found that IOP was the highest outside clinic hours in 66.2% of patients, while IOP was the lowest during clinic hours in 72.5% [20]. The present study also found that the highest IOP was outside clinic hours in 62.5% of subjects, which was in good agreement with the findings of Nakakura et al. These results suggest that triple eye drop treatment markedly changes the pattern of the 24-hour IOP variation and reduces the IOP variation, but is associated with a risk of the IOP elevation during nighttime (outside clinic hours). Moreover, Konstas et al. reported that the IOP with multiple eye drops elevated at night, and the peak IOP was 14.2 ± 3.8 mmHg at 2:00 measuring the 24-hour IOP [22].

The mechanism by which IOP tended to increase at nighttime in patients treated with triple eye drops is not known. Since the parasympathetic nervous system becomes dominant during the night, the IOP-lowering effect of β-blocker may be reduced during the nighttime, resulting in a tendency of the IOP increase at night [16, 23]. However, Gulati et al. examined the effects of a PG, β-blocker, and CAI on the aqueous humor dynamics in patients with ocular hypertension and found that all agents had a smaller effect during the night than during daytime [24]. It is possible that individual IOP-lowering effects of PG, β blocker, and CAI are attenuated during nighttime, and concomitant use of these three agents may have further reduced the effect at night. Larsson et al. also reported that the effect of PG peaks 10–12 hours after administration [25]. Thus, the IOP-lowering effect of PG could be suboptimal during nighttime in patients who were administered PG eye drop at night.

In this study, subjects with high myopia (HM) and those with low or no myopia (LNM) were compared in a subanalysis. There were no significant differences in the IOP between the two groups at all time points, but the daytime IOP tended

to be lower in the LNM group than in the HM group. In addition, a significant rise in the IOP was observed during the night in the LNM group. Previous literatures have suggested that IOP tends to be higher in myopic patients who have a long eye axis, than in emmetropic or hyperopic patients who have a short eye axis [26, 27]. We found similar results during daytime in patients on triple eye drop treatment, but the IOP at 1:00 and 3:00 was higher in the LNM group.

Loewen et al. studied three groups of healthy individuals with spherical equivalent $\geq$ +1D (hyperopia), −2D to 0 (emmetropia), and $\leq$−3D (myopia), comparing visual field during daytime in sitting position and during nighttime in supine position, as well as the 24-hour IOP in supine position [11]. They found more prominent variation in the hyperopia group than in the other groups, and nighttime increases in IOP in the former group. Similarly, we found a tendency toward nighttime IOP increase in patients with hyperopia, even though all subjects were on medications and IOP was measured in the sitting position.

The mechanisms underlying nighttime IOP increase in hyperopia individuals remain unclear, regardless of nontreatment and treatment. Read et al. reported that the eye axis length reaches a minimum during the night and that the eye axis length correlates with daily IOP variation [28]. Such circadian changes in the eye axis length may have induced nighttime IOP increases in hyperopia individuals in whom the eye axis length is already short. Although all patients were examined by gonioscopy and those with synechial angle closure were excluded from this study, it is possible that the nonmyopic subjects with a shallow anterior chamber were prone to have functional angle closure causing increases in outflow resistance and nighttime IOP.

There are some limitations to this study. This study examined 24-hour IOP variation in patients treated with triple eye drops, but subjects with progressive visual field loss despite therapy may have been included. Other limitations include variations in eye drop type and number of eye drop instillations among subjects. In this study, we measured IOP in the sitting position at all time points. Significant elevation of IOP in the supine position during sleep at night has been reported [29–31]. There is no doubt that measuring IOP in different measurement positions in daily life is important in studying 24-hour IOP variation. However, a Goldmann applanation tonometer is still considered to give a greater precision and has remained the clinical standard for the care of glaucoma patients, and Liu et al. reported IOP variation of the sitting position to predict the IOP variation in the supine position [32]. We think that it is meaningful to know the tendency of nighttime IOP by sitting position measurement with triple eye drop treatment. Further studies are needed to answer the following intriguing questions: how IOP changes depending on the measurement position in daily living and how nighttime IOP elevation impacts the progression of visual field loss.

5. Conclusions

We measured 24-hour IOP variation in POAG patients treated with triple eye drops (PG, β-blocker, and CAI). The peak IOP was observed outside clinic hours in many eyes. Furthermore, our study showed that nighttime IOP increases even during triple eye drop treatment, especially in patients with spherical equivalent of −2D or less. Because changes in IOP could be a potential risk factor for progression of visual field loss [33, 34], careful observation is required especially for low- or nonmyopic patients who are at risk of nighttime IOP elevation even during triple eye drop treatment.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Clinical Study

A Comparative Study: The Use of Collagen Implant versus Mitomycin-C in Combined Trabeculotomy and Trabeculectomy for Treatment of Primary Congenital Glaucoma

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Purpose. To compare Ologen implant versus mitomycin-C (MMC) in combined trabeculotomy and trabeculectomy as a treatment of primary congenital glaucoma. *Setting*. Sohag University Hospital, Egypt. *Design*. A prospective comparative study. *Methods*. Thirty-four eyes of twenty-one patients with primary congenital glaucoma were included in this study. All patients were subjected to preoperative evaluation including complete anterior segment examination under general anesthesia. The patients were divided into two groups: patients of the first group (group A) underwent combined trabeculotomy and trabeculectomy with Ologen implantation while those of the second group (group B) underwent combined trabeculotomy and trabeculectomy with MMC application. *Results*. Postoperatively, the IOP in group A was as follows: 8 eyes developed IOP levels less than 14 mmHg (complete success), 3 eyes had levels between 14 and 16 mmHg (accepted result), 2 eyes had levels between 16 and 20 mmHg (guarded result), and only 2 eyes showed levels exceeding 20 mmHg (failed procedure), while in group B, 7 eyes showed complete success, 3 eyes had accepted result, 3 eyes had guarded result, and 2 eyes had failed procedure. *Conclusion*. Ologen is a safe and effective adjuvant in combined trabeculotomy and trabeculectomy for treatment of primary congenital glaucoma.

1. Introduction

Congenital glaucoma (CG) is a major cause of blindness in children, despite its low incidence (1 : 10,000 births). It may be isolated (primary congenital glaucoma) or associated with other developmental anomalies, either systemic or ocular. The eyes with primary congenital glaucoma have an isolated maldevelopment of the trabecular meshwork not associated with other developmental ocular anomalies or ocular diseases that can raise intraocular pressure. It is the most common glaucoma of infancy, occurring in about 1 : 30,000 live births [1].

Primary congenital glaucoma (PCG) is a bilateral disease in about 75% of cases, with males accounting for approximately 65% of cases. Most cases are sporadic in occurrence, with no evident hereditary pattern. In approximately 10% of cases, a hereditary pattern is evident; it is believed to be autosomal recessive. Many authors believe that the inheritance pattern is polygenic [2].

Congenital glaucoma is essentially a surgical disease, in which surgery must be performed as early as possible. Goniotomy and trabeculotomy are usually the first procedures of choice. Both are safe and have a low incidence of complications. When goniotomies or trabeculotomies fail or are impossible, trabeculectomy is the usual alternative. Glaucoma drainage implants, nonpenetrating surgery, and cyclodestructive procedures are other options [3, 4].

Combined trabeculotomy and trabeculectomy is the most common procedure for congenital glaucoma in our locality because many cases present late with advanced disease. It allows high chance of success from the first

intervention and reduces the need for secondary intervention which carries high failure rate.

MMC is a chemotherapeutic agent that has been widely used intraoperatively to enhance the success rate of glaucoma filtration surgery [5–8]. However, it is frequently accompanied with short- and long-term postoperative complications such as hypotony, bleb leaks, cataract formation, avascular filtering blebs, thinning of the conjunctiva, subsequent blebitis, choroidal effusions, maculopathy, and endophthalmitis [9]. Therefore, there is still a need for other adjuvants with similar or better efficacy and less complications.

Recently, several tissue-engineered biodegradable implants have been introduced to augment success of trabeculectomy with less complications than MMC [10].

Ologen (Aeon Astron Europe BV, Leiden, The Netherlands) is a biodegradable collagen-glycosaminoglycan (GAG) implant which decreases early postoperative scarring and prevents collapse of the subconjunctival space [11–13]. It is a disc-shaped porcine-derived collagen matrix that is inserted under the conjunctiva at the time of trabeculectomy, acting as a reservoir and helping to mechanically separate the conjunctiva from episcleral surface preventing adhesions between them. After implantation, the device should completely degrade within 90–180 days [14, 15].

This study aims to verify the safety and efficacy of Ologen implant compared to MMC application as an adjuvant in the surgical treatment of primary congenital glaucoma.

2. Patients and Methods

Thirty-four eyes of twenty-one patients with primary congenital glaucoma were included in this study. Thirteen patients underwent surgery in their both eyes and eight patients had surgery in one eye. Approval from ethical committee of Sohag Faculty of Medicine was obtained, and a written informed consent was obtained from the parents of all children after explaining the benefits and risks of the procedure.

Surgery was done by 4 surgeons to all infants and children with primary congenital glaucoma admitted to the Department of Ophthalmology in Sohag University Hospital in the period from April 2014 to October 2015.

The inclusion criteria of the study were patients aged less than three years with primary congenital glaucoma as evidenced by history of lacrimation, photophobia, blepharospasm, and/or eye enlargement in addition to the signs of elevated IOP, increased corneal diameters, corneal haze, and/or increased cup-to-disc ratio, while the exclusion criteria included patients with secondary glaucoma; patients with other ocular pathologies, for example, congenital cataract; patients with previous ocular surgery including glaucoma surgery; and patients who could not adhere to the follow-up schedule (lost from follow-up for more than two visits).

All patients were subjected to preoperative evaluation including history taking from the parents; the data collected included age, sex, main symptoms, family history, and medical history. The patients were referred for full systemic evaluation by a pediatrician to rule out any associated systemic anomalies. Under general anesthesia, complete anterior segment examination was done including measurement of the corneal diameters with surgical caliper (*vertical and horizontal*) and measurement of IOP using Perkin's applanation tonometer. Indirect fundus examination and refraction were done if the corneal clarity permits. Preoperative ocular ultrasonography was done for cases in which the fundus cannot be seen.

The patients were divided into two equal groups, each included 17 eyes (odd numbers for the first group and even numbers for the second group). In the first group (OLO group, group A), the patients had combined trabeculotomy and trabeculectomy with Ologen implantation while in the second group (MMC group, group B), the patients had combined trabeculotomy and trabeculectomy with MMC application.

3. Surgical Techniques

All surgeries were done under general anesthesia.

3.1. Group (A): Combined Trabeculotomy and Trabeculectomy with Collagen Matrix Implant (OLO Implant). Antiseptic solution (povidone-iodine 7.5%) was applied to the periocular area, and a sterile ophthalmic surgical drape was applied.

The technique started with corneal traction suture including partial thickness at 12 o'clock using 6-0 silk and with creating a superior fornix-based conjunctival flap by dissection of the conjunctiva and Tenon's fascia to show bare sclera. Compression hemostasis was attained by cotton sponge compression or gentle diathermy if needed.

A 4×4 mm triangular limbal-based partial-thickness scleral flap was dissected extending into about 1 mm of the clear cornea leaving about two-thirds of the scleral thickness as a scleral bed. A radial incision was then carried out about 2 mm from the limbus at the junction between white and bluish zones of the sclera to enter the Schlemm's canal, evidenced by a gush of aqueous humour and/or blood, its characteristic pearly white color and appearance of transverse fibers running at the floor of the canal. Trabeculotomy was then performed using the internal arm of Harm's trabeculotome probes, first to the left and then to the right to complete about 100–120° of the circumference. Then, a 2×2 mm trabecular meshwork block was excised and a peripheral iridectomy was then performed.

A cylindrical collagen matrix implant (1 mm in height and 12 mm in diameter) was used. The implant was divided unequally into two parts: a smaller part and a larger part. The smaller part was implanted under the scleral flap over the scleral bed, and the scleral flap was closed with one 10-0 nylon suture leaving the two ends of the smaller part bulging from both sides of the scleral flap. The remaining larger part was inserted in the sub-Tenon's space over the scleral flap, and then, a watertight closure of the conjunctival flap was done with continuous buried 10.0 nylon stitches.

3.2. Group (B): Combined Trabeculotomy and Trabeculectomy with MMC Application. The technique was similar to that of the first group except that four sponges soaked with MMC with a concentration of 0.4 mg/ml were placed deeply in the

subconjunctival space as follows: one sponge at 12 o'clock, two sponges on both sides of superior rectus position, and the fourth sponge was applied between the scleral bed and the scleral flap and left for 2 minutes followed by irrigation of the eye with balanced salt solution. The scleral flap was closed with one tight 10-0 nylon suture at its apex and two 10-0 nylon sutures at both sides of the scleral flap.

The postoperative treatment of all patients included moxifloxacin 0.5% eye drops 5 times daily for 2 weeks and prednisolone acetate 1% eye drops five times daily for one week, three times daily for another week, and once daily for a final week, as well as cyclopentolate eye drops twice daily for one week.

4. Schedule of Follow-Up Visits

All patients were seen daily for the first few days looking for eye injection, corneal edema, anterior chamber formation, and red reflex; then, postoperative visits were scheduled at one week; two weeks; and one, two, four, six, nine, and twelve months. Patient examination was performed under general anesthesia for IOP, corneal clarity and diameters, bleb status, fundus examination, and postoperative complications.

5. Statistical Analysis

Data was analyzed using SPSS computer program version 16.0. (SPSS Inc, Chicago, Intl). The data were tested for normality using Shapiro-Wilk test which was insignificant indicating the use of parametric tests as data was normally distributed. Quantitative data were expressed as means ± standard deviation and were analyzed by using *t*-tests and paired samples *t*-test. Independent samples *t*-test was used to assess statistical significance between both groups in predetermined parameters. While paired samples *t*-test was used to assess statistical significance within the same group. Chi-square (χ^2) test and Fisher's exact tests were used for comparison regarding qualitative variables. A 5% level was chosen as a level of significance in all statistical tests used in the study.

6. Results

This study included thirty-four eyes of twenty-one patients having primary congenital glaucoma. Thirteen patients had surgery in both eyes and eight patients in only one eye. These eyes were divided equally into two groups: seventeen eyes for the OLO group (group A) and seventeen eyes for the MMC group (group B). Three eyes did not complete the follow-up schedule and lost from follow-up for more than two visits, so they were excluded from the study. In addition, intraoperative inadvertent scleral perforation occurred in one case, and thus, such case was excluded from the study. Finally, thirty eyes of eighteen patients fulfilled the inclusion criteria. Fifteen eyes of nine patients (six bilateral and three unilateral) were included in each group for this study.

The preoperative characteristics did not differ significantly between the 2 groups. In group A, there were 7 (77%) boys and 2 (23%) girls while in group B, 6 (66%) boys and 3 (33%) girls. The mean age was 9 ± 4 months in group A and 8 ± 5 months in group B with a *P* value of 1.00.

The mean preoperative IOP was 30.5 ± 2.6 mmHg in group A and 31.1 ± 3.3 mmHg in group B with a *P* value of 0.50. The mean TCD was 12.5 ± 0.50 mm in group A and 13 ± 1 mm in group B with a *P* value of 0.21. Corneal edema was present in 13 eyes (86.7%) of group A and in 11 eyes (73.3%) of group B.

7. Postoperative Results

7.1. The Intraocular Pressure. According to the level of IOP, the patients in each group were included in one of the four subgroups as follows:

(i) Subgroup I: IOP range was less than or equal to 14 mmHg. The surgery was successful especially if associated with improvement of symptoms, stable transverse corneal diameter, and improvement of corneal haze and edema. Cases complicated with early bleb leakage and hypotony were excluded from this subgroup.

(ii) Subgroup II: IOP range was between 14 and 16 mmHg reflecting accepted results with remote possibility of additional surgical procedures in the future.

(iii) Subgroup III: IOP level was between 16 and 20 mmHg reflecting guarded results with the possibility of the need for antiglaucoma medication or even additional surgical procedures in the future specially if there was persistence of symptoms or corneal edema.

(iv) Subgroup IV: IOP level exceeded 20 mmHg reflecting unsuccessful procedure with the need for another surgical procedure to control the IOP.

8. Group A (OLO Group)

The mean preoperative IOP was 30.5 mmHg, and the mean postoperative IOP at the end of the study was 15.4 mmHg with a *P* value of 0.00 indicating a highly significant reduction in the mean IOP level. The mean reduction of IOP was 15.1 mmHg.

One week postoperatively, 12 eyes (80%) had IOP levels less than or equal to 14 mmHg; one eye showed IOP level between 14 and 16 mmHg while the remaining two eyes had IOP levels between 16 and 20 mmHg.

By the end of the study (after one year), 8 eyes (53.3%) developed IOP levels less than 14 mmHg, that is, complete success; three eyes (20%) had IOP levels ranging between 14 and 16 mmHg, that is, accepted result; two eyes (13.3%) had IOP levels ranging between 16 and 20 mmHg, that is, guarded result; and only two eyes (13.3%) showed IOP levels exceeding 20 mmHg, that is, failed procedure.

9. Group B (MMC Group)

The mean preoperative IOP was 31.1 mmHg, and the mean IOP at the end of the study was 17.3 mmHg with a *P* value

Table 1: Results of IOP during the follow-up period in both groups.

Follow-up visits	Group A (OLO)				Group B (MMC)				P value
	Subgroup (I)	Subgroup (II)	Subgroup (III)	Subgroup (IV)	Subgroup (I)	Subgroup (II)	Subgroup (III)	Subgroup (IV)	
1st week	12 (80%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	14 (93.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0.399
2nd week	12 (80%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	13 (86.7%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0.35
1st month	12 (80%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	12 (80%)	2 (13.3%)	0 (0.0%)	1 (6.7%)	0.85
2nd month	10 (66.7%)	3 (20%)	1 (6.7%)	1 (6.7%)	8 (53.3%)	3 (20%)	1 (6.7%)	1 (6.7%)	0.523
4th month	8 (53.3%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	9 (60%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	0.511
6th month	9 (60%)	2 (13.3%)	3 (20%)	1 (6.7%)	5 (33.3%)	5 (33.3%)	4 (26.7%)	1 (6.7%)	0.323
9th month	8 (53.3%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	5 (33.3%)	4 (26.7%)	4 (26.7%)	2 (13.3%)	0.263
12th month	8 (53.3%)	3 (20%)	2 (13.3%)	2 (13.3%)	7 (46.7%)	3 (20%)	3 (20%)	2 (13.3%)	0.471

Table 2: Bleb height during follow-up in both groups.

	OLO group			MMC group		
	1st month	At 6th month	At 12th month	1st month	At 6th month	At 12th month
Flat	1 (6.7%)	3 (60%)	4 (26.7%)	9 (60%)	6 (40%)	7 (46.7%)
Moderate elevation	3 (20%)	5 (33.3%)	6 (40%)	4 (26.7%)	5 (33.3%)	4 (26.7%)
Well formed	11 (73.3%)	7 (46.7%)	5 (33.3%)	2 (13.3%)	4 (26.7%)	4 (26.7%)

of 0.00 indicating a highly significant reduction in IOP level. The mean reduction of IOP was 13.9 mmHg.

One week postoperatively, 14 eyes (93.3%) had IOP levels less than or equal to 14 mmHg; one eye (6.7%) showed IOP level between 16 and 20 mmHg.

By the end of the study, 7 eyes (46.7%) developed IOP levels less than 14 mmHg, that is, complete success; three eyes (20%) had IOP levels ranging between 14 and 16 mmHg, that is, accepted result; three eyes (20%) had IOP levels ranging between 16 and 20 mmHg, that is, guarded result; and only two eyes (13.3%) showed IOP levels exceeding 20 mmHg, that is, failed procedure.

During the whole follow-up period, there was statistically insignificant difference between both groups with P values of 0.399, 0.35, 0.85, 0.523, 0.511, 0.323, 0.263, and 0.471 for follow-up visits (Table 1).

10. Corneal Diameters

The mean TCD was 12.5 ± 0.50 mm in group A and 13 ± 1 mm in group B with a P value of 0.21 while the average postoperative TCD at the end of the study was 13.01 mm in group A and 13.34 mm in group B (P value = 0.466; statistically insignificant). In group A, TCD was stable in 8 eyes (53%) and increased by average 0–0.5 mm in 7 eyes (47%). In group B, TCD was stable only in 5 eyes (33%) and increased by 0.5–1 mm in 10 eyes (66%).

11. Corneal Clarity

Corneal edema was present in 13 eyes (86.7%) of group A and in 11 eyes (73.3%) of group B. By the end of the follow-up period, 9 eyes (60%) of group A and 7 eyes (46.7%) of group B showed a clear cornea. 5 eyes (33.3%) of group A and 6 eyes (40%) of group B showed persistent corneal haze. Only one eye (6.7%) in group A and two eyes (13.3%) in group B developed permanent corneal opacification.

12. Bleb Evaluation

All cases of both groups were subjected to surgery at 12 o'clock, so in all cases, the bleb was present superiorly and the bleb height was evaluated under a surgical microscope under general anesthesia (Table 2).

Bleb vascularity is shown in Table 3.

13. Postoperative Complications

The frequency of postoperative complications did not significantly differ between the two groups (Table 4).

No allergic reaction to the OLO, matrix extrusion, or conjunctival erosion was noted in the OLO group. No cases of endophthalmitis were encountered in both groups. Only 2 cases (13.3%) in the OLO group necessitated the use of antiglaucoma medications during the follow-up period in the form of B-blockers and dorzolamide to control IOP level and other parameters. While in MMC, similar medications were to be prescribed in 4 cases (26.7%).

In the OLO group, only one case (6.7%) with IOP exceeding 21 mmHg failed to be controlled on two antiglaucoma medications necessitated a secondary surgical intervention in the form of combined procedure using MMC. Unfortunately, the second intervention also failed to halt the progression, and the case is still under follow-up waiting for glaucoma shunt surgery.

On the other hand, two cases (13.3%) in the MMC group necessitated a secondary surgical intervention in the form of combined procedure using MMC. The average IOP level

Table 3: Bleb vascularity during follow-up in both groups.

	OLO group			MMC group		
	1st month	At 6th month	At 12th month	1st month	At 6th month	At 12th month
Avascular	0 (0.00%)	2 (13.3%)	4 (26.7%)	1 (6.7%)	3 (20%)	5 (33.3%)
Normal vascularization	10 (66.7%)	11 (73.3%)	10 (66.7%)	11 (73.3%)	9 (60%)	8 (53.3%)
Vascular inflammation	5 (33.3%)	2 (13.3%)	1 (6.7%)	3 (20%)	3 (20%)	2 (13.3%)

Table 4: Frequency of postoperative complications in both groups.

Complication	Hypotony	Corneal scarring	Hyphema	Choroidal detachment	Failed procedure
OLO group	0 (0.0%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	2 (13.3%)
MMC group	3 (20%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)
P value	0.072	0.559	1	0.559	1

reached 17 mmHg in one case and 19 mmHg in the other case with the use of antiglaucoma medication.

Regarding hyphema (two eyes in each group), it improved conservatively by mydriatics and steroids in all cases within 7 days.

In MMC, one of 3 cases complicated with hypotony and early bleb leakage was managed conservatively by mydriatics and withdrawal of steroids, while the other two cases necessitated surgical intervention in the form of tight resuturing of the conjunctival flap to prevent bleb leakage.

No cases of hypotony or early bleb leakage were encountered in the OLO group. Three cases encountered choroidal detachment (one eye in the OLO group and two eyes in the MMC group). All cases were managed conservatively by mydriatics and steroids.

Regarding corneal scarring, only one eye (6.7%) had postoperative scarring in the OLO group while two eyes (13.3%) in the MMC group.

14. Discussion

Congenital glaucoma is a major cause of blindness in children, despite its low incidence (1 : 10,000 births) [1]. In this study, a comparison between Ologen (group A) and MMC (group B) application in combined trabeculotomy and trabeculectomy for treatment of primary congenital glaucoma was done to verify efficacy and safety of Ologen.

As regards preoperative characteristics of the patients, there was no significant difference between the 2 groups. Postoperatively, the two groups showed a highly significant reduction (P value < 0.01) in IOP levels.

This significant reduction in both groups can be explained by the surgical procedure which was combined trabeculotomy and trabeculectomy. However, this level of reduction in the mean IOP cannot be relied on as an indicator of success due to presence of cases with very high preoperative IOP on the one hand and cases complicated with bleb leakage and hypotony on the other hand.

Although the frequency of postoperative complications especially hypotony was higher in the MMC group than the OLO group, the difference does not reach statistical significance probably due to the small sample size of the study.

Ologen implant could have a tamponading effect and provide a controlled drainage of aqueous. In addition, the implant might have a valve-like mechanism through its two parts: subscleral and subconjunctival parts; when they were inflated with aqueous, more pressure on the sclera flap would be exerted decreasing aqueous flow and vice versa.

After its success in animals [16, 17], many studies tried to verify the efficacy and safety of Ologen in trabeculectomy for primary open-angle glaucoma and other glaucomas of adults [18–22]. However, few studies verified it in primary congenital glaucoma.

In his pilot study, Hamdi [23] used subconjunctival Ologen implant as an adjuvant to subscleral trabeculectomy in 3 cases of primary congenital glaucoma. After a follow-up of 6–8 months, results were as follows: "satisfactory success" for the first case, "full success" for the second case, and "poor success" for the third case. He reported that the advantages of this implant are its safety over MMC and its ease of use. Ologen would prevent secondary interference such as needling after the use of antifibrotic agents and also would avoid tube-related complications.

Unlike Hamdi, we used Ologen both subconjunctivally and subsclerally to augment effects of combined trabeculotomy and trabeculectomy and avoiding risks of MMC and we followed up cases for one year.

In his study over twenty eyes of 15 patients with primary congenital glaucoma, Hafez [24] divided cases into two groups. The first group (MMC group) included 10 eyes and was subjected to trabeculectomy with MMC. The second group (OLO group) included 10 eyes and was subjected to trabeculectomy with a collagen matrix implant (Ologen). The postoperative IOP level was classified into four groups (>21, >17–21, 15–17, and <15 mmHg). At the end of the sixth postoperative follow-up month, in the MMC group, only 10% of eyes achieved the target IOP, 10% of eyes had failed surgery, and 80% of eyes had IOP ranging from 15 to 21 mmHg. However, in the Ologen group, 40% of eyes achieved the target IOP, 60% of eyes had IOP ranging from 15 to 21 mmHg, and there were no failed surgeries. In terms

of complications, the MMC group had a higher rate of complications than the Ologen group in the form of early hyphema, bleb leakage, hypotony, and choroidal detachment.

Unlike Hafez, we used Ologen with combined trabeculotomy and trabeculectomy and we followed up cases for one year.

Elmallah et al. [25] compared trabeculotomy with deroofing of Schlemm's canal augmented with subconjunctival Ologen implant (study group) and conventional trabeculotomy (control group) in primary congenital glaucoma and found that the success rate was higher in the study group (100%) than in the control group (75%) after a 6 month follow-up period.

Unlike Elmallah et al., this study used Ologen (both subscleral and subconjunctival) with combined trabeculotomy and trabeculectomy and cases were followed up for one year with a success rate of about 87%.

The major limitations of this study are the small sample size and the relatively short follow-up period. Future studies should be carried out on larger samples and for longer follow-up periods to establish the long-term safety and efficacy of this new device. Ologen implant can be also tried in cases with secondary glaucoma, resistant glaucoma, and congenital glaucoma associated with other ocular congenital anomalies.

In conclusion, this study suggests that the collagen matrix implant (Ologen) is a safe and effective adjuvant in combined trabeculotomy and trabeculectomy for treatment of primary congenital glaucoma. Although there was insignificant difference between Ologen and MMC as regards efficacy, Ologen appears to be safer than MMC regarding postoperative complications especially postoperative hypotony.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

The Effect of Corneal Refractive Surgery on Glaucoma

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Laser-assisted refractive procedures have become very popular in the last two decades. As a result, a "generation" of patients with altered corneal properties is emerging. These patients will require both cataract extraction and glaucoma follow-up in the future. Since the glaucoma examination largely depends on the corneal properties, the reshaped postrefractive surgery cornea poses a challenge in the diagnosis, follow-up, and management of the glaucomatous patient. In order to overcome this problem, every patient who is planned to undergo corneal refractive surgery must have a thorough glaucoma examination in order for the ophthalmologist to be able to monitor their patients for possible glaucoma development and/or progression. Some examinations such as tonometry are largely affected by the corneal properties, while others such as the evaluation of the structures of the posterior pole remain unaffected. However, the new imaging modalities of the anterior segment in combination with the most recent advances in tonometry can accurately assess the risk for glaucoma and the need for treatment.

1. Introduction

Laser-assisted refractive corrections constitute a large part of the ophthalmic surgeries that take place every year. It is estimated that about 4 million refractive procedures were performed in 2014 throughout the world. On the other hand, glaucoma is an optic neuropathy, the incidence of which is increasing steadily over time. In 2013, the number of glaucoma patients was estimated at about 64.3 million and is expected to reach 118.3 million by 2040 [1]. Given the frequency of refractive corrections and the incidence of glaucoma in the general population, it becomes necessary for the ophthalmologist to assess the risks of a laser-assisted refractive operation in a glaucoma patient or a patient at a high risk of developing glaucoma in the future.

2. Preoperative Assessment

Every patient who is planned to undergo laser-assisted refractive correction should be evaluated for the risk of developing glaucoma in the future. Among others, the following factors should be taken into consideration.

2.1. Family History of Glaucoma. Epidemiological studies have shown that people with familiar predisposition for glaucoma (especially with first-degree relative) have increased risk of developing ocular hypertension (OHT) and glaucoma. Moreover, these individuals tend to develop glaucoma/OHT at a younger age than the general population [2, 3]. The assessment of the presence of glaucoma in a patient's family is therefore of great importance in order to estimate the risk of developing glaucoma in the future.

2.2. Intraocular Pressure (IOP). Elevated IOP remains the most important, modifiable, risk factor for developing glaucoma [4, 5]. However, a single IOP measurement is not sufficient to assess the actual risk of glaucoma, especially when there are other coexisting risk factors. A better understanding of the characteristics of the IOP (average IOP, highest reading, and diurnal fluctuation) is achieved by taking more than one measurements of the IOP in a 24-hour period. Large diurnal fluctuations of the IOP and/or IOP asymmetry between the two eyes are an indication of increased likelihood of developing glaucoma [6, 7].

2.3. Myopia. Myopia is a risk factor of developing glaucoma, and most patients undergoing refractive surgery are potentially glaucoma patients. High myopes (>6.00 D) have a higher risk [8]. Furthermore, tilted discs and peripapillary

atrophy are more often seen in high myopes and this can complicate the clinical assessment of the glaucomatous optic neuropathy and monitor changes of the disc structure and the retina over time. As the modern imaging tools do not include high myopes in their database (high myopes are rather excluded), the measurements that they provide are unreliable. In these cases, preoperative photography of the disc is of great value.

2.4. High Vertical Cup-to-Disc Ratio. Although the cup-to-disc ratio in the vertical axis shows great diversity, a high vertical C/D ratio is a risk factor of developing glaucoma [9]. The parameters of the optic disc and the thickness of peripapillary layer of nerve fibers play a pivotal role in the postoperative follow-up of patients who have undergone refractive surgery.

2.5. Central Corneal Thickness. It is well known that a thin cornea is not only a limiting factor for laser-assisted surface ablations but also an independent risk factor for developing glaucoma [9, 10].

2.6. Race. People of Afro-Caribbean origin develop open-angle glaucoma more often and at an earlier age than white people [11], although this may be partly due to the fact that black people have thinner corneas [12].

2.7. Other Ophthalmic Diseases. Pseudoexfoliation syndrome [13–15] and pigment dispersion syndrome [16] are known risk factors for secondary open-angle glaucoma. A study of 12 patients (22 eyes) with pigment dispersion syndrome showed that its presence does not affect the results of refractive surgery, but the authors indicate that the final refractive outcome in patients who receive topical antiglaucoma medication before surgery is less predictable and the healing process of the corneal wound can last longer [17].

2.8. Hypermetropia. Hypermetropes are more likely to have narrow anterior chamber angles and a case of acute angle closure after LASIK in a hypermetropic patient has been reported [18]. Preoperative gonioscopy will help the surgeon to recognize patients with narrow angles.

2.9. Previous Antiglaucoma Procedure. Photorefractive keratectomy (PRK) is the safest surgical option in patients with previous antiglaucoma filtering operation [19]. The creation of the corneal flap with the mechanical keratome or the femto-second laser (docking) during LASIK may damage the filtering bleb and compromise its function. The new refractive lenticule extraction surgery still requires docking of the femto-laser operating system on the eye and should be carefully used in eyes with thin blebs.

2.10. Visual Fields. Preoperative visual fields help the surgeon identify the following:

(i) The presence of established glaucomatous damage

(ii) The extent of glaucomatous damage

(iii) The risk of developing glaucoma. Patients with high PSD have a greater chance of developing glaucoma, even in the absence of visual fields scotomas [20]. Consequently, the preoperative examination of the visual fields, especially in patients with predisposing factors for glaucoma, is a useful tool for the future monitoring of refractive patients.

2.11. Modern Imaging Modalities. Modern imaging methods (OCT, HRT, and GDx) provide quantitative analysis of the peripapillary optic nerve fibers at a particular distance from the center of the optic disc. They also provide information for several structural parameters of the optic nerve head. In order to differentiate between the disc cup and the nerve fiber rim, they use a reference plane. The structures above the reference plane are read as the rim of the nerve fibers, and the structures below it are recognized by the device as the disc cup. The advantages include objective and reproducible measurements that can be compared with future measurements. The disadvantage is that their databases (although constantly enriched) include limited number of people, while "unusual" discs (tilted, high ametropias) are excluded from the databases. Unfortunately, many candidates for refractive surgery have optic discs with "unusual" appearance that cannot be meaningfully compared with the "normal" optic discs of the databases. In these cases, the digital photographing of the optic disc and the comparison with future photos will give valuable information about the changes of both the optic nerve and retinal nerve fibers.

The red-free imaging of the optic disc is as valuable in differentiating between normal and glaucomatous patients as the OCT (optical coherence tomography), the SLP (scanning laser polarimetry), and the CSLO (confocal scanning laser ophthalmoscope) [21–24].

3. Intraoperative Risk Factors for Glaucoma Progression

During the corneal flap creation in LASIK, the intraocular pressure can go as high as 90 mmHg [25, 26]. The effect of high IOP on the vascular perfusion of the retina has been studied experimentally in pigs but not in glaucoma patients. Research has shown that increased IOP significantly lowers the blood flow through the vessels. The point at which the flow stops completely depends not only on the level of the IOP but also on the blood pressure as well [27]. LASIK surgery does not seem to affect the structure and function of the optic nerve (visual fields, color perception, contrast sensitivity, and pupillary reflex) despite the transient significant elevation of the IOP during surgery [28]. Additionally, it has not been shown that the LASIK affects the structure of the optic nerve or the thickness of the layer of nerve fibers [29–31]. Some studies have reported a reduction of the nerve fiber layer after LASIK [32] with the SLP technology used by the GDx machines, but these effects are probably due to the change of the corneal birefringence and are not real damage of the retinal nerve fibers [33–35]. The new GDx machines with enhanced corneal compensator (ECC) seem to overcome this issue [36].

However, cases of ischaemic optic neuropathy following LASIK and epi-LASIK that can cause permanent damage to the optic nerve have been reported [37–39].

The visual fields, as assessed by automated static perimetry, do not seem to be affected after refractive surgery in the glaucoma and normal population [40]. Nevertheless, there have been reports of visual field deterioration in people with and without glaucoma [41, 42]. It is possible that a small group of glaucoma patients are prone to develop optic nerve damage following an elevation of the IOP during LASIK, but the visual field defects are either very mild or masked by the learning effect of the visual field examination [40]. There have also been reports of loss of the contrast sensitivity and scotoma development from the transition zone [43, 44].

In summary, although the sudden increase of the IOP during LASIK surgery does not appear to affect significantly the structure and function of the optic nerve, it is recommended that the PRK is the preferred method of refractive surgery in the case of the glaucoma patient [19].

4. Postoperative Patient Assessment

4.1. The Effect of the Central Corneal Thickness on the Measurement of the IOP. Goldmann applanation tonometry is still the gold standard method of measuring the IOP. This tonometer was first described by Hans Goldmann and Theo Schmidt in 1957 [45], and it is based on the Imbert-Fick principle.

Both PRK [46–48] and LASIK [49–52] cause a reduction of the postoperative IOP. This reduction (and consequently the clinical underestimation of the actual postoperative IOP) depends on the depth of the ablation and the preoperative IOP. The deeper the ablation and the higher the preoperative IOP, the greater the postoperative reduction of the IOP will be. In addition, the myopic refractive surgery causes larger underestimation of IOP compared to the hypermetropic corrections which are thought to cause negligible IOP change. The postoperative reduction of the IOP is due to the thinning of the corneal stroma, the change in corneal curvature, the instability of the corneal flap (LASIK) [50, 51], and the removal of the Bowman's layer (PRK) [46]. In order to calculate the reduction of the postoperative IOP, Kohlhaas et al. [51] proposed an algorithm that computes the actual IOP after myopic LASIK [IOP (real) = IOP (measured) + (540 − CCT)/71 + (43 − K − value)/1.7 + 0.75 mmHg], where IOP (real) is the actual IOP; IOP (measured) is the measured IOP; CCT is the central corneal thickness postoperatively; and K is the average of keratometry readings postoperatively. However, there is not still a commonly accepted algorithm that can calculate with high accuracy the level of the actual postoperative IOP [52].

In order to overcome the problem of the postoperative IOP underestimation with the Goldmann tonometer, some authors suggest that the measurement (in myopic eyes) is done in the periphery of the cornea where less corneal tissue is removed.

The pneumatonometer applanates a smaller area of the corneal surface than the Goldmann tonometer does. It also records a lower IOP postoperatively [50, 53, 54], but some writers argue that the underestimation is lower than that of the Goldmann tonometer [48, 55].

Tonopen is a popular applanation tonometer based on the Mackay-Marg principle. Compared to the Goldmann tonometer, its measurements are less influenced by the thinning of the stroma and the reduction of the corneal curvature [56]. The advantage is that it can record IOP measurements from the periphery of the cornea where the measurement is considered more representative of the true intraocular pressure as the stromal thinning and the change of curvature are smaller there [57–59].

The Pascal Dynamic Contour Tonometer (DCT) is based on contour matching. Its advantage lies on the fact that the measurements are not influenced by the viscoelastic properties of the cornea. It is generally thought that the DCT understates to a lesser extent of the IOP compared to the Goldmann tonometer after both LASIK and PRK [60, 61]. It is also more accurate than the pneumatonometer [62, 63].

4.2. Effect on the Corneal Viscoelastic Properties. Several studies have shown that the viscoelastic properties of the cornea are reduced after LASIK *και* PRK [64–66] because of the corneal thinning and the creation of the corneal flap. IOPcc is affected to a lesser extent than the IOPg [65], while the IOPg and the IOP estimations with the Goldmann tonometer are reduced to the same extent [67].

The corneal viscoelastic properties have shown a reduction after LASIK [68], which can be attributed to the corneal thinning and the formation of the corneal flap. The IOP measurement with the Corvis ST seems to underestimate the IOP reduction less than the IOPg reading of the ORA and the IOP measurement with the Goldmann tonometer. The postoperative estimation of the IOP with the ORA's IOPcc reading and Corvis ST are the most accurate methods.

The biomechanical properties of the cornea can also be measured with the Corvis ST tonometer which applanates the cornea with a jet of air and the surface deformation is recorded by a high speed and high resolution Scheimpflug camera [69]. The deformation pattern as captured by the Scheimpflung also changes after corneal refractive surgery which is attributed to the corneal changes incurred by the stromal ablation and flap formation [70].

4.3. Interface Fluid Syndrome, IFS. This syndrome is due to fluid accumulation between the corneal flap and the underlying stroma after LASIK surgery. This fluid may act as a "cushion" resulting in a falsely low IOP reading as measured with the Goldmann tonometer, while the IOP with other tonometers may be measured correctly high [71–75]. If this condition remains undiagnosed and the IOP is not assessed correctly with a different type of tonometer (other than the Goldmann tonometer), visual capacity may be threatened due to a continuous deterioration of the glaucomatous damage. Pham et al. [76] report a case of this syndrome that appeared 6 years after LASIK following an eye injury with a substantial increase of the IOP. The patient showed signs of ischemic optic neuropathy as the rise of the IOP were not detected by the Goldmann tonometer. Rehany et al. describe a patient with high IOP after LASIK where the Tonopen and

the Goldmann tonometers failed to unveil a high IOP which was measured correctly with the Schiøtz tonometer [77]. Najman-Vainer et al. [78] and Shaikh et al. [79] warn even for end-stage glaucoma risk if the IOP is not measured correctly and the ophthalmologist does not rely on functional tests (visual field). This syndrome should be distinguished from the diffuse lamellar keratitis (DLK) as it does not respond to topical steroids and requires treatment aqueous suppressants.

4.4. Steroid Responders. The international literature [80] has shown that the use of topical steroids postoperatively can lead to a significant rise of the IOP especially in patients with the following:

(i) Primary open-angle glaucoma (POAG)

(ii) Glaucoma suspects

(iii) People with first-degree relatives suffering from POAG

(iv) Diabetes mellitus type I

(v) High myopia

(vi) People with a previous episode of steroid responsiveness

(vii) Patients with rheumatic diseases (e.g., rheumatoid arthritis)

(viii) Advanced age.

Increased IOP leads to a spectrum of clinical manifestations in the cornea that ranges from a simple rise of the IOP to pressure induced stromal keratitis (PISK) and to IFS [81, 82]. In the early stages of the IOP rise, there is stromal swelling which causes corneal haze. The corneal swelling then leads to fluid accumulation between the corneal flap and the stroma [83, 84]. If there is fluid accumulation under the flap, the IOP should be measured with a tonometer other than the Goldmann tonometer so as not to miss the diagnosis of IFS. In this case, topical steroids must be stopped and treatment with topical aqueous suppressants must be initiated.

4.5. Corneal Permeability after Refractive Surgery. Studies in patients have shown that the corneal permeability increases after PRK and LASIK surgery. Specifically, the corneal permeability to fluorescein increased the first 2 months postoperatively and then decreased gradually from the second until the sixth month postoperatively when it returned to normal levels. Indeed, the deeper the ablation, the higher the corneal permeability [85]. Chung and Feder [86] also noted that three months after LASIK instillation of tropicamide drops caused greater pupil mydriasis 10, 15, and 20 minutes after instillation. Unlike the above reports, the experimental PRK and LASIK in hares caused nonsignificant increase of corneal permeability to timolol 1 month after surgery [87]. The concentration of timolol in the aqueous was measured by liquid chromatography.

4.6. Topical Antiglaucoma Medication after Refractive Surgery. Unfortunately, little evidence exists about the effectiveness of the topical antiglaucoma drops in refractive patients. The combination of timolol 0.5% twice a day and dorzolamide 3 times a day is more effective in lowering the IOP after PRK in ocular hypertensive patients compared to timolol twice daily alone or dorzolamide 3 times a day alone [88]. Latanoprost and timolol have the same hypotensive effect in ocular hypertension due to steroid responsiveness [89].

5. Conclusions

The preoperative assessment of glaucoma patients who are candidates for refractive surgery should be based on a set of tests which starts from the family history, IOP measuring (even performing a 24-hour IOP phasing in some cases), visual field test, and imaging of the optic nerve and the peripapillary nerve fiber layer. Because age is a strong risk factor [90], it is easily understood that all young refractive patients are potentially glaucoma patients over time. Therefore, the preoperative glaucoma risk assessment should be performed in every patient.

The preoperative imaging of the structures of the posterior pole can be done with digital photography or/and with one of the newer imaging methods (OCT, HRT, and GDx). Fundus photography does not give objective measurements of the structures but enables us to monitor the changes over time even in "unusual" discs (tilted and myopic discs). The other imaging modalities provide detailed measurements of various parameters of the structures of the posterior pole. They also compare the parameters of each individual patient to a database of normal individuals. However, these comparisons may not be entirely reliable in patients with "unusual" discs as occurs in many myopic patients who are excluded from the database of these machines.

The correct measurement of the postoperative IOP is an important challenge for the ophthalmologist. The changes in the corneal thickness, curvature, viscoelastic properties, and the creation of the corneal flap (in LASIK and epi-LASIK) make the assessment of IOP with the Goldmann tonometer unreliable. The clinician should not rely only on the IOP measurement for the diagnosis and monitoring of glaucoma suspects or true glaucoma patients. Visual field tests and imaging of the optic nerve are needed to monitor these patients. In order to accurately estimate the true IOP, the measurements should be done with the Tonopen (which has a smaller applanation surface than the Goldmann tonometer) from the periphery of the cornea or with the DCT whose measurements are not affected by the viscoelastic properties of the cornea. The ORA's IOPcc, which is less affected by the corneal changes, and the Corvis ST are thought to estimate more accurately the true level of the IOP following a refractive procedure.

The clinician should always bear in mind the possible diagnosis of PISK which has a similar clinical picture with DLK but does not respond to topical steroids and should be treated with aqueous suppressants. PISK can be complicated by fluid accumulation under the corneal flap, in which case,

the Goldmann tonometer can significantly underestimate the true IOP. As a consequence, the IOP must be monitored with more than one tonometer.

In summary, every young glaucoma patient should be treated as a future glaucoma patient and baseline tests should be carried out preoperatively. In this way, the ophthalmologist will be able to recognize the development of glaucomatous optic neuropathy in the future.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Research Article

Long-Term Clinical Course of Normal-Tension Glaucoma: 20 Years of Experience

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Purpose. The purpose of this study was to investigate the long-term clinical course of NTG patients who initiated intraocular pressure- (IOP-) lowering therapy. *Methods*. The present study included 72 normal-tension glaucoma (NTG) patients. The mean deviation (MD) was measured with visual fields. Nocturnal hypotension with weighted standard deviation (wSD) was determined by 24-hour ambulatory blood pressure monitoring. To identify risk factors for NTG progression, linear logistic regression analysis was employed. *Results*. The mean follow-up period was 21.2 ± 1.1 years. The mean MD progression rate was -0.28 ± 0.24 dB/year. The mean ocular perfusion pressure (OPP) was 52.1 ± 5.9 mmHg. The mean wSD was 14.5 ± 2.2. In the univariate model, disc hemorrhage (RR 7.12; $P = 0.004$), IOP reduction rate (RR 2.12; $P = 0.045$), and OPP (RR 1.94; $P = 0.027$) were associated with glaucomatous visual field progression. However, in the multivariate model, the IOP reduction rate (RR 2.45; $P = 0.048$) and OPP (RR 2.02; $P = 0.004$) were detected to be significant factors associated with progression. *Conclusions*. The mean rate of visual field progression was −0.28 dB/year in NTG patients treated with medical therapy. The IOP reduction rate and OPP were associated with glaucomatous visual field progression.

1. Introduction

Glaucoma describes a group of optic neuropathies that result in the progressive loss of ganglion cells. It manifests as characteristic optic disc cupping, nerve fiber layer loss, and visual field defects [1].

Normal-tension glaucoma (NTG) is more prevalent than high-tension glaucoma in Asia. In addition, a recent population-based study reported that the most common type of glaucoma in Koreans was NTG [2, 3].

NTG is a widely known multifactorial disease in pathogenesis and disease progression. Although the pathogenesis and disease progression in NTG has not been fully elucidated, several factors affecting disease progression have been found [4–6].

Many risk factors for the development and progression of NTG have been identified, of which intraocular pressure (IOP) is considered the most important modifiable factor [7, 8]. However, IOP alone can explain only a small proportion of the pathogenesis of glaucoma [9].

IOP independent factors, such as vascular factors, can lead to hypoperfusion of the optic disc head. And consequently glaucomatous optic disc change has occurred [10–12]. Among several vascular factors, low BP, BP variability, nocturnal hypotension, and low or fluctuating ocular perfusion pressures (OPP) represented major risk factors for the prevalence, incidence, and progression of glaucoma in large epidemiological surveys [13–16].

Clinical data about the disease, such as the rate of glaucomatous visual field defect progression and risk factors for disease progression, might be helpful to clinicians to estimate prognosis and devise treatment regimens.

The representative, population-based, cross-sectional studies of early open-angle glaucoma were those of the Collaborative Normal-Tension Glaucoma Study (CNTGS) [7] and Early Manifest Glaucoma Trial (EMGT) [8]. These data suggested the rates of glaucomatous visual field progression or the natural course of NTG. However, the average follow-up period of these studies was approximately 12 years, which was insufficient to represent the long-term clinical course of NTG.

Because of the lack of long-term follow-up data, we investigated the long-term clinical courses of NTG patients who initiated IOP-lowering therapy. In addition, this study evaluated the risk factors, including vascular factors for glaucomatous visual field defect progression.

2. Methods

2.1. Subjects. This study was approved by the Institutional Review Board of Dong-A University. Informed consent was obtained from each participant, and all of the study conduct adhered to the tenets of the Declaration of Helsinki.

The medical records of patients who had been diagnosed and followed up for NTG from 1994 to 2015 at Dong-A University Hospital were retrospectively examined.

At the initial glaucoma evaluation, each patient underwent a comprehensive ophthalmologic examination, including a review of the patient's medical history, measurement of best-corrected visual acuity (BCVA), IOP, gonioscopy, central corneal thickness (CCT) measurement, dilated funduscopic examination, retinal nerve fiber layer (RNFL) photography, and standard automated perimetry using a 24-2 Swedish Interactive Threshold Algorithm (SITA; Carl Zeiss Meditec, Dublin, CA, USA).

NTG was diagnosed as glaucomatous optic neuropathy using funduscopic examination, characteristic visual field defects, open anterior chamber angles on gonioscopy, and pretreatment IOP never exceeding 21 mmHg, as measured by the Goldmann applanation tonometer (GAT). IOP was tested by the same examiner during the day, and the average of the three measurements was used in the analyses.

The visual field test was performed on patients whose follow-up was at least 5 years, which equated to more than 10 follow-ups with a minimum 6-month interval. Eyes with glaucomatous visual field defects were defined as those that met two of the following criteria as confirmed by more than two reliable consecutive tests, in addition to compatibility with optic nerve appearance: (1) a cluster of three points with a probability of less than 5% on a pattern deviation map in at least one hemifield and including at least one point with a probability of less than 1% or a cluster of two points with a probability of less than 1%; (2) a glaucoma hemifield test (GHT) result beyond 99% of the age-specific normal limit; and (3) a pattern standard deviation (PSD) beyond 95% of the normal limit. Reliable visual field assessment was defined as a visual field test with a false-positive error < 15%, a false-negative error < 15%, and a fixation loss < 20%. The first perimetric result was excluded from the analysis to obviate learning effects.

Mean deviation (MD) value was used to determine visual field progression. Glaucomatous visual field progression was defined as one of the following findings: (1) significant deterioration from the baseline pattern deviation at three or more test points that were evaluated on three consecutive examinations or as a significantly negative slope ($P < 0.05$) in linear regression analysis using the mean deviation (MD) data (criteria A) [8] and (2) an annual decrease in MD slope of less than 0.5 dB/year (criteria B) [17]. The rate of progression was determined according to the slope of the linear regression analysis of MD values over time.

The 24 hr ABPM was performed using an electronic sphygmomanometer (TONOPORT V., GM Medical System, Germany) on the patient's nondominant arm. Daytime BP (7 AM to 10 PM) was measured at 30-minute intervals, and nighttime BP was measured (10 PM to 7 AM) at one-hour intervals. The patient was allowed to lead a normal active life as much as possible during the monitoring of ambulatory blood pressure.

MAP is calculated as [18]

$$\text{MAP} = \text{diastolic BP} + \frac{1}{3}\left(\text{systolic BP} - \text{diastolic BP}\right). \quad (1)$$

OPP is calculated as [19]

$$\text{OPP} = \frac{2}{3}\,\text{MAP} - \text{IOP}. \quad (2)$$

Nocturnal hypotension represents how much the average value of nighttime BP decreases compared to the average of daytime BP, and it can be calculated using the following equation:

$$\text{Nocturnal hypotension} = \frac{\left(\text{avarage of daytime MAP} - \text{avarage of nighttime MAP}\right)}{\text{avarage of daytime MAP}} \times 100. \quad (3)$$

Based on the above equation, patients with <10% nocturnal hypotension were defined as "nondippers," those with ≥10% but <20% nocturnal hypotension were defined as "dippers," and those with ≥20% nocturnal hypotension were defined as "overdippers" [15, 20].

BP variability was represented by weighted standard deviation (wSD), which can be calculated using the following equation [21]:

$$\text{weighted standard deviation (wSD)} = \frac{(\text{daytime SD} \times \text{daytime valid measurement}) + (\text{nighttime SD} \times \text{nighttime valid measurement})}{\text{all time valid measurement}}. \quad (4)$$

Patients were included in the study if they fulfilled the following criteria: (1) newly diagnosed early NTG; (2) a follow-up period of more than 20 years; (3) a visual field test performed on patients whose follow-up lasted at least 5 years, which equated to more than 10 follow-ups with a minimum 6-month interval; and (4) 24 hr ambulatory blood pressure monitoring (24 hr ABPM) performed on patients whose follow-up lasted at least 5 years, which equated to more than 5 follow-ups with a minimum 12-month interval.

The exclusion criteria were as follows: (1) eyes with other visually significant ocular pathology (e.g., visually significant cataracts, diabetic retinopathy, vascular occlusions, and macular degeneration); (2) patients on medications (e.g., steroids, hydroxychloroquine) that could affect visual sensitivity and IOP; (3) a history of ocular surgery, including cataract operations; (4) any significant medical problems with ocular manifestations, such as diabetes, hypertension, and other systemic diseases that might result in a visual field defect; (5) improper recording of the timing of IOP measurements during the follow-up periods; and (6) failure to attend outpatient visits regularly.

We also excluded patients using beta-blockers or dorzolamide antiglaucoma eye drops because of the systemic effects of eye drops on blood pressure or ocular blood flow.

One eye from each subject was used for the analysis, and when both eyes had the same glaucoma diagnosis and visual field progression, the right eyes were used for the analysis.

2.2. Statistical Analysis. Statistical analyses were performed using the SPSS software program (version 20.0; SPSS Inc., Chicago, IL, USA). Categorical variables were investigated by cross-tables and the chi-square test. Student's paired *t*-test or the Mann-Whitney *U* test was used for the analysis of continuous variables. Univariate and multivariate logistic regression analyses were used to identify the risk factors for glaucomatous visual field progression. One-way analysis of variance (ANOVA) was performed to compare the three groups, and Bonferroni's test was performed for post hoc comparisons. *P* values less than 0.05 indicated statistical significance.

3. Results

A total of 158 NTG patients were followed over 20 years. Of these 115 patients, 72 eyes of 72 NTG patients (62.6%) were enrolled in the study and 43 NTG patients (37.4%) were excluded. The reasons for exclusion were as follows: (1) lack of total number of 24 hr ABPM exam (16 patients, 16 eyes); (2) inadequate result of 24 hr ABPM exam (11 patients, 11 eyes); (3) received cataract surgery during the follow-up period (9 patients, 9 eyes); and (4) usage of beta-blockers or dorzolamide eye drops during the follow-up period (7 patients, 7 eyes). All of the enrolled patients were Koreans. The mean age at initial examination was 58.4 ± 12.4 years old, and the mean follow-up period was 21.2 ± 1.1 years. The central corneal thickness averaged 535.4 ± 13.2 μm. The mean baseline IOP was 16.6 ± 3.1 mmHg, the mean IOP after IOP-lowering therapy was 11.9 ± 2.2 mmHg, and the average reduction rate of IOP was 28.3%. Baseline MD was −3.59 ± 2.21 dB. The mean MD progression rate was −0.28 ± 0.24 dB/year. The mean OPP was 52.1 ± 5.9 mmHg. The mean rate of systolic nocturnal hypotension was 7.6 ± 4.5%, and that of diastolic nocturnal hypotension was 8.5 ± 5.9%. The mean wSD was 14.5 ± 2.2 (Table 1).

The mean MD progression rate of all of the patients was −0.28 ± 0.24 dB/year. Rates of visual field progression between 0 dB/year and 0.5 dB/year were observed in 9.7% (7/72), rates from 0 dB/year to −0.5 dB/year were observed in 73.6% (53/72), rates from −0.5 dB/year to −1.0 dB/year were observed in 11.1% (8/72), and rates greater than −1.0 dB/year were observed in 5.6% (4/72).

Among the 72 NTG patients, 28 patients (38.9%) showed glaucomatous visual field progression. Of these 28 patients, 11 patients (11 eyes, 15.3%) showed significant glaucoma visual field progression according to criteria A, and 10 patients (10 eyes, 13.9%) showed significant glaucoma visual field progression. Seven patients (7 eyes, 9.7%) showed glaucomatous visual field progression by both criteria A and B.

Results of the logistic regression analysis identified factors associated with glaucomatous visual field progression results, which are presented in Table 2. In the univariate model, disc hemorrhage (RR 7.12; $P = 0.004$), IOP reduction rate (RR 2.12; $P = 0.045$), and OPP (RR1.94; $P = 0.027$) were associated with glaucomatous visual field defect progression. In the multivariate model, IOP reduction rate (RR 2.45; $P = 0.048$) and OPP (RR 2.02; $P = 0.004$) were detected to be significant factors associated with progression (Table 2).

Comparison results of the clinical characteristics among the three groups (nondippers, dippers, and overdippers) are shown in Table 3. In the nondippers group, the mean progression rate was −0.20 ± 0.21 dB/year, OPP was 52.3 ± 6.1, and wSD was 14.0 ± 2.0. In the dippers group, the mean progression rate was −0.24 ± 0.20 dB/year, OPP was 51.7 ± 4.7, and wSD was 13.9 ± 2.1. In the overdippers group, the mean progression rate was −0.28 ± 0.30 dB/year, OPP was 46.2 ± 5.4, and wSD was 15.3 ± 1.3 (Table 3).

4. Discussion

Previous population-based research has suggested rates of visual field progression. The CNTGS reported that annual decrease in MD was −2 dB in NTG [7]. The EMGT reported that the mean rate of visual field defect progression in untreated NTG patients was 0.36 dB/year [8]. Broman et al.

Table 1: Baseline demographics and characteristics of study participants.

Characteristic	
M : F (*N*)	32 (44.4%) : 40 (55.6%)
Age (years)	58.4 ± 12.4
Mean follow-up period (years)	21.2 ± 1.1
CCT (mmHg)	535.4 ± 13.2
Mean baseline IOP (mmHg)	16.6 ± 3.1
Mean IOP (mmHg)	11.9 ± 2.2
Mean reduction rate of IOP (%)	28.3%
Baseline MD of visual field (dB)	−3.59 ± 2.21
MD slope (dB/year)	−0.28 ± 0.24
OPP	52.1 ± 5.9
Nocturnal hypotension (systolic/diastolic) (%)	7.6 ± 4.5/8.5 ± 5.9
wSD	14.5 ± 2.2

Expressed as the mean ± SD; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; OPP: ocular perfusion pressure; wSD: weighted standard deviation.

Table 2: Logistic regression analysis of the association between the clinical parameter and glaucomatous visual field progression.

Variables	Univariate model RR (95% CI)	*P* value	Multivariate model RR (95% CI)	*P* value
Female sex	1.97 (0.52–4.39)	0.859	2.04 (0.50–5.32)	0.442
Age	1.27 (0.78–2.12)	0.682	1.12 (0.75–3.02)	0.248
CCT	0.34 (0.12–1.92)	0.897	0.42 (0.22–2.93)	0.617
Baseline IOP	0.87 (0.71–1.82)	0.537	0.57 (0.41–1.52)	0.313
Mean IOP	0.77 (0.67–1.54)	0.265	0.92 (0.57–1.44)	0.331
IOP reduction rate	1.12 (0.95–2.92)	**0.045**	1.45 (0.83–2.43)	**0.048**
Disc hemorrhage	7.12 (4.57–13.29)	**0.004**	8.11 (3.53–16.33)	0.051
Baseline MD	1.02 (0.88–2.36)	0.518	1.56 (0.83–2.39)	0.501
Sys. nocturnal hypotension	0.69 (0.52–1.54)	0.248	0.73 (0.42–1.64)	0.243
Dia. nocturnal hypotension	1.25 (1.01–3.92)	0.254	1.15 (0.95–4.12)	0.319
OPP	1.94 (0.97–3.12)	**0.027**	2.02 (0.84–3.92)	**0.004**
wSD	1.01 (0.71–1.78)	0.362	1.32 (0.61–2.15)	0.321

Expressed as the mean ± SD; bolded *P* values indicate statistical significance; RR: relative risk; CI: confidence interval; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; Sys.: systolic; Dia.: diastolic; OPP: ocular perfusion pressure; wSD: weighted standard deviation.

Table 3: Comparisons among 3 groups (nondippers, dippers, and overdippers).

	Nondippers	Dippers	Overdippers	*P* value
MD slope (dB/y)	−0.20 ± 0.21	−0.24 ± 0.20§	−0.28 ± 0.30†‡	**0.000***
MAP (mmHg)	95.1 ± 4.4	94.6 ± 3.3	90.7 ± 5.9†‡	**0.000***
OPP (mmHg)	52.3 ± 6.1	51.7 ± 4.7	46.2 ± 5.4†‡	**0.000***
wSD	14.0 ± 2.0	13.9 ± 2.1	15.3 ± 1.3†‡	**0.014***

Expressed as the mean ± SD; *comparison among 3 groups by one-way analysis of variance; statistical significance: $P < 0.05$; †significantly different compared with nondippers by post hoc multiple comparison (Bonferroni's test); ‡significantly different compared with dippers by post hoc multiple comparison (Bonferroni's test); §significantly different compared with nondippers by post hoc multiple comparison (Bonferroni's test); MD: mean deviation; MAP: mean arterial pressure; OPP: ocular perfusion pressure; wSD: weighted standard deviation.

[22] reported that the mean worsening of visual fields in Chinese POAG patients was −1.56 dB/year. Komori et al. [17] also reported that the mean visual field progression rate in Japanese NTG patients was −0.30 dB/year. In our study, the mean rate of visual field progression was −0.28 dB/year in treated NTG patients. This result was similar to previous studies. However, despite achieving an almost 30% reduction rate in IOP by medical therapy, 26.4% of treated NTG patients experienced progressed glaucomatous visual field defects. Therefore, when making decisions for glaucoma

management, clinicians should consider mechanisms other than IOP-dependent factors that might contribute to glaucomatous visual field progression.

The risk factors for glaucomatous visual field progression or poor prognosis have been reported in previous studies, including IOP, disc hemorrhage, myopia, age, low blood pressure, nocturnal hypotension, migraine, Raynaud's phenomenon, and sleep apnea [7, 8, 23–27].

In the present study, IOP reduction rate and OPP were found to be risk factors for glaucomatous visual field progression. However, disc hemorrhage, which is a well-known risk factor for glaucoma progression in previous studies, was not detected to be a risk factor in multivariate analysis.

The importance of IOP reduction rate has been emphasized in many previous studies [7, 8, 28]. In the CNTGS [7], visual field defect progression was more common in the untreated group than in the treated group (30% IOP reduction from baseline). In the EMGT [8], risk decreased by approximately 10% with each mmHg of IOP reduction from baseline. The result of our present study that IOP reduction rate was associated with glaucomatous visual field defect progression was consistent with previous studies.

OPP is a well-known and important factor of disease progression in NTG [8, 29]. In EMGT [8], lower systolic OPP was confirmed to be a significant predictive factor for glaucoma progression. Sung et al. [29] reported that higher levels of 24 hr mean OPP fluctuation were associated with greater glaucoma visual field defect progression. In the present study, lower levels of OPP were a significant risk factor for glaucoma visual field progression other than systemic blood pressure. As a result, low OPP could lead to ischemic changes in the optic nerve head and glaucomatous visual field defect progression.

Among the IOP-independent risk factors for NTG progression, vascular factors play important roles in disease progression [10, 14–16]. We divided the patients into 3 groups as nondippers, dippers, and overdippers to evaluate the effects of vascular factors on disease progression. Compared to the nondippers and dippers, overdippers showed a worse MD slope, lower OPP, and higher blood pressure variability. This result suggested that, even in NTG patients who achieved target IOP, nocturnal hypotension over the physiological dip and large variation in blood pressure led to progression of glaucomatous visual field defects. Therefore, these patients might be considered for correction of severe nocturnal hypotension and large variability in blood pressure.

This study had the following limitations. First, this study was a retrospective study and had a high rate of exclusion; there might have been selection bias. Second, the sample size was small. Therefore, we believe that additional studies are needed. Third, we have evaluated the glaucoma progression using visual field criteria only. Further studies, evaluating glaucoma progression using both optic nerve head and retinal nerve fiber layer changes, are needed. Fourth, OPP was calculated with an indirect method by brachial BP; therefore, our OPP data were not actual OPP. Finally, our results did not reflect other risk factors of NTG progression, such as diurnal IOP fluctuation. However, we believe that our study provided clinicians useful long-term clinical data about NTG and the risk factors for NTG progression.

In conclusion, the mean rate of visual field progression was −0.28 dB/year in NTG patients treated with medical therapy. However, despite achieving an almost 30% reduction rate in IOP by medical therapy, disease progression occurred in some cases. Therefore, clinicians should consider mechanisms other than IOP-dependent factors that might contribute to glaucomatous visual field progression. Concerning the analysis of risk factors for NTG progression, adequate IOP reduction and correction of low OPP might help to slow or stop NTG progression.

Ethical Approval

This study was approved by the Institutional Review Board of Dong-A University. All of the participants were treated in accordance with the tenets of the Declaration of Helsinki.

Consent

Informed consent was obtained from each participant.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Gradually Then Suddenly? Decline in Vision-Related Quality of Life as Glaucoma Worsens

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Purpose. To evaluate the relationship between self-reported vision-related quality of life (VRQL) and visual field (VF) loss in people from glaucoma clinics. *Methods.* A postal survey using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was administered to people with a range of VF loss identified from a UK hospital-based glaucoma service database. Trends were assessed in a composite score from NEI VFQ-25 against better-eye mean deviation (BEMD) using linear regression and a spline-fitting method that can highlight where a monotonic relationship may have different stages. *Results.* A total of 636 patients (median [interquartile range] BEMD −2.1 [−5.2, −0.4] dB, median age 70 [60, 77] years) were analysed. Analysis of trends in the data revealed an average patient loses approximately 2 units (out of 100) on NEI VFQ-25 for every loss of 1 dB (BEMD) as VF defects first become bilateral, up to BEMD −5 dB. NEI VFQ-25 deterioration then appears to slow before a more rapid phase of change (4–5 units per 1 dB loss) after BEMD worsens beyond −15 dB. *Conclusions.* Relationship between decline in VRQL and VF worsening in glaucoma is unlikely to be linear; it more likely has different phases, and these should be further explored in longitudinal studies.

1. Introduction

Loss of visual field (VF) sensitivity is a hallmark in patients with glaucoma [1]. VF loss can pose a significant threat to patients' everyday functioning and quality of life. It is often the case that patients report greater difficulty in performing vision-related tasks as the severity of their glaucoma increases and VF worsens [2–7]. However, it is not uncommon for the effects of glaucoma to go undetected by the patient [1, 8]. For example, many performance-based studies demonstrate that glaucoma patients can perform within the normal expected range, even in cases of advanced VF loss [9–13]. Conversely, other evidence suggests that even mild or moderate disease may have an impact on the patient's quality of life [14].

Assessment of vision-related quality of life (VRQL) typically involves self-reported responses to questionnaires. These questionnaires, also referred to as "instruments," feature items whereby patients mainly document the extent to which they struggle to complete routine tasks. The National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was developed more than 15 years ago [15] and has been widely used in ophthalmology research as a measure of VRQL. This instrument was used in a landmark report revealing the association between VF loss and health-related quality of life in glaucoma [7] and has been widely used in other cross-sectional studies [3–6, 14, 16, 17]. However, these studies report only a modest relationship between VRQL and VF damage. More recently, longitudinal studies of glaucoma patient cohorts have highlighted NEI VFQ-25 scores to be impacted by location and speed of VF loss [18–20].

Association between VF loss and worsening of VRQL reported in the literature mainly implies that the relationship is a linear one [7, 14, 18, 19]. That is, VRQL constantly declines as the VF worsens. In fact, the relationship between loss of VRQL and VF worsening is likely better described as a monotonic one. In other words, whilst VRQL never improves as the VF worsens, the decline could have slow or rapid stages or even remain relatively constant for a phase. This idea, relatively unexplored, is the subject of our report.

Patients with glaucoma are typically asymptomatic in the early stages of the disease process. Any change in VF status

may be compensated for by good binocular vision or is simply not noticed. As VF loss becomes symptomatic, a patient is more likely to self-report an impact on VRQL, but in turn, patients may adapt to their vision loss. Indeed, there is some evidence that behavioural adaptions, such as adjusted head and eye movements, can help glaucoma patients compensate for their vision loss when completing everyday tasks [9, 10, 21–25]. Eventually as glaucoma worsens, more complete binocular VF loss will impact on legality of driving and restrict mobility and confidence [24–31].

Patients with more advanced glaucoma report significantly worse scores on the NEI VFQ-25 compared to their better-sighted peers. In a recent cross-sectional analysis of an established cohort of 233 patients from the Early Manifest Glaucoma Trial (EMGT) [32] (trial registration: NCT00000132), Peters et al. hinted at the idea of accelerated worsening of VRQL once patients reach a certain VF threshold in their least-affected (or better) eye [33]. This evidence suggests a "tipping point" after which each decibel of VF loss will have more severe consequences for patients' VRQL. This observation is worth further study. Here, we investigate the relationship between VRQL (using NEI VFQ-25 scores) and a summary measure of VF loss amongst a spectrum of disease severity in a large number of patients from a glaucoma clinic. Specifically, we consider that the rate of decline in VRQL may not simply be a linear process and we look for statistical evidence of different phases of decline or periods where there might be more or less rapid reduction as the VF worsens.

2. Materials and Methods

This study took advantage of anonymised patient data collected as part of an investigation of conducting a randomised controlled trial for glaucoma screening in the United Kingdom (UK) [34]. The data, collected from a cross-sectional postal survey, is described in detail elsewhere [35], but we summarise it here too.

Potential participants were identified by an ophthalmologist from an electronic patient record (Medisoft, Leeds, UK) of VFs at a hospital-based glaucoma service in London (Moorfields Eye Hospital NHS Foundation Trust). Recruitment criteria required potential patients to have at least two entries in the database having undergone VF testing on a Humphrey visual field analyser (HFA; Carl Zeiss Meditec, CA, USA) between January 2007 and September 2009. To be included, patients were required to have reproducible HFA 24-2 (SITA Standard) VF defects in both eyes at the two most recent visits as determined by the glaucoma hemifield test (GHT) [36]. The GHT results had to be "borderline" or "outside normal limits" as recorded in the electronic patient record on both occasions. A total of 1349 patients were considered suitable for study recruitment. Ethical approval was granted and the study adhered to the Declaration of Helsinki.

Questionnaires were posted to all patients considered suitable for the study in March 2010. Included in the survey was the vision-specific patient-reported outcome measure, the NEI VFQ-25 [15]. This instrument consists of 25 items across 12 subscales, where 11 constructs are vision-related (general vision, ocular pain, near activities, distant activities, social functioning, role difficulties, mental health, dependency, driving, colour vision, and peripheral vision) and one construct regarding general health. A reminder letter was sent two weeks after initial contact. The return of completed questionnaires was considered as consent to take part in the study. A total of 656 questionnaires were returned.

We used HFA mean deviation (MD) in the least-affected eye (best eye MD; BEMD) recorded at the most recent clinical visit when the questionnaire was administered as our surrogate measure of VF loss. The MD is conventionally used in the clinic and in clinical trials; it is a summary measure of the overall reduction in VF sensitivity relative to a group of healthy age-matched observers with more negative values indicating more vision loss. We used the BEMD since this best reflects the patients' VF morbidity [37]. Numeric responses on the NEI VFQ-25 were recoded in line with the scoring guidelines [15]. Each item is converted into a value ranging from 0 to 100 where higher scores indicate greater VRQL and lower scores are indicative of poorer VRQL. A composite score for VRQL was then calculated by averaging all vision-related subscales. In cases where more than 5% of the questionnaire data were missing, or where subscale scores were unable to be calculated due to insufficient data, responses were excluded from our analysis. In line with scoring guidelines, patients who had never driven a car had responses coded as "missing" for the driving subscale [15].

A total of 636 patients with complete NEI VFQ-25 and BEMD data were used for our analysis. No other data, apart from age (years) at the time of the most recent VF, was considered.

We explored the relationship between BEMD and NEI VFQ-25 using the `freeknotspline` package in the statistical programming language R (http://www.R-project.org). This package fits free-knot splines to data with one independent variable and one dependent variable [38, 39]. This technique will automatically highlight phases where a monotonic relationship between two variables may change. The points where the phases (segments) connect are called the knots of the spline. The knots can be determined a priori or by allowing the data to dictate areas where change occurs. A knot-search algorithm is provided for the case where the number of knots is not known in advance, as with our data. We can then compare the model that describes this relationship against a linear relationship (using ordinary least squares regression (OLSR)) by considering the Akaike information criterion (AIC); this is a measure of the relative quality of statistical models for a given set of data and provides a means for model selection [40]. Phases in the relationship between BEMD and NEI VFQ-25 identified by this approach were then further analysed using linear OLSR where a series of separate OLSR lines are fitted to appropriate ranges of BEMD. All this subsequent analysis, including plotting the data, was carried out in R (http://www.R-project.org).

3. Results and Discussion

Median (interquartile range (IQR)) age of the 636 patients analysed was 70 (60, 77) years. Median (IQR) BEMD

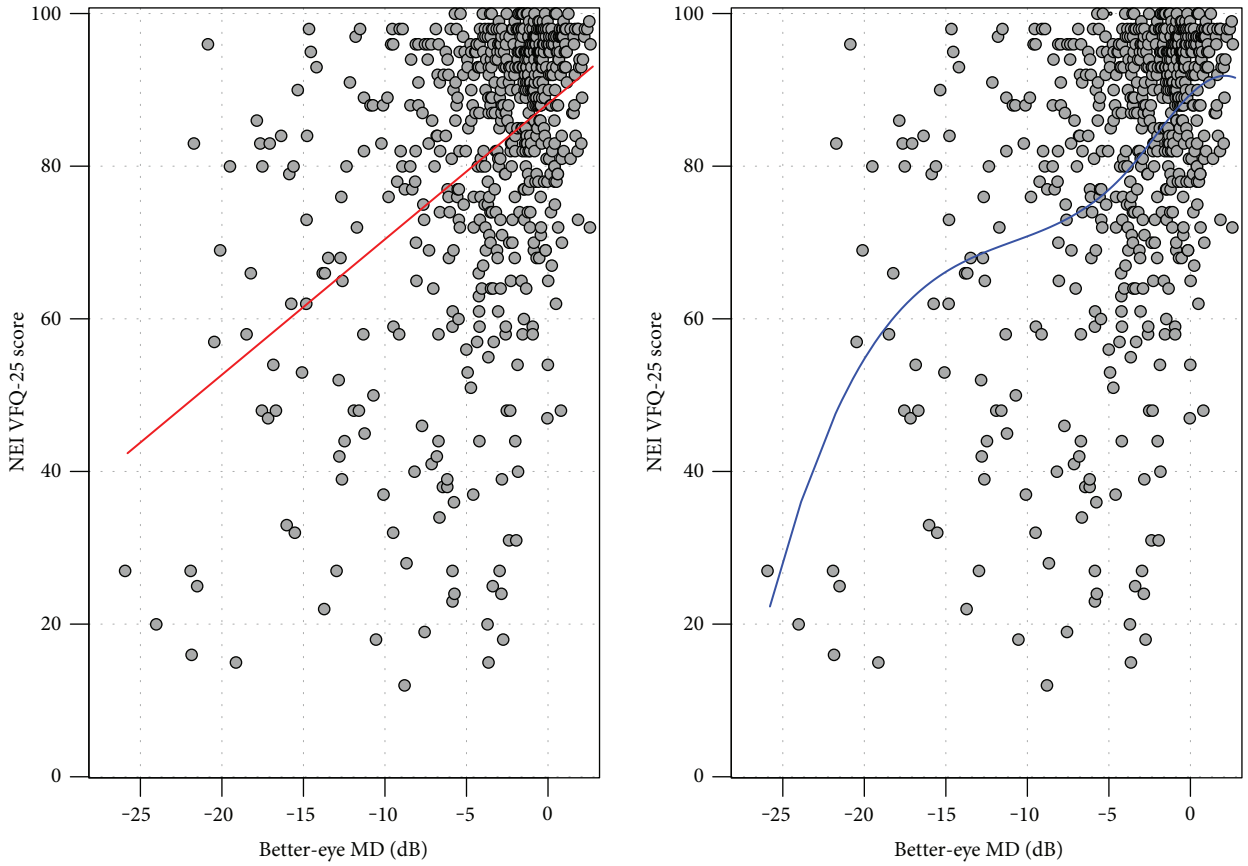

Figure 1: Points represent scores on NEI VFQ-25 compared to BEMD (dB) for 636 patients. The use of linear (red line) and spline (blue line) regression modelling assessing trend in relationship between the two variables.

was −2.1 (−5.2, −0.4) dB and worst eye MD was −5.5 (−11.3, −2.3) dB. Median (IQR) composite score on the NEI VFQ-25 was 89 (74, 95) points. The majority of patients (97%) scored their general health to be good or better on the general health item of the NEI VFQ-25.

Figure 1 shows the distribution of patients' BEMD score against composite scores from the NEI VFQ-25. The red line (left-hand side plot) gives the best-fitting linear OLSR line (red line). This model assumes a linear association between BEMD and the NEI VFQ-25. The blue line (right-hand side plot) shows the automatically chosen penalised spline model which had two knots with a polynomial of degree 3. The AIC index for the linear and spline models was 3601.7 and 3596.0, respectively. In simple terms, the AIC index indicates stronger evidence for a preference of one model over another (the lower the better). There is some debate in the applied statistics literature about the meaning of small differences in AIC, but differences > 5 (as with our data) indicate that the model with the lower AIC is likely to be more informative [41]. For our purposes, this statistical interrogation of the relationship mainly suggests demarcated phases where NEI VFQ-25 deteriorates with more or less acceleration as a patient's BEMD worsens. On inspection, there seems to be three phases in the association. For BEMD up to about −5 dB, there is a distinct slope followed by a phase (between −5 dB and −15 dB) where the line flattens before it becomes much steeper again (worse than −15 dB). Three OLSR lines were fitted to these three phases, and the results along with 95% confidence limits are shown in Figure 2 with model parameters given in Table 1. Simply put, the average patient loses about 2 units (out of 100) on the NEI VFQ-25 for every loss of 1 dB (BEMD) as their glaucomatous VF loss becomes bilateral, up to −5 dB. Worsening on the NEI VFQ-25 then appears to slow down: the average patient loses about 1 unit (out of 100) on the NEI VFQ-25 for every loss of 1 dB (BEMD) from −5 to −15 dB. Finally, a more rapid phase of deterioration in VRQL seems to occur: after the BEMD worsens to around −15 dB, the average patient starts to lose 4 to 5 units on the NEI VFQ-25 for every remaining loss of 1 dB (BEMD).

4. Discussion

Economists anecdotally refer to bankruptcy happening in two stages—gradually then suddenly [42]. Hence, it is a monotonic process but not necessarily a linear one. In this study, we provide some evidence that this is what happens in patients' perception of their VRQL as their glaucomatous VF worsens in their better eye over time. Rather than a linear decline, we suggest that there are phases of change attributed to progression in the VF in the least-affected eye. The phases illustrated in the statistical associations we report make clinical sense. As the better-seeing eye gets measurable VF loss (bilateral disease), the previously asymptomatic patient may begin to notice the impact of scotoma as they perform visual

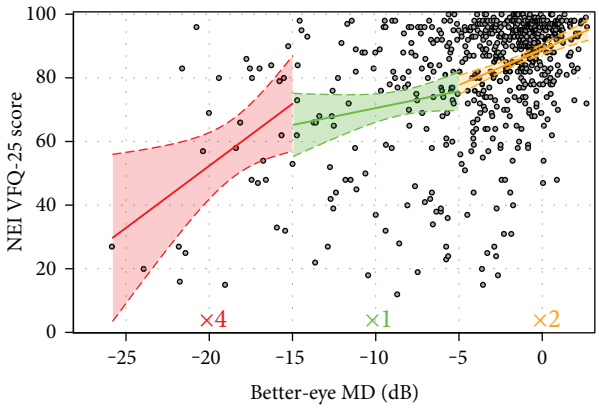

Figure 2: Fitting of three OLSR lines with 95% confidence limits for each phase of decline in VRQL. Points represent scores on the NEI VFQ-25 and BEMD in 636 patients. The green phase shows the slowest decline in NEI VFQ-25 score; the yellow line shows quicker decline where NEI VFQ-25 scores reduce 2 times faster than that in the green phase. The red line shows decline on NEI VFQ-25 as about four times quicker than that in the green phase.

tasks. A phase of adaptation to this loss then might likely precede another phase where advanced loss in both eyes really impacts on VRQL. Our evidence is not strong; it is merely based on a cross-sectional survey of people from glaucoma clinics with no supplementary clinical information. Yet our results support a concept that ought to be tested with other datasets or longitudinal studies. Better knowledge on how visual function decline may accelerate at different stages of the disease process would be useful for the clinical management of patients and also for health economists as they determine better utilities for evaluating glaucoma treatments.

Our findings add to the current understanding of how patients perceive their difficulty living with glaucoma. VRQL deteriorates as glaucoma worsens and our data supports this. This association is not particularly a strong one. For example, the R-squared (%) for the linear association between VRQL and BEMD data is 21% suggesting that only part of the variance in VRQL is explained by the VF. Moreover, it is quite remarkable how some patients with BEMD worse than −20 dB (top left hand corner of graph depicted in Figure 2) report VRQL to be the same or better than many patients with a BEMD of 0 dB or higher. This observation coincides with the findings of others indicating only a modest relationship between NEI VFQ-25 scores and VF status [3–6, 14, 16, 17]. Our statistical treatment of the large cross-sectional data implies that this weak association may behave differently at different stages of BEMD severity and this is new knowledge. Our findings give some weight to the idea that the speed at which VRQL declines may alter during different phases of the disease and that specific markers for BEMD could indicate change points in patient-reported functional ability.

Our observations of different phases of association between VRQL and BEMD are supported by the results from a twenty-year follow-up of patients in the EMGT [33]. In a cross-sectional analysis of this cohort of 233 patients, Peters et al. found a significant difference in Rasch-calibrated scores

Table 1: Relationship between decline in NEI VFQ-25 score for piecewise regression analysis for each 1 dB decline in BEMD score.

BEMD (dB)	N	Slope (95% confidence interval)	Standard error	p value
+2 to −5 (yellow)	475	2.3 (1.5, 3.0)	0.40	<0.001
−5 to −15 (green)	132	1.1 (−0.3, 2.5)	0.70	0.14
<−15 (red)	29	4.6 (1.2, 8.0)	1.64	0.009

on the NEI VFQ-25 for patients with BEMD worse than −18 dB and those with BEMD better than −18 dB. In cases where BEMD was worse than −18 dB, patients' scores on the NEI VFQ-25 did not exceed 70 out of 100. This suggests different phases in the relationship between BEMD and the NEI VFQ-25, with a threshold where impact of VF loss accelerates. A strength of this study is that a wide range of glaucoma severity was analysed, whereas other studies consider only patients with early glaucomatous damage [3, 14].

In addition to supporting the concept of a nonlinear relationship between VRQL and BEMD, our results also support recent findings regarding the impact of glaucoma on VRQL in the earlier stages of the disease. Our results indicate that a 1 dB decline in BEMD is associated with an average reduction of 2.3 units on the NEI VFQ-25 for patients with BEMD between +2 dB and −5 dB. This finding is similar to that of a longitudinal study by Alqudah et al. [14] who found an association between scores on the NEI VFQ-25 and BEMD in the early stages of glaucoma. Their study was restricted to patients with BEMD between approximately +2.5 dB and −5 dB, and they reported a decline of 0.5 units on the NEI VFQ-25 for each 1 dB reduction.

Our findings become important when considering treatment options for patients with advanced stage glaucoma. It is evident that patients' VRQL reduces rapidly once BEMD loss becomes advanced. Decline in VRQL is approximately four times faster than that in the previous stages of the disease after patients' vision deteriorates beyond −15 dB. This threshold may have important clinical implications when treating patients in the advanced stages of the disease. Due to the potential for fast decline in VRQL, this point could be used to guide potential intervention options when treating patients with advanced glaucoma. The suggestion has been made that more research is needed in order to determine the best treatment option for advanced glaucoma [43], and this is currently under investigation in a randomised clinical trial [44]. Our results may also have implications for those developing utilities for health economic models for glaucoma treatments [45].

There are some strengths to our study. The sample size was large and we took advantage of a large database of recorded VF data. These data represent unselected people in glaucoma clinics that are receiving routine care, and therefore, estimates are directly meaningful to "real-world" practice. In addition, the patients in this study had a wide range of glaucoma severity. However, the proportion of patients with early VF damage was greater than the advanced cases and this could be perceived as a limitation.

Our investigation also had some limitations. The data used is cross-sectional and so we only consider patients' VRQL and VF loss at a single time point. Moreover, measures of VRQL are self-reported. We are, for example, unable to account for the rate at which patients' VF defect has progressed, and this has been shown to influence VRQL [19, 46, 47]. A better study design would use longitudinal data [18, 19]. Additionally, our study has the potential for response bias (49% response rate). However, given the adoption of a postal survey design and adherence to an ethical study protocol, a full response rate would be unlikely. As VF data were unavailable for those who did not choose to participate, we were not able to consider the characteristics of nonresponders. Nevertheless, 49% is higher than the response rates observed in studies using a similar design [48]. We did not have information on race, educational level, and marital status, and these factors can influence quality of life. In addition, there may have been a large gap in time between patient's latest VF data and when the completed NEI VFQ-25 was returned. The main problem with the design of this study is the absence of any clinical indictors on the eyes other than the VFs. We did not, for example, have information on coexisting cataract or detailed treatment history. Additionally, for this unselected sample, we did not have measures of visual acuity. A further disadvantage of our analysis is that we did not use a Rasch model to analyse the results of the NEI VFQ-25, whereas studies similar to ours have done this [18, 19, 33].

Our study opens up avenues for future research into the association between VRQL and clinical measures of vision loss. We found that the rate of decline in glaucoma patients' VRQL begins to slow after BEMD is reduced to −5 dB. This slow decline in NEI VFQ-25 scores remains evident until BEMD is reduced to −15 dB, where rapid decline occurs. More research is needed in order to understand what factors can influence the rate at which patient VRQL declines. A well-designed prospective study should consider VRQL in people at this moderate or middle stage of disease and consider how they might be adapting to their VF loss. Moreover, we used only one measure of VRQL, namely the NEI VFQ-25. Previous research has indicated that no single instrument covers all aspects of patients' VRQL [49]. As such, replication of this study assessing responses on an instrument specific to glaucoma would be an interesting addition to the literature.

5. Conclusion

In conclusion, the relationship between VRQL and BEMD is a weak monotonic one. However, we provide some evidence to suggest that this relationship may not be a linear one. The speed at which VRQL declines might better be described as gradually, where patients experience a period of adaption to their vision loss, and then suddenly, once patients' functional abilities become significantly impaired.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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Review Article

Eye-Tracking as a Tool to Evaluate Functional Ability in Everyday Tasks in Glaucoma

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To date, few studies have investigated the eye movement patterns of individuals with glaucoma while they undertake everyday tasks in real-world settings. While some of these studies have reported possible compensatory gaze patterns in those with glaucoma who demonstrated good task performance despite their visual field loss, little is known about the complex interaction between field loss and visual scanning strategies and the impact on task performance and, consequently, on quality of life. We review existing approaches that have quantified the effect of glaucomatous visual field defects on the ability to undertake everyday activities through the use of eye movement analysis. Furthermore, we discuss current developments in eye-tracking technology and the potential for combining eye-tracking with virtual reality and advanced analytical approaches. Recent technological developments suggest that systems based on eye-tracking have the potential to assist individuals with glaucomatous loss to maintain or even improve their performance on everyday tasks and hence enhance their long-term quality of life. We discuss novel approaches for studying the visual search behavior of individuals with glaucoma that have the potential to assist individuals with glaucoma, through the use of personalized programs that take into consideration the individual characteristics of their remaining visual field and visual search behavior.

1. Introduction

Glaucoma is one of the main causes of visual field loss in older populations [1], affecting approximately 60 million people worldwide, with the numbers estimated to increase significantly in the future as the population ages [2, 3]. For this reason, the impact of glaucoma on everyday activities such as reading, walking, shopping, or driving, and quality of life has been the focus of numerous research studies [4–12]. Nevertheless, the relationship between functional measures and patients' visual disability in everyday life is still not well understood and requires further research [13].

Many studies have assessed the impact of glaucomatous vision loss on everyday activities through questionnaires or patient-reported outcome measures [8, 9, 14–19], simulators [20–22], or under laboratory conditions [23–26], and some have incorporated measures of visual search behavior. Results from these studies suggest that visual search behavior plays a key role in the ability of individuals with glaucoma to complete everyday activities. More specifically, several studies have reported that some individuals with glaucoma process visual information differently than controls during everyday tasks. For example, Wiecek et al. [27] reported that patients with glaucomatous visual field loss tend to ignore the region of the computer-based image where their scotoma is located, rather than making more eye movements to compensate for their loss. Conversely, another study demonstrated that when viewing dynamic movies of road traffic scenes, glaucoma patients made more fixations and saccades than controls [23]. In a recent study, Crabb et al. [28] showed that visual scanpaths, derived from a passive watching task, can be used to differentiate between individuals with glaucomatous

visual field loss and those with no visual field loss. In less dynamic tasks, glaucomatous visual field loss was associated with restricted eye movements; that is, patients performed fewer saccades than controls and viewed different locations of static naturalistic scenes than controls [25, 29]. However, the most valid approach to assessing the functional impairment of patients with glaucoma in everyday activities is by conducting real-world experiments (i.e., observing the person undertaking a particular activity in a field-based environment). However, since such experiments are expensive, time-consuming, and often difficult to standardize, to date few everyday activities have been investigated. Indeed, most of the work on everyday activities has focused on assessing the driving ability and safety of individuals with glaucoma [5–7, 10, 16, 21, 30–32].

Importantly, while the methodological approaches of these studies have varied, they have reached similar conclusions: (1) task performance varies among individuals, (2) glaucomatous field loss does not always lead to poorer performance, and (3) visual field defects related to glaucoma can be compensated for in some individuals through effective head and eye movement strategies. Furthermore, it has been suggested that the results of different studies may relate specifically to that set of circumstances and not reflect individuals' visual behavior in other everyday activities, given that compensatory gaze patterns are highly specific and intrinsically related to the specific task [33]. Furthermore, there appears to be a wide degree of variability in patients' compensatory strategies that are adopted during activities of daily living.

One approach to evaluate the real-world impact of glaucomatous loss and potential compensatory strategies is through assessment of visual search and scanning during daily activities. Assessment of visual search in this way also enables better understanding of the link between visual function and ability, as well as providing a basis for designing training strategies for improvement of daily functioning, and the development of assessment tools for use in a clinical setting.

Eye movements are important in directing gaze and attention towards important task-relevant areas within the visual scene, in order to guide subsequent actions when completing everyday activities [34]. Gaze position identifies where foveal vision is directed towards, known as overt attention. At the same time, attention can also be directed towards peripheral areas of the visual field without reorientating gaze, known as covert attention [35]; when something important is identified in peripheral vision, overt attention can be shifted via a corresponding eye movement. While eye-tracking analysis provides information specifically regarding overt attention, it is also the key technology that helps us in the understanding of visual search and scanning behaviors during daily activities. Importantly, patients with glaucoma may have impaired covert attention capacity, relative to the extent of their visual field loss. Indeed, the ability to simultaneously extract central and peripheral visual information within a single glance, as measured with attentional or useful field of view tests, has been shown to be reduced among older adults with glaucoma, compared to normally sighted controls [36, 37].

Incorporating eye movement analysis in settings that reflect everyday activities is becoming an increasingly popular approach, given that several studies have reported that the ability of patients with glaucoma to perform these activities of daily living is only weakly associated with the extent of their visual field defects, but may be mediated through the complex interaction between field loss and visual scanning strategies. The study of eye movements in glaucoma, particularly in comparison to participants with normal visual fields, is also becoming more common, with advances in eye-tracking technology and analytical approaches making it a more practical approach, particularly for assessing task performance while individuals complete everyday tasks in natural environments.

In this paper, we review existing methods that quantify the effect of glaucomatous visual field defects on the ability to undertake everyday activities through the use of eye movement analysis. Although there is a large body of work investigating eye movements in those with glaucoma, the focus of this narrative review is on studies that have employed eye-tracking while participants complete everyday tasks such as reading, mobility and walking, and driving. We also discuss studies that explored the gaze patterns of individuals with glaucoma while shopping [38], during a face recognition task [26], and making a sandwich [39]. Published studies in peer-reviewed journals were identified through searches using Google Scholar and searches of MEDLINE, PubMed, and Cochrane databases using the following combinations of keywords and phrases: "glaucoma", "visual field loss", "eye-tracking", "eye movements", "visual search", "scanpath", "everyday tasks", "driving", "mobility", "walking", "stepping", and "shopping". Studies of other eye conditions causing visual field loss were also considered, where appropriate, to inform future research directions. Relevant studies from these searches were sourced and reviewed and are discussed as appropriate; only studies that were published in English were included.

2. Eye-Tracking Technology

The use of eye-tracking as a tool to assess and analyze visual search strategies under real-world conditions is growing, given improvements in eye-tracking technology which make it increasingly applicable to the study of both simple and complex scenarios. Video-based eye-tracking is available as head-mounted and remote technology. Recent developments in head-mounted, mobile eye-tracking technology (e.g., Dikablis Mobile eye-tracker, Pupil Labs eye-tracker, SMI Glasses, and Tobii Glasses) have enabled the study of visual perception and visual behavior in natural environments. Some of these eye-trackers, such as the Dikablis Mobile system, can be worn with spectacles, thus interfering only minimally with the participant's natural viewing behavior. On the other hand, observation and monitoring of scanning behavior can benefit from the use of non-intrusive systems, where cameras are positioned remotely at some distance from the participant.

While eye-tracking can be accomplished successfully under laboratory conditions, many studies report difficulties

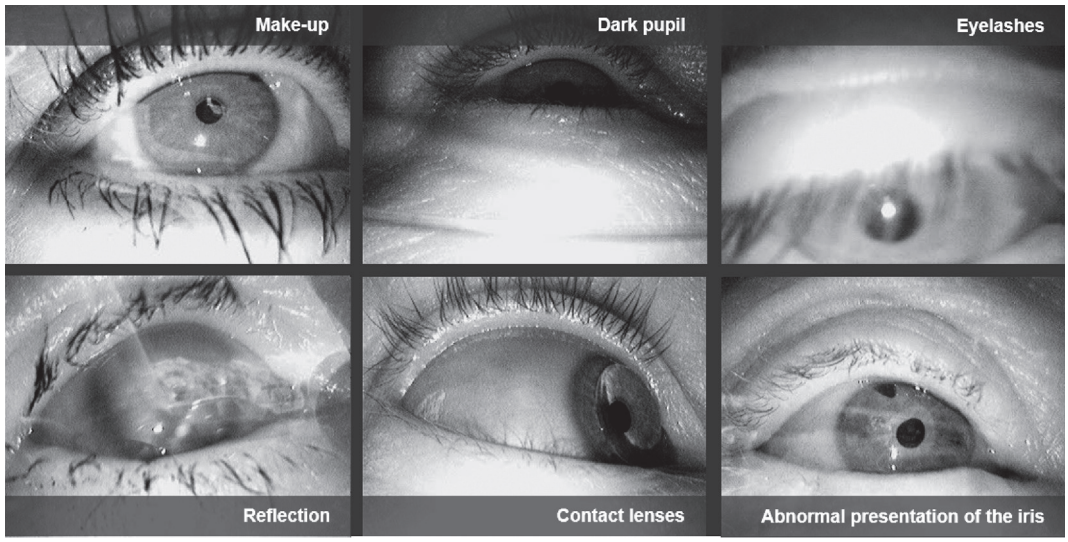

Figure 1: Eye images recorded by mobile, head-mounted eye-trackers in outdoor experiments.

when video-based eye-trackers are employed in natural environments, such as driving [21, 30, 40], shopping [38, 41], or simply walking [42]. The main source of error in such settings is a non-robust pupil signal which primarily arises from challenges in the image-based detection of the pupil. More specifically, a variety of difficulties may occur when using eye-trackers, such as changing illumination (especially problematic when walking outside during the daytime), motion blur, recording errors, and eyelashes covering the pupil (Figure 1). Rapidly changing illumination conditions arise primarily in tasks where the participant is moving rapidly (e.g., while driving), or where the participant rotates relative to unequally distributed light sources. Particularly for older populations, it is important to test the tracking quality of the eye-tracker with the participant's spectacles. Often the tracking rate (i.e., the percentage of video frames where pupil information can be extracted, and consequently, the gaze position can be calculated) and accuracy are significantly degraded when strong illumination and reflections on the spectacle lenses are present. A further issue arises due to the off-axis position of the eye camera in head-mounted eye-trackers. Therefore, studies based on eye-tracking in uncontrolled environments frequently report low pupil detection rates. As a consequence, the data collected in such studies has to be manually post-processed, which is laborious and time-consuming.

Recently, several algorithms have been introduced to tackle these challenges and report very high pupil detection rates in both head-mounted [43–45] and remote eye-tracking [46] technology. Among the state-of-the art algorithms for head-mounted and remote eye-tracking, ExCuSe [43] and ElSe [44], two decision-based approaches based on edge detection and ellipse fitting, show very high accuracy combined with real-time processing capability. When eye-trackers with low sampling rates up to 60 Hz are incorporated, the PupilNet algorithm based on advanced machine learning techniques (i.e., Convolutional Neural Networks), achieves even higher robustness with regard to the above-mentioned sources of noise [47]. The tracking rate is an important parameter and is reported as the proportion of frames where the pupil is detected. It can easily be computed and is usually also reported by the manufacturer's software. The second important parameter is the calibration accuracy, that is, how exactly the position of the participant's gaze is projected into world coordinates (or pixel coordinates in a video for head-mounted devices). Contrary to the tracking rate, a dedicated calibration measurement during the experiment has to be performed, for example, by instructing the participant to fixate on specific markers. As calibration quality is likely to decrease over the duration of the experiment, it is important to assess accuracy before and after the experiment.

Given a reliable eye-tracking signal, several processing steps have to be applied on top of the raw data stream to derive information about visual search behavior. As mentioned in the introductory section, several studies have collected eye movement data on glaucoma patients while they complete everyday tasks, in order to identify their exploratory search patterns. The data recorded in these studies has been mainly analyzed manually and post-experimentally. Basic fixation filters are then applied to extract fixation locations and saccades.

Eye-tracking technology, however, has huge potential beyond that of simply measuring eye movements. Online analysis of eye-tracking data could help to design gaze-based interactive and assistive systems for patients with impaired vision, such as in glaucoma. A crucial prerequisite towards the development of such interactive systems is a robust data analysis pipeline. The first processing step in this pipeline addresses the automated detection of the eye movement type (i.e., fixation, saccade, or smooth pursuit), to extract the spatiotemporal sequence of eye movements (also known as the visual scanpath). Other movements, such as smooth pursuits, microsaccades, ocular drifts, and microtremor, are

usually ignored, since it is difficult to extract them from the eye-tracking signal, especially when recorded at low sampling rates (below 120 Hz). For some tasks, information on gaze density in specific areas of interest is sufficient. Such information can be derived from heatmap visualization, as provided by most eye-tracking data analysis software. More sophisticated methods require the examination of a fixation sequence in combination with information from the scene. Several algorithms are available for event detection, such as [54–56], and have been applied in some studies with glaucoma patients. For example, Sippel et al. [38] used advanced data analysis to identify characteristic visual exploration patterns of glaucoma patients during a shopping task. In Kübler et al. [21], such methods were used to investigate eye movement patterns in patients with glaucoma while driving.

To date, most eye movement analytical approaches are based on time-integrated measures, such as the average fixation duration, or the number of fixations directed towards a specific region of interest. Several studies have described such exploratory eye movement patterns in glaucoma patients during everyday tasks. But extracting these at the scanpath level (i.e., the sequence of fixations and saccades) from the large amount of data generated is highly challenging. A manual analysis is very laborious and only applicable to experiments of short duration involving static stimuli (e.g., such as in reading). Dynamic activities such as walking or driving, where the scene is changing with the ego perspective, require automated methods to compare eye-tracking data of different participants (or even more demanding, that of different participant groups), in order to identify common patterns of eye movements, as well as those that differentiate between participant groups. Only a few approaches, such as those based on string similarity [57] which compare scanpaths as a whole, or in segments as described by Kübler et al. [51, 58], can be applied to the analysis of eye-tracking data derived while completing interactive tasks. Such methods are only rudimentarily implemented in most analysis software, yet determining gaze patterns that distinguish between two experimental groups can be highly valuable.

A major issue that needs to be considered prior to undertaking eye-tracking experiments, is the reference coordinate system that the eye-tracker works within. Head-mounted devices record the gaze position relative to the head position (scene video image), which can be challenging to analyze automatically. If the participants move their head, the position of the objects in the video image also changes. Placing easily traceable markers for further image analysis close to relevant objects can speed up data analysis significantly. Remote trackers more commonly provide a gaze vector in a world reference system. Therefore, the exact position of relevant objects with regard to the eye-tracker is helpful to automatically determine whether a certain object was looked at. A relevant issue for recording naturalistic viewing behavior is that the areas over which head movements can be recorded are limited. For tasks that require a large freedom of head movement and rotation, it is possible to combine multiple remote cameras or a head-mounted device and a head tracker. Some eye-trackers also measure head position and orientation within a limited area; for example, the EyeLink tracker can detect a marker placed on the participant's forehead, while Smart Eye fits a head model to multiple camera perspectives.

Recently, eye-tracking has been integrated into virtual reality devices. These have enormous potential to study eye movements in glaucoma, through the provision of ecologically valid measures to individually assess viewing behavior in a well-circumscribed environment.

3. Eye Movements and Glaucoma in Everyday Tasks

Table 1 provides a summary of eye-tracking studies that have investigated eye movements of individuals with glaucoma, or other relevant conditions causing visual field loss, while undertaking a range of everyday tasks. The main findings from these studies will be discussed in more detail in the following subsections.

3.1. Insights from Reading Experiments. Reading is an everyday task that requires good central vision. Although glaucoma is mainly associated with impaired peripheral vision, many patients also experience paracentral and central visual field loss and difficulties with reading are commonly reported [8, 9, 11, 59, 60]. In support of these self-reported reading difficulties, studies that have measured reading performance in individuals with glaucoma report reduced reading speeds compared to those with normal vision for small size text [61], at low contrast levels [48], or when reading for sustained periods of time [9]. Those individuals with central glaucomatous field loss [62], or who have advanced field loss [9, 63], are also particularly impaired in terms of reading ability. Importantly, as outlined by Crabb [13] in his viewpoint on glaucoma, the reading capacity of those with glaucomatous field loss varies considerably between individuals; studies of eye movements and reading by his research group suggest that differences in eye movement patterns in those with glaucomatous loss may account for some of this variability [48, 49].

Smith et al. [49] reported that reading performance was significantly worse in the eye with more glaucomatous field loss compared to the better eye in a given individual, but that this was not related to the extent of field loss, but rather to measures of contrast sensitivity and visual acuity. Furthermore, those individuals, whose reading speeds were particularly affected in their worse eye, made a larger proportion of backward saccades and "unknown" eye movements (not adhering to expected reading patterns) when reading with this eye in comparison to the better eye [49]. A study by the same research group [50] demonstrated that some of the variability in reading speed in those with advanced glaucomatous loss could be explained by eye movement patterns. A significant association was found between increased saccadic frequency in those with higher reading speeds (for short passages of text) in individuals with glaucoma, which suggested the adoption of compensatory mechanisms to improve task performance. In addition, those who read more slowly tended to read every word in a line (termed text saturation) compared to those with higher reading speeds

Table 1: Summary of eye-tracking studies referenced in this work with regard to their participants and eye-tracking devices.

Study	Cohort demographics	Eye-tracker (fps)	Main findings
Burton et al. [48]	53 bilateral glaucoma (mean age 66 ± 9); 40 controls (mean age 69 ± 8)	EyeLink 1000 (1000)	Reduction in reading speed for lower contrast text was greater in glaucoma patients than controls.
Smith et al. [49]	14 bilateral glaucoma (median age 69, IQR 64 to 81)	EyeLink 1000 (1000)	Slower performance and more regression when reading with the worse eye, compared to better eye. Differences in performance not related to magnitude of difference in VF mean deviation index between eyes.
Burton et al. [50]	18 advanced bilateral glaucoma (mean age 71 ± 7); 39 controls (mean age 67 ± 8)	EyeLink 1000 (500)	Similar reading speeds between groups. Some glaucoma patients read slower than controls, partly explained by differences in eye movement behavior.
Prado Vega et al. [20]	23 glaucoma (mean age 65 ± 12); 12 controls (mean age 65.7 ± 9.4)	Smart Eye (60)	Glaucoma patients missed more peripherally projected stimuli during driving in a simulator than controls. Glaucoma patients did not use compensatory visual search patterns.
Kübler et al. [21]	6 binocular glaucoma (mean age 62 ± 7); 8 controls (mean age 602 ± 10)	Dikablis (25)	Glaucoma patients who passed the driving test in the simulator showed increased number of head and gaze movements toward eccentric regions of the VF in comparison to patients who failed.
Crabb et al. [23]	9 binocular glaucoma (mean age 67.6 ± 9.3); 10 controls (mean age 64.4 ± 11.4)	EyeLink (250)	Patients showed different eye movement characteristics (more saccades) than controls when viewing driving scenes in a hazard perception test.
Kasneci et al. [30]	10 binocular glaucoma (mean age 61 ± 9); 10 controls (mean age 60 ± 9)	Dikablis (25)	Patients who passed the on-road driving test focused longer on the central VF and performed more glances towards the area of their VF defect than patients who failed.
Kübler et al. [51]	10 binocular glaucoma (mean age 61 ± 9); 10 controls (mean age 60 ± 9)	Dikablis (25)	Patients can be identified based on their visual scanpath while driving above chance levels.
Sippel et al. [38]	10 binocular glaucoma (mean age 61 ± 9); 10 controls (mean age 60 ± 9)	Dikablis (25)	Patients who showed good performance during supermarket shopping made more glances towards the VF defect area.
Vargas-Martín and Peli [52]	5 retinitis pigmentosa (mean age 58 ± 16); 3 controls (mean age 67 ± 5)	ISCAN (60)	Retinitis pigmentosa patients exhibited narrower scanning strategy than controls.
Ivanov et al. [53]	25 retinitis pigmentosa (mean age 54 ± 13)	Tobii Glasses (30)	An exploratory saccadic training improved search performance, as well as mobility performance.
Dive et al. [39]	12 bilateral glaucoma (mean age 64 ± 15); 13 controls (mean age 73 ± 9)	iViewX^{TM} (50)	Glaucoma patients took longer to complete the task, with longer fixations and more eye and head movements, than controls.
Smith et al. [24]	20 bilateral glaucoma (mean age 67 ± 10); 20 controls (mean age 67 ± 11)	EyeLink II (500)	Glaucoma patients took longer to find targets in photographs.
Crabb et al. [28]	44 glaucoma (median age 69, IQR 63–77); 32 controls (median age 70, IQR 64–75)	EyeLink 1000 (1000)	Differences in signature scanpath patterns when watching television could separate glaucoma from controls.

and controls; these effects were exacerbated during longer periods of sustained reading.

In summary, the incorporation of eye-tracking provides a useful experimental approach for exploring differences in reading performance in those with glaucoma and better understanding of the mechanisms underlying these reading difficulties.

3.2. Glaucoma, Mobility, and Walking. Peripheral vision is important for spatial orientation, balance control, and efficient navigation when walking, particularly guiding obstacle avoidance, locomotion planning, and foot placement. Adults with glaucomatous visual field loss have been shown to demonstrate altered balance control when standing [64, 65], along with impaired mobility performance when walking,

including slower walking speeds and increased contacts with obstacles, especially in those with bilateral visual field loss [4, 12]. Impaired balance and mobility performance in those with glaucoma is likely to negatively impact on the health and well-being of older adults. For example, greater glaucomatous visual field loss has been linked to reductions in physical activity levels [66], greater levels of fear of falling [67], and increased risk of falls and injuries [5, 68].

Studies have also explored whether specific areas of the visual field are more important for mobility and falls in adults with glaucoma. Murata et al. [69] reported significant associations between central and inferior hemifield regions and self-reported walking difficulties. Other studies also highlight the importance of the inferior visual field region for postural stability [64] and falls risk [68] in glaucoma. These associations are likely to reflect natural human gaze behavior when walking. In uncluttered environments, such as an unobstructed level footpath, gaze is generally directed several steps ahead in the direction of travel to guide route planning and to scan for potential hazards [70, 71]; therefore the inferior visual field area is used to provide important information guiding foot placement and detection of hazards. In more challenging or cluttered environments, where precise foot placement is important for safety, gaze tends to shift towards the stepping locations to optimize stepping accuracy [72].

While inefficient visual scanning of the environment is likely to be an important factor linking visual field loss and impaired mobility and falls in adults with glaucoma, there have been few studies that have assessed the link between eye movements and gaze behavior while walking in individuals with glaucoma. Eye-tracking studies have been undertaken in other ocular conditions with peripheral visual field loss, such as retinitis pigmentosa (RP). Patients with RP have been shown to exhibit narrower horizontal scanning patterns when walking in real environments compared to healthy controls [52], potentially due to the absence of peripheral visual stimulation to trigger eye movements and attention towards these areas. Indeed, recent research using saccadic training has shown promise in improving mobility for RP patients, by consciously directing eye movements and attention outside of the seeing region of the visual field [53]. Further research using robust eye-tracking technology and advanced data analysis, with respect to the dynamic nature of walking, is needed to better understand the eye movement patterns of adults with glaucomatous visual field loss, and explore potential saccadic training paradigms to improve their mobility and quality of life.

3.3. Glaucoma and Driving. A large body of work has been conducted over the last two decades to investigate the impact of glaucoma on driving, which has drawn a range of conclusions regarding the impact of glaucoma on driving ability and safety, as summarized in a recent review [73]. Glaucoma has been shown to be an important risk factor for self-reported crashes over the previous 10 years [74–76] and state-recorded crashes [5, 77–80]; however, the underlying reasons for this increased crash risk are unclear. Simulator-based assessments have revealed equivocal results, with some studies reporting increased simulator crashes [81], while others reveal only small differences in performance between those with glaucoma and age-matched controls [20, 21]. On-road performance is also impaired in some drivers with glaucoma compared to those without glaucoma [6, 30–32], with drivers with glaucoma demonstrating difficulties in observation, maintaining their lane position, changing lanes, and planning ahead [31]. Interestingly, while some studies report links between the extent of field loss and driving ability and safety [77, 80, 81], others have failed to find a link [21, 30, 82]. Importantly, few studies have investigated the eye movement patterns of individuals with glaucoma while undertaking driving tasks, which might provide insight into the link between visual field loss and driving ability. Indeed, specific eye movement patterns might act as a compensatory mechanism for the loss of visual function and ultimately provide the basis for effective visual rehabilitation and coping strategies.

In the few on-road studies that have involved eye movements, those glaucoma patients who were rated as safe to drive showed increased exploration activity, in terms of more eccentric head movements, compared to those drivers with glaucoma who were rated as unsafe to drive [21, 30, 83]. Indeed, in a recent study conducted in a driving simulator, driving behavior and gaze patterns of a small group of participants with bilateral glaucoma were investigated by employing recently developed mobile eye- and head-tracking technology [21]. Results from this study demonstrated that those drivers scored as unsafe displayed less eye movements (shorter saccade amplitudes, longer fixation durations, and less fixations), a gaze bias to the right, and a more straight-ahead eye position [21]. The effect of head movements has been shown to be most important in realistic experimental setups and in those driving simulations with a wide field of view which were more representative of the driving scene. Simple driving simulations with a narrow field of view and relatively simple tasks are unlikely to reflect naturalistic viewing behaviors. Differences in eye movement patterns have also been reported in those with glaucoma compared to controls when completing video-based hazard perception tasks [23]. A reduction in saccade rates and smaller number of fixations indicates decreased eye scanning activity, and longer fixation durations appear to be associated with an inability to acquire visual information in a quick and effective manner, as observed in patients who passed the driving assessment in the study by Kübler et al. [21]. Because new information is acquired during fixations, the finding that patients who failed the driving test made fewer saccades suggests that they were unable to process as much of the visual scene as those patients who passed the test. The finding that unsafe glaucoma drivers showed a gaze bias to the right [21] is also in line with Prado Vega et al. [20], who attributed this finding to the optimal control theory of manned-vehicle systems. A possible explanation is that safe glaucoma drivers pay more attention to avoiding traffic hazards (by gaze scanning), whereas unsafe glaucoma drivers attempt to maintain a stable lane position but fail to recognize traffic hazards because of limited gaze compensatory reserves.

3.4. Other Everyday Tasks. Very few studies have investigated the link between task performance and eye movements in other everyday tasks.

Glen et al. [26] studied the performance of individuals with advanced glaucoma in a face recognition task and demonstrated that some patients showed good task performance despite their visual field defects. More specifically, the authors found that in patients with bilateral visual defects in the central 10° of their visual field, larger saccades led to better face recognition performance [26]. In contrast, the authors found no significant association between saccade amplitude and task performance in people with normal vision. These findings are in line with several studies described previously, which report that some individuals with glaucomatous visual field loss adopt compensatory eye movements during visual tasks.

Two recent studies, involving the everyday tasks of shopping and sandwich making, provide further interesting insight into this issue. In a real-world shopping task, Sippel et al. [38] compared the functional ability and eye movements of 10 patients with bilateral glaucomatous field loss in comparison to 10 normally sighted subjects. Overall, the glaucoma group took longer to complete the task, yet 8 of the glaucoma patients were able to successfully complete the task within a time frame commensurate with the controls, and showed a significantly higher number of glances towards their visual field defect area. Therefore, systematic exploration of the area of visual field defects seems to be a "time-effective" compensatory mechanism during supermarket shopping, which mirrors the results of on-road driving for those with hemianopic field defects [30, 84].

Recently, Dive et al. [39] showed that while patients with glaucoma were slower than controls to complete naturalistic tasks, such as making a sandwich, as well as an unfamiliar task of building a model, they could still complete these tasks efficiently. Assessment of eye movements while doing these tasks revealed that the glaucoma participants made more head and eye movements and had longer fixation durations compared to the controls; the authors suggested that this may have been a strategy to compensate for reduced visibility when key targets fell within their visual field defects.

4. Eye-Tracking as a Means to Assist Individuals with Glaucoma

An interesting research question that arises from the study of eye movements in glaucoma, is whether specific training procedures can assist in the adoption of compensatory gaze patterns in patients with glaucoma that are effective in improving task performance. However, since gaze patterns are task-dependent, it is unclear to what extent eye movement patterns that have been adopted during training on a specific visual search task, can be transferred to real-world tasks, such as driving, walking around, or shopping. For example, Kasneci et al. [30] reported that safe drivers with glaucoma employed a similar viewing strategy in an on-road setting as in a simulated drive [21]. More specifically, the viewing strategy of glaucoma patients who passed the driving tests concentrated on the central 20° visual field area and was combined with frequent but short gazes towards their field defect area and the peripheral visual field. Furthermore, the authors reported that those glaucoma patients who failed the on-road driving test tended to also fail the simulator drive. These researchers investigated task performance and gaze patterns of the same glaucoma group in comparison to normally sighted subjects during a shopping task. Interestingly, there was very high agreement between "good performers" in the driving task and "good performers" in the shopping task, although the compensation strategy employed during shopping differed from that adopted during driving.

In light of these findings, we propose that new methods need to be developed to assess task performance and train and assist glaucoma patients. This is an area where eye-tracking technology could be extremely beneficial. In particular, the combination of eye-tracking and virtual reality offers the potential for evaluating functional ability in glaucoma in complex, yet standardized tasks that mimic everyday tasks. Particularly, in the driving context, this technology could facilitate the systematic assessment of driving safety and viewing behavior during driving. Furthermore, measurements of the visual field could be used to assess individual viewing behavior with respect to the impaired areas in the visual field in an automated way. In this way, personalized training could be developed, for example, by guiding the gaze of an individual towards specific regions through visual or acoustic stimuli.

Moreover, in the driving context, driving assistance systems could utilize unique information regarding an individual driver's eye movements and visual field defects. The design and implementation of such systems is, however, highly challenging, since the visual search behavior (i.e., the visual scanpath) of the driver has to be analyzed in real-time in alignment with objects presented in the dynamically changing driving scene. Kasneci et al. [85] recently introduced a framework based on several machine learning methods to explore hazard perception based on eye movements, where a reliable alignment of gaze and the scene provides the foundation for detection of potentially overlooked traffic hazards. For those cases where the system predicts that the driver has not seen the upcoming hazard, the driver's gaze could be guided towards the hazard by means of visual or acoustic stimuli. If the driver does not react in time, the system should intervene to avoid the collision. Gaze guidance for drivers with visual impairments is particularly challenging, however, as it has to be performed taking into consideration the specific type and location of visual field loss.

In summary, eye-tracking technology is currently a research tool that provides insights into how glaucoma alters attention and viewing behavior. There is huge potential for further development, especially due to advanced analytics that might enable the detection of visual field defects from eye movement recordings during everyday tasks. In recent work, Crabb et al. [28] showed that it might be possible to detect glaucoma during a simple everyday task, such as watching television. Beyond the diagnosis aspects and knowledge of

gaze behavior adaptation, it may be possible to design assistive systems that help individuals with glaucomatous visual field loss to maintain or even improve their performance on everyday tasks, increase their independence, and hence improve their long-term quality of life.

5. Conclusion

Visual search behavior plays a key role in the ability of individuals with glaucoma to complete everyday activities. With the development of more sophisticated eye-tracking technology, assessment of eye movements is transitioning out of the laboratory to encompass activities such as walking, driving, or other real-world tasks and, hence, provides a powerful tool for better understanding the visual search mechanisms of individuals with glaucoma and their implications for everyday tasks. Combined with virtual reality technology, eye-tracking offers the possibility for focused eye movement research under standardized experimental conditions and the development of personalized solutions to assist glaucoma patients.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Examining Delay Intervals in the Diagnosis and Treatment of Primary Open Angle Glaucoma in an Egyptian Population and Its Impact on Lifestyle

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Purpose. To examine causes as well as extent of delay in diagnosis and treatment of primary open angle glaucoma patients in a sample of Egyptians. *Patients and Methods*. 440 patients with primary open angle glaucoma were interviewed to evaluate delay in their diagnosis and treatment. The extent and cause of delay were investigated. The total delay interval, if any, was correlated with socioeconomic and other factors. *Results*. The median total delay was one year, with 50% of patients having a total delay of 1 year or less, of which 25% exhibited zero total delay. 25% of patients had a delay ranging from 1 to 3 years, and 25% had a total delay ranging from 3 to 27 years. Diagnostic delay accounted for 43.03% of cases. Longer delays were met in patients with certain socioeconomic factors. Patients with a positive family history of glaucoma displayed shorter delay periods. *Conclusion*. Significant delay in the diagnosis and treatment of glaucoma was found. Poor socioeconomic status seems to hinder timely diagnosis and treatment of POAG. Certain socioeconomic factors seem to correlate with the extent of delay. More effort is thus needed to subsidize the cost of investigations and treatment for glaucoma patients.

1. Introduction

The magnitude of glaucoma as a potentially blinding disease is continually under study. The risk of blindness from treated primary open angle glaucoma (POAG) over a period of 12–20 years is estimated to range from 14.5% to 27% in unilateral cases and from 7 to 9% in bilateral cases [1]. These figures may slightly differ in developing countries like Egypt. However, the timing of diagnosis and management of glaucoma are of crucial importance to the prognosis of the disease and its effect on the patient's lifestyle. Earlier treatment of patients will alter their mode of progression and thus may delay or totally prevent patients from reaching the stage of visual disability during their lifetime [2]. A patient with visual disability may have to resign from his job, stop driving, and/or become more dependent. Visual disability is likely once the patient reaches scale 8 on the disc damage likelihood scale (DDLS) [3].

A large percentage of glaucoma patients reside in developing countries where there are special challenges. The low socioeconomic status of most patients and the lack of facilities and scarcity of glaucoma specialists, well equipped glaucoma clinics, and screening programs may all contribute to the difficulty of timely detection of disease [4, 5].

In our glaucoma practice, we noted that a lot of patients exhibit a well established to advanced optic disc damage (DDLS 5–10) at first presentation. These patients suffered from restrictions in some of their life activities. Some patients had to change or resign from a certain job. Others stopped driving or felt dependent on other people. The authors did not find enough studies on the problem of delay in diagnosis and management of open angle glaucoma in Egypt or the Middle East [5]. This compelled the authors to conduct a study to further evaluate the causes and extent of this delay, if any.

The authors, however, found a few studies addressing the delay in diagnosis and management of other diseases like pulmonary tuberculosis in developing countries like India and Ethiopia [6, 7].

In this cross-sectional survey study, we interviewed a sample of 440 Egyptian patients, all previously diagnosed

with primary open angle glaucoma (POAG) [8] with the aim of understanding the extent and causes of delay (if any) in their diagnosis and management. We also looked at the correlation between the extent of this delay and other demographic as well as socioeconomic factors. We asked the patients about restrictions in their life activities, for example, if they ever had to change or resign from a job or stop driving after being diagnosed with glaucoma or as a sequel of poor vision or poor visual field.

2. Patients and Methods

Five hundred and thirty Egyptian patients with a confirmed diagnosis of primary open angle glaucoma according to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification [8] were initially approached at the glaucoma clinic of Cairo University Hospital (Kasr Al-Ainy) from June 2012 till January 2015. Of these, 28 patients declined participating in the study. Sixty-two patients were willing to participate in the study but were excluded mainly for being unable to provide clear data as regards the period of delay and its causes (58 patients), as well as not wishing to answer the full questionnaire including data related to their socioeconomic status (4 patients).

Four hundred and forty participants eventually took part in this study. Informed consent was taken from all patients. The study adhered to the guidelines of the declaration of Helsinki [9] and was approved by the institutional ethics committee.

Cases of open angle glaucoma were diagnosed in accordance with the International Society of Geographical and Epidemiologic Ophthalmology (ISGEO) classification [8]. Accordingly, primary open angle glaucoma was classified based on three levels of evidence into three categories. The first category is based on the presence of structural and functional evidence. It requires a CDR or CDR asymmetry ≥97.5th percentile (CD 0.7) of the normal population with a visual field defect that is consistent with glaucoma. The second category included patients with advanced structural damage and unproven visual field loss. It included those subjects in whom visual field testing could not be performed or yielded unreliable results, with a CDR or CDR asymmetry ≥99.5th percentile for the normal population (CDR 0.85, CDR asymmetry 0.3). The third category consisted of patients with an IOP ≥99.5th percentile (CDR 0.85) of the normal population, whose optic discs could not be assessed due to media opacities. POAG was diagnosed if a subject fell under any of the three categories in the presence of an open and normal appearing angle on gonioscopy [8].

Inclusion criteria were POAG patients, above 20 years of age, who were on regular antiglaucoma medications or who underwent argon laser trabeculoplasty (ALT) or glaucoma surgery and who were coming for follow-up in our glaucoma clinic.

Exclusion criteria were patients with other types of glaucoma (chronic angle closure, pigmentary glaucoma, pseudoexfoliation, or any secondary open angle glaucoma). Patients who could not remember when they were first diagnosed with POAG or when they started medications, patients who wished to keep their data personal, and/or those with a documented psychiatric condition which interfered with taking the questionnaire were also excluded from the study.

The authors met two types of glaucoma patients; type A patients who had symptoms that were likely caused by glaucoma (like visual field defects consistent with glaucoma) and who consequently sought ophthalmological advice and were eventually diagnosed with POAG and type B patients who were opportunistically discovered during routine medical checkup or those who presented to an ophthalmologist with a complaint that is mostly unrelated to glaucoma (e.g., to renew their glasses, to treat conjunctivitis, or for LASIK assessment) and were advised to be investigated for glaucoma.

One-to-one in-depth interview was held with each patient during one of his/her follow-up visits. Patients were thoroughly interviewed about the history of their disease. The patient was asked if he/she can clearly state when was the very first time that he/she sought ophthalmological advice (in type A patients) or the first time that he/she was told there was a suspicion of glaucoma (in type B patients). The patient was then asked when his/her diagnosis was confirmed for glaucoma, and since when he/she was on antiglaucoma medications or underwent ALT or glaucoma surgery.

The period between the very first appearance of a problem (symptoms in type A patients or suspicion of POAG in type B patients) and the date of initiation of antiglaucoma therapy (whether medical or interventional) was calculated in years—or fraction of years—and was recorded as the "*total delay*." Patients in whom the total delay did not exceed one month (0.08 years) were considered to have zero total delay. Since typically it takes up to a month for a newly diagnosed glaucoma patient in Egypt to have the required investigations done, book a follow-up appointment, and get started on antiglaucoma medications.

The patient was then further asked about the predominant reason for this delay. The predominant cause of delay *(the type of delay)* was further classified by the authors as either patient, diagnostic, or treatment delay (Figure 1). *Patient delay* was defined as the time between the onset of a complaint (in type A patients) and the patient's first presentation to an ophthalmologist. Type B patients who were discovered opportunistically were considered to have zero patient delay and were opt to be evaluated only for "diagnostic and/or treatment delay" because these patients' delay cannot be attributed to them as they had no ocular complaint.

Diagnostic delay was defined as the interval between the first consultation with an ophthalmologist and the confirmed diagnosis of glaucoma. *Treatment delay* was defined as the interval between the confirmed diagnosis of glaucoma and the actual initiation of therapy whether topical medications, ALT, or surgery whichever came first.

All questions were asked by the same investigator and each interview took about twenty minutes. The interviewer asked the patients in a relaxed atmosphere, posing the questions in a nonleading, open discussion manner. The interviewer stressed on the importance of receiving accurate information rather than just getting all his questions

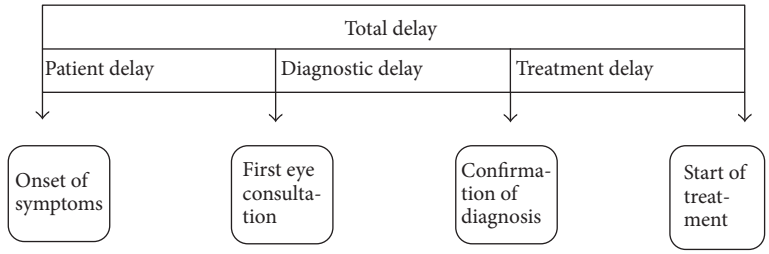

Figure 1: Conceptual diagram on the definition of delays, adapted from Yimer et al. [7].

answered and encouraged the patient to inform him of not being able to give an accurate answer rather than speculating. The patients were asked to bring or show any supportive documents (like old prescriptions, old field test printouts, or requests for investigations) with a date on them which helped to further validate the dates that they reported.

To further understand the reasons behind this type of delay, further questions were asked about the cause which has led to this type of delay. The exact cause behind a certain type of delay was enquired about. The patient was also asked if he had encountered any restrictions on his daily activities, for example, if he had to resign from or change a certain job or stop driving or cycling because of his visual disability.

After the "cause of delay" was thoroughly investigated, the patient was then asked about his education level (classified by authors into the following: illiterate, finished elementary education, middle or high school, and having a university degree or higher), the presence or absence of a family history of glaucoma, the presence of an associated systemic disease (diabetes, hypertension, ischemic heart disease, or others), whether he had enough knowledge about the risk and possible consequences of glaucoma, and finally whether the patient is covered by medical insurance or not (whether partially or totally). The participant's age, sex, and laterality of disease were also recorded for all patients. Statistical correlations were then examined between the extent of total delay and all these socioeconomic factors.

Data were statistically described in terms of mean ± standard deviation (±SD), median, range and percentiles, or frequencies (number of cases) and percentages when appropriate. Correlation between various variables was done using Spearman rank correlation equation. A P value less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science, SPSS Inc., Chicago, IL, USA).

3. Results

Our study included 143 (32.5%) females and 297 (67.5%) males with a mean age of 52.05 ± 8.42 years.

The mean total delay was 2.31 ± 3.51 years, ranging from zero to 27 years. The median total delay was one year with half the number of patients falling below and the other half falling above a total delay of one year.

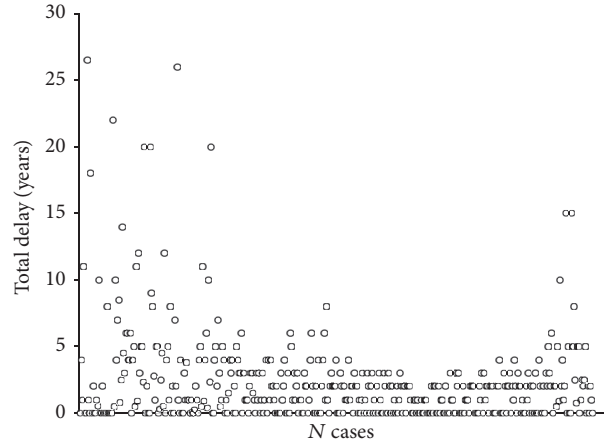

Figure 2: Distribution of total delay in years (y-axis) among number of cases (x-axis).

The twenty-fifth percentile was found to be at zero years (i.e., 25% of patients had zero total delay), the 50th percentile was at one year (50% of patients showed a total delay of 1 year or less), the seventy-fifth percentile was at 3 years with 75% of patients showing a delay of 3 years or less, and the last 25% of patients showed a total delay between 3 and 27 years. Interquartile range (IQR) ranged from 1 to 36 months. Figure 2 shows the individual distribution of total delay in years among our 440 patients.

Upon further analysis of data, we found that, out of the 330 patients (75%) who exhibited a positive total delay, "patient delay" accounted for 56 patients (16.96%) "diagnostic delay" for 142 patients (43.03%), and "treatment delay" for 132 patients (40%).

3.1. Upon Analyzing Causes of "Patient Delay". 21.05% were type A patients who had poor vision and/or a visual field defect which they initially ignored. 78.95 % were type B patients who were advised to seek an ophthalmologist for suspicion of glaucoma. Of these, 10.52% had miscellaneous personal reasons for not promptly seeking specialized eye care, like being pregnant and preferring to wait for delivery first, working abroad or repeated business travel, and being on a waiting list to see a special doctor, and some said they had personal issues that they did not want to reveal. The

remaining 68.43% stated that they simply ignored a doctor's advice to see a specialized ophthalmologist for suspected glaucoma because they did not think it was a serious problem.

3.2. The Main Reasons for Diagnostic Delay. The main reasons for diagnostic delay were inability to afford the cost of investigations needed to confirm the diagnosis (36.96%), delay in performing the needed investigations due to prolonged paper work with medically insured patients (36.96%), controversial doctor's opinions in patients who preferred to take a second opinion (17.39%), and patients with ocular hypertension (OHT), suspicious cupping, or visual field defects, who later progressed into glaucoma and were not timely diagnosed at the transition into actual glaucoma that required treatment (8.69%).

3.3. The Main Reasons for Treatment Delay. The main reasons for treatment delay were inability to afford the cost of medications and other therapy forms (68.3%) and patient delay in the execution of the prescribed treatment regimen due to ignorance and/or nonadherence or poor explanation of the importance of treatment by the treating doctor (31.7%).

Upon correlating the extent of total delay period with the patients' age, sex, and other socioeconomic factors we found the following (Table 1).

3.3.1. Age and Sex of the Patient. A positive correlation was found between the extent of total delay in years and the age of the patient ($r = 0.438$), which was statistically of high significance ($P < 0.001$). However, no significant correlation was found ($r = 0.058$) between the patient's sex and the extent of delay in years ($P = 0.225$).

3.3.2. Level of Education and Knowledge about the Disease. A negative correlation of high statistical significance ($P < 0.001$) was found between the level of education of patients and the total delay in years, with the delay increasing the less the patient's education level ($r = -0.366$).

Another highly significant ($P < 0.001$) negative correlation was found between the patient's knowledge about glaucoma as a disease and its possible sequelae and the delay in years. Again longer delays were met in patients with poor knowledge about glaucoma ($r = -0.283$).

3.3.3. Laterality of Glaucoma and the Presence of Associated Systemic Disease. No statistically significant correlation ($r = 0.030$) was found between the disease being unilateral or bilateral and the delay in years ($P = 0.533$). However, a statistically highly significant ($P < 0.001$) positive correlation was found between the presence of associated systemic disease and the extent of delay in years ($r = 0.219$).

3.3.4. Family History of Glaucoma and the Presence of Medical Insurance. A highly significant negative correlation ($P < 0.001$) was found between having a positive family history of glaucoma and the extent of delay in years, with patients exhibiting shorter delay if they had a positive family history of glaucoma ($r = -0.305$). Another statistically significant ($P = 0.010$) weak positive correlation ($r = 0.122$) was found between having a medical insurance and the delay in years with patients having medical insurance exhibiting longer delay intervals. Table 1 summarizes the correlations between the total delay in years and demographic as well as other socioeconomic variables.

Table 1: Correlations between delay in years and different variables.

	Delay in yrs.
Spearman's rho	
Sex	
Correlation coefficient	0.058
P value	0.225
N	440
Age	
Correlation coefficient	0.438
P value	0.000
N	440
Education level	
Correlation coefficient	−0.366
P value	0.000
N	440
Bilaterality	
Correlation coefficient	0.030
P value	0.533
N	440
Family history	
Correlation coefficient	−0.305
P value	0.000
N	440
Associated disease	
Correlation coefficient	0.219
P value	0.000
N	440
Knowledge about glaucoma	
Correlation coefficient	−0.283
P value	0.000
N	440
Insurance	
Correlation coefficient	0.122
P value	0.010
N	440

Of our 440 interviewed patients, 14 patients (3.18%) had to quit their job or change it to a less visually demanding one. Twenty-nine patients have stopped driving cars, buses, or tricycles (6.59%). Most patients gave positive complaints about becoming less independent at home, a complaint which was not considered statistically because of its possible psychological origin (false sense of insecurity).

4. Discussion

The mean total delay in this study was 2.31 ± 3.51 years. The median total delay was one year, and interquartile range

(IQR) was 1–36 months. The main type of delay in our study was diagnostic delay, where it took patients longer than usual to get an accurate and confirmed diagnosis of glaucoma. This has an impact on the prognosis of disease. Our results which showed a positive delay in 75% of our cases were similar to those reported in a study done in Iran on 258 newly diagnosed glaucoma patients [5]. However, this study focused on low socioeconomic status effect on the severity of disease at initial presentation and not on the types and causes of delay. Socioeconomic factors seem to have a direct impact on the prognosis of chronic diseases, including glaucoma [10–14].

In our study, a main cause of both diagnostic and treatment delay in POAG patients was financial incapacity, either to perform the investigations needed (36.96%) or to buy the required medication (68.3%). This also agrees with the previous studies.

Our main type of delay was diagnostic delay, being responsible for 43.03% of patients who suffered delay. We presume that the lack of medical insurance in most patients would account for this delay in diagnosis, as the cost of initial investigations is high. However, we found that 36.96% of our patients who had diagnostic delay complained of prolonged paper work which delayed the course of diagnosis despite the fact that they were medically insured. It seems that having medical insurance may contribute to delay by the prolonged paper work in our healthcare system.

Developing countries often have highly heterogeneous healthcare delivery system, with both public and private sector healthcare providers. Patients tend to move from one provider to another before they are finally properly diagnosed by a specialist and given proper treatment [6, 15, 16]. This was also true with our patients, who spent some time looking for the right eye specialist and/or whose diagnosis was sometimes delayed due to controversial doctors' opinions from different healthcare providers. The patient finally settles with the specialist whom he follows up with but some time may elapse until this is attained.

Delay in the diagnosis and treatment of POAG seemed to affect our patients' lifestyle as well, with 9.77% of our patients having had to either resign from or change a job or stop driving vehicles as a result of their visual impairment.

Upon studying the correlations between the extent of total delay in years and patient's socioeconomic factors, we found that higher patient education level, a positive family history of glaucoma, and knowledge about the nature of glaucoma were all associated with shorter periods of delay, as opposed to increasing patient's age, the presence of associated disease, and the presence of medical insurance which seemed to be associated with longer delay periods. These findings agree with what other studies found that patient awareness and level of education are important factors for prompt diagnosis and management of disease [17]. A higher male-to-female ratio was noted in our sample population. Whether that represents a true gender difference in disease distribution or is just due to males having easier access to healthcare providers due to cultural factors needs to be further investigated.

However, there are limitations to our study. POAG, unlike other diseases like tuberculosis or cancer, is largely initially asymptomatic inevitably leads to some sort of "natural delay" so long as the patient is not yet discovered. Besides, being a questionnaire based study, there is a chance of some recall bias among patients. However, we tried to minimize that by excluding any patients who did not give clear-cut dates about their delay period (at least with respect to number of years and months). We believe that the results we got can still contribute to evaluating the magnitude of the problem of delay in POAG diagnosis and treatment in our society.

Since the high costs of investigations and treatment were found to be major obstacles leading to diagnostic and treatment delay in our study, the authors recommend that more money should be spent subsidizing treatment of glaucoma patients. More efforts should be done to provide adequate medical insurance minimizing the steps involving paper work so the patients can be promptly put on track for glaucoma diagnosis and treatment. Glaucoma awareness programs should have more weight in the media and in clubs, youth organizations, and universities. Explanatory posters should be hanged and seminars held to educate the general population about glaucoma and its long term effects as this shall decrease possible future patient delay.

Competing Interests

The authors declare that they have no competing interests.

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