



# Fast Visual Field Progression Is Associated with Depressive Symptoms in Patients with Glaucoma

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**Purpose:** To evaluate the association between the rates of progressive visual field loss and the occurrence of depressive symptoms in patients with glaucoma followed over time.

**Design:** Prospective observational cohort study.

**Participants:** The study included 204 eyes of 102 patients with glaucomatous visual field defects on standard automated perimetry (SAP).

**Methods:** All patients had Geriatric Depression Scale (GDS) questionnaires and visual field tests obtained over a mean follow-up time of  $2.2 \pm 0.6$  years. Change in depressive symptoms was assessed by calculating the difference between GDS scores at the last follow-up visit from those at baseline. Rates of visual field loss were assessed by SAP. An integrated binocular visual field was estimated from the monocular SAP tests, and rates of change in mean sensitivity (MS) over time were obtained from linear mixed models. Regression models were used to investigate the association between progressive visual field loss and changes in depressive symptoms, adjusting for potentially confounding clinical and socioeconomic variables.

**Main Outcome Measures:** The association between rates of change in binocular SAP MS and change in GDS questionnaire scores.

**Results:** There was a significant correlation between change in the GDS scores during follow-up and change in binocular SAP sensitivity. Each 1 decibel (dB)/year change in binocular SAP MS was associated with a change of 2.0 units in the GDS scores during the follow-up period ( $P = 0.025$ ). In a multivariable model adjusting for baseline disease severity, change in visual acuity, age, gender, race, Montreal Cognitive Assessment score, education, income, and comorbidity index, each 1 dB/year change in binocular SAP MS was associated with a change of 3.0 units in the GDS score ( $P = 0.019$ ).

**Conclusions:** Faster visual field progression was associated with the occurrence of depressive symptoms in patients with glaucoma. *Ophthalmology* 2016;123:754-759 © 2016 by the American Academy of Ophthalmology.



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Glaucoma is a progressive optic neuropathy and one of the leading causes of visual impairment and decrease in vision-related quality of life.<sup>1-3</sup> Because of its chronic nature, its potential for causing irreversible blindness, and the inherent side effects of the treatment, glaucoma often can impose a psychologic burden to patients.<sup>3-6</sup> The prevalence of depressive symptoms among patients with glaucoma varies from 6% to 16% in different studies and has been reported to be higher than in patients without the disease.<sup>7-12</sup>

Several previous studies have shown a relationship between the severity of visual field loss and the occurrence of depressive symptoms in patients with glaucoma.<sup>7-16</sup> These studies have used a cross-sectional design and suggested that worse disease severity was associated with higher prevalence of depressive symptoms.<sup>11,12,14-17</sup> However, the cross-sectional design may impose limitations to the study of this association, because it does not allow an assessment of how visual

field changes over time would affect patients' well-being and how they might be associated with depressive symptoms. In previous studies, we have shown that the rate of visual field loss was associated with decline in self-reported quality of life as measured by the 25-item National Eye Institute Visual Function Questionnaire.<sup>18-21</sup> The 25-item National Eye Institute Visual Function Questionnaire measures several aspects of quality of life, including the ability to perform everyday tasks such as reading and driving.<sup>22</sup> It is likely that a patient with a fast rate of visual field loss experiences greater difficulty with activities of daily living, potentially leading to depressive symptoms, compared with a subject whose disease has been progressing slowly. In fact, a study by Kiely et al<sup>23</sup> suggests that functional impairment in physical or social domains explains much of the longitudinal association between sensory loss and depressive symptoms.

In this study, we investigated the relationship between the rate of visual field loss and the occurrence of depressive symptoms in a cohort of patients with glaucoma followed over time.

## Methods

Participants from this study were included in a prospective longitudinal study designed to evaluate functional impairment in glaucoma conducted at the Laboratory of Performance and Visual Function of the University of California San Diego. The institutional review board at the University of California San Diego approved the methods, and written informed consent was obtained from all participants. The study adhered to the laws of the Health Insurance Portability and Accountability Act, and all study methods complied with the Declaration of Helsinki guidelines for human subject research.

All participants underwent a comprehensive ophthalmologic examination, including review of medical history, visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, corneal pachymetry, gonioscopy, dilated funduscopy examination using a 78-diopter lens, stereoscopic optic disc photography, and standard automated perimetry (SAP) using the 24-2 Swedish Interactive Threshold Algorithm Standard of the Humphrey Field Analyzer II, model 750 (Carl Zeiss Meditec, Inc, Dublin, CA). Only subjects with open angles on gonioscopy were included. Patients with coexisting retinal disease, uveitis, or nonglaucomatous optic disc neuropathy were excluded from the study.

Glaucoma was defined by the presence of 2 or more consecutive abnormal SAP test results at baseline, defined as a pattern standard deviation with  $P < 0.05$  and/or glaucoma hemifield test results outside normal limits, and evidence of glaucomatous optic neuropathy based on masked assessment of stereophotographs. A subject was considered to have glaucoma if damage was present in at least 1 eye.

The presence of depressive symptoms was evaluated with the Geriatric Depression Scale (GDS) questionnaire. For inclusion in the study, subjects were required to have completed a baseline and a follow-up GDS questionnaire over a minimum period of 1 year. In addition, they were required to have had at least 3 visual fields during the corresponding period. Data for this study were obtained during the period extending from March 2011 to April 2015. During follow-up, each patient was treated at the discretion of the attending ophthalmologist.

## Monocular and Binocular Visual Fields

Monocular SAP was performed using the 24-2 Swedish Interactive Threshold Algorithm Standard test at all visits during the follow-up period. Only reliable tests ( $\leq 33\%$  fixation losses and  $\leq 15\%$  false-positives) were included. In addition, visual fields were reviewed and excluded in the presence of artifacts, such as eyelid or rim artifacts, fatigue effects, inattention, or inappropriate fixation. Visual fields also were reviewed for the presence of abnormalities that could indicate diseases other than glaucoma, such as homonymous hemianopia. To evaluate binocular visual field (BVF) loss, sensitivities of the monocular SAP threshold sensitivities of the right and left eyes were used to calculate an integrated BVF. The sensitivity for each point of the BVF was estimated using the binocular summation model described by Nelson-Quigg et al.<sup>24</sup> Evaluation of rates of visual field change was performed using the mean sensitivity (MS) of the BVF. The MS was calculated

as the average of the BVF threshold sensitivities for the integrated field.

## Geriatric Depression Scale

The GDS questionnaire is a self-reported tool that has been validated for screening depression in the elderly and is used commonly as part of a geriatric assessment.<sup>25</sup> The 15-item GDS consists of 15 dichotomous (yes/no) questions about depressive symptoms in the past week (Fig 1, available at [www.aaojournal.org](http://www.aaojournal.org)). One point is assigned to each answer, and the cumulative score is rated on a scoring grid, so possible scores range from 0 to 15. Scores  $>5$  are suggestive of depression, and scores  $\geq 10$  almost always are indicative of depression. A more detailed scoring also can be used to stage depression: from 5 to 8 is indicative of mild depression, from 9 to 11 is indicative of moderate depression, and from 12 to 15 is indicative of severe depression. We obtained an estimate of the change in the occurrence of depressive symptoms by subtracting the final GDS score from the baseline GDS score. Therefore, an increase in the scores indicated increased incidence of depressive symptoms during follow-up.

## Demographic, Clinical, and Socioeconomic Variables

Socioeconomic and clinical questionnaires also were administered to patients at the time of the baseline GDS. These questionnaires contained a survey about demographics, history of ocular and medical conditions, degree of education, and income level. Because depressive symptoms can have multiple causes and several factors might contribute to depression, these factors were included as potential confounding factors in the analysis of the relationship between change in GDS scores and progressive field loss. Variables were categorized for inclusion in the multivariable models as degree of education (at least graduate school degree [yes/no]), income ( $< \$25\,000/\text{year}$  [yes/no]), use of antidepressants (yes/no), and use of topical nonselective beta-blockers (yes/no). For comorbidities, we investigated the presence or history of the following conditions: diabetes mellitus, arthritis, autoimmune diseases, high blood pressure, heart disease, asthma, stroke, and cancers. A simple summation score was used to create a comorbidity index.<sup>19</sup> All subjects also completed the Montreal Cognitive Assessment (MoCA) test. The MoCA test is a 30-point cognitive screening tool developed to detect mild cognitive impairment. Change in visual acuity during follow-up was calculated as the difference between the logarithm of the minimum angle of resolution (logMAR) visual acuity at the last follow-up visit and baseline visit for each eye. The eye with better visual acuity at baseline was considered as the better eye for the purpose of analysis of change in visual acuity.

## Statistical Analysis

Rates of visual field loss from SAP were obtained by linear mixed models.<sup>26–28</sup> A univariable linear regression model then was used initially to evaluate the relationship between change in GDS scores and rates of visual field loss. Subsequently, the relationship was studied after adjustment for potentially confounding factors, such as visual acuity, age, gender, race, disease severity, use of antidepressants, use of topical nonselective beta-blockers, presence of comorbidities, degree of cognitive impairment, and socioeconomic variables.

Table 1. Baseline Demographic and Clinical Characteristics of Subjects Included in the Study (n = 102)

Characteristic	Value
Age, yrs	67.4±12.2
Gender, n (%) female	47 (46.1)
Race, n (%)	
White	54 (52.9)
African American	34 (33.3)
Asian	9 (8.8)
MD SAP 24-2 (worse eye), dB	-4.6±6.2
MD SAP 24-2 (better eye), dB	-1.8±4.0
Binocular MS SAP 24-2, dB	29.2±3.7
Visual acuity (worse eye), logMAR	0.01±0.12
Visual acuity (better eye), logMAR	-0.05±0.10
GDS score	2.3±2.6
Educational level (at least college degree), n (%)	88 (86.3)
Income (<\$25 000), n (%)	13 (12.8)
Use of antidepressants, n (%)	11 (10.8)
Use of topical nonselective beta-blockers, n (%)	29 (28.4)
MoCA score	27.8±2.2
Comorbidity index	1.5±1.3

dB = decibels; GDS = Geriatric Depression Scale; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; MoCA = Montreal Cognitive Assessment; MS = mean sensitivity; SAP = standard automated perimetry. Values are presented as mean ± standard deviation, unless otherwise noted.

All statistical analyses were performed using commercially available software, Stata version 13 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

## Results

The study included 204 eyes of 102 subjects with glaucomatous visual field loss. Table 1 shows the clinical and demographic characteristics of the included subjects. Mean age at baseline was 67.4±12.2 years. There were 55 male subjects (53.9%) and 47 female subjects (46.1%). At baseline, average mean deviation

(MD) of the worse and better eyes of patients with glaucoma were -4.6±6.2 decibels (dB) and -1.8±4.0 dB, respectively. However, there was a wide range of MD values of visual fields included in the study, ranging from -26.4 to 2.6 dB. The average binocular MS at baseline was 29.2±3.7 dB. Baseline GDS score was 2.3±2.6 units, ranging from 0 to 8 units.

Subjects were followed for an average of 2.2±0.6 years (range, 1.0–3.9 years), from the date of the first visual field to the date of the last visual field closest to the GDS questionnaire. The median number of available SAP visual field tests during follow-up was 7 (interquartile range, 4–10). Mean rate of change in binocular MS was -0.3±0.3 dB/year (range, -1.5 to 0.1 dB/year). Mean change in GDS scores was -1.2±2.5 units (range, -8 to 5 units). Table 2 shows results of univariable models investigating factors associated with change in GDS scores over time. There was a significant relationship between change in the GDS scores during follow-up and rates of change in binocular SAP sensitivity. Each 1 dB/year faster decline in binocular SAP MS was associated with an increase of 2.0 units in the GDS scores during the follow-up period (95% confidence interval [CI], 0.3–3.7;  $P = 0.025$ ;  $R^2 = 5.0\%$ ). When rates of visual field change were assessed by the SAP MD values of the better eye, as defined by the eye with higher SAP MD (less field defect) at baseline, the relationship was similar. Each 1 dB/year faster rate of progression in SAP MD of the better eye was associated with a 1.8-unit increase in GDS scores over time (95% CI, 0.3–3.3;  $P = 0.017$ ;  $R^2 = 5.5\%$ ). No statistically significant association was seen between change in SAP MD of the worse eye and change in GDS scores ( $P = 0.281$ ).

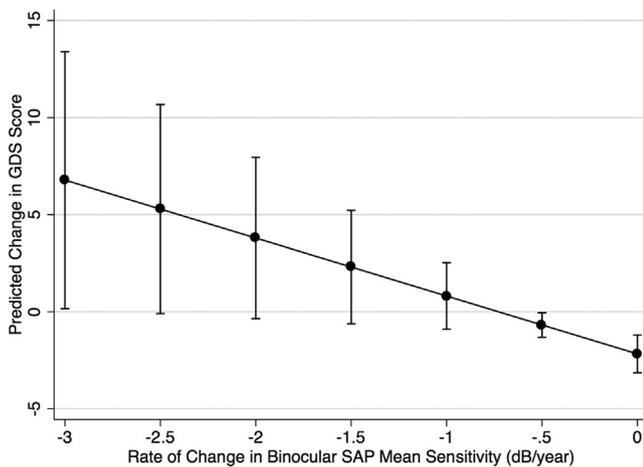
Baseline disease severity and change in visual acuity were not significantly associated with change in GDS scores during follow-up. Age, gender, and race also were not significantly associated with change in GDS scores over time in the univariable models. There was also no relationship between change in GDS scores and the variables education, income, use of antidepressants, use of topical nonselective beta-blockers, MoCA score, and the comorbidity index.

In the multivariable model adjusting for potentially confounding variables, the rate of change in binocular MS was still significantly associated with change in the GDS scores (Table 2). Each 1 dB/year faster decline in binocular SAP MS was associated with an increase of 3.0 units in the GDS scores (95% CI, 0.5–5.5;  $P = 0.019$ ) (Fig 2). In the multivariable model using the rate of

Table 2. Results of the Univariable and Multivariable Regression Models for Explaining Change in Geriatric Depression Scale Score in Patients with Glaucoma

Characteristic	Univariable Model		Multivariable Model	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Rate of change in binocular MS, per 1 dB/yr faster loss	2.0 (0.3 to 3.7)	0.025	3.0 (0.5 to 5.5)	0.019
Baseline binocular MS, per 1 dB lower	0.1 (0.0 to 0.2)	0.191	0.0 (-0.2 to 0.2)	0.878
Change in visual acuity of better eye, per 0.1 logMAR higher	0.0 (-0.6 to 0.5)	0.954	-0.1 (-0.7 to 0.4)	0.671
Age, per 1 decade older	-0.1 (-0.5 to 0.3)	0.541	-0.4 (-0.9 to 0.1)	0.093
Gender, female	0.4 (-0.6 to 1.4)	0.446	0.3 (-0.7 to 1.3)	0.556
Race, white	0.5 (-0.6 to 1.6)	0.352	0.3 (-1.1 to 1.7)	0.707
Educational level, at least college degree	-0.4 (-1.9 to 1.0)	0.549	-0.4 (-2.1 to 1.2)	0.599
Income, <\$25 000	-0.6 (-2.1 to 0.9)	0.428	-1.0 (-2.5 to 0.6)	0.214
Use of antidepressants, yes	1.3 (-0.3 to 2.9)	0.108	1.6 (-0.1 to 3.4)	0.072
Use of topical nonselective beta-blockers, yes	0.6 (-0.5 to 1.7)	0.270	0.4 (-0.8 to 1.6)	0.506
MoCA score, per 1 unit lower	-0.1 (-0.3 to 0.2)	0.550	-0.1 (-0.4 to 0.2)	0.412
Comorbidity index, per 1 unit higher	-0.1 (-0.5 to 0.3)	0.789	-0.1 (-0.6 to 0.4)	0.826

CI = confidence interval; dB = decibel; logMAR = logarithm of the minimum angle of resolution; MoCA = Montreal Cognitive Assessment; MS = mean sensitivity.



**Figure 2.** Predicted changes with 95% confidence interval (CI) in the Geriatric Depression Scale (GDS) score for different values of rate of change in binocular standard automated perimetry (SAP) mean sensitivity (MS) (decibels [dB]/year).

change in SAP MD values of the better eye, each 1 dB/year faster decline in SAP MD values of the better eye was associated with an increase of 2.8 units in the GDS scores (95% CI, 0.5–5.0;  $P = 0.015$ ).

## Discussion

In this study, we showed that rates of visual field change as assessed by SAP were significantly associated with depressive symptoms in patients with glaucoma followed over time. Patients with rapidly progressing disease showed an increase in the incidence of depressive symptoms, as assessed by changes in a previously validated depression scale. To the best of our knowledge, such association has not been demonstrated in the literature. Our findings indicate that assessment of rates of visual field progression in glaucoma may be important for indicating patients at risk for developing depressive symptoms over time.

Patients with rapid visual field progression had greater change in GDS scores compared with those with slower field changes over time. In the univariable model, each 1 dB per year faster loss in binocular SAP MS was associated with a change of 2.0 units in the GDS scores during follow-up. This finding indicates that faster visual field loss can increase the occurrence of depressive symptoms in patients with glaucoma. It is possible that increased difficulties with activities of daily living or impaired social engagement could explain this association.<sup>23</sup> In fact, in previous studies we demonstrated that faster rates of visual field loss were associated with longitudinal decline in self-reported quality of life.<sup>18–21</sup> Patients with relatively slower visual field progression may have more time to adapt to their limited functional status by developing compensatory strategies that might decrease the impact of the disease and, therefore, would have lower chance of developing or reporting depressive symptoms.

It should be noted that despite the statistically significant association with change in GDS scores, rates of visual field

change explained only a relatively small proportion of the change seen in the responses to GDS questionnaires over time. This is probably explained by the multifactorial cause of this condition. Nevertheless, rates of visual field loss were still significantly associated with depressive symptoms after adjustment for confounding factors. Each 1 dB loss in binocular SAP MS per year was associated with a change of 3.0 units in the GDS score in the multivariable model.

Depression is one of the leading causes of disability, and most studies have reported a higher prevalence of depression in patients with glaucoma compared with controls.<sup>7,9–12</sup> Glaucoma was a significant predictor of depression after adjustment for demographic factors and comorbidities in a nationally representative population sample, but not after adjustment for self-reported general health condition.<sup>12</sup> The same study showed that, among participants with glaucoma, self-reported measures of vision were significant risk factors for depression, whereas objective measures of vision were not.<sup>12</sup> Jampel et al<sup>14</sup> reported that symptoms of depression were related to worse self-reported visual function in patients with newly diagnosed glaucoma from the Collaborative Initial Glaucoma Treatment Study. However, the same study failed to correlate monocular objective measures of visual function with most of the symptoms of depression.<sup>14</sup> Although these results may seem to contrast to the positive relationship between rates of visual field change and depressive symptoms found in our study, the differences might be explained, at least in part, by the different study designs. Previous investigations have used cross-sectional data, which may be affected by the wide inter-individual variability in subjective perceptions about the impact of disease on well-being.<sup>11,12,14–17</sup> In addition, the impact of disease severity on a patient's quality of life may be affected by the possible development of compensatory mechanisms, as described previously. By using a longitudinal design, this study may be able to provide a better evaluation of how functional loss in glaucoma would affect quality of life and patient well-being. In fact, we demonstrated that rates of visual field loss were more important in predicting change in depressive symptoms than disease severity as assessed in a single point in time.

## Study Limitations

The present study has limitations. The average follow-up time was relatively short, considering the long-term duration of a disease such as glaucoma. Despite that, we found statistically significant and relevant associations between longitudinal changes in SAP and GDS scores, but longer-term follow-up may provide us with improved estimates of this relationship. Another limitation of our study is that we included only baseline values for a number of potentially confounding clinical and socioeconomic variables, such as comorbidities. It probably would have been better to assess whether change occurred in these variables over the duration of follow-up. However, investigating change in the impact of comorbidities over time would be an extremely difficult if not impossible task to conduct because of the many variables that could affect it, such as change in the severity of

many conditions, impact of a variety of treatments, and their side effects. Although we evaluated the impact of baseline MoCA scores on GDS changes over time, longitudinal changes in cognitive status also could be a potential confounding factor affecting the report of depressive symptoms. However, repeated MoCA evaluations were available during follow-up for 80 (78.4%) of the 102 subjects, and there was no significant relationship between change in MoCA scores and change in GDS scores ( $P = 0.199$ ). When the multivariable model also included change in MoCA scores in this restricted sample, rates of visual field progression were still significantly associated with change in GDS scores ( $P = 0.013$ ). Another limitation of our study is that we did not perform longitudinal systematic lens opacity grading to evaluate a possible effect of worsening cataracts in explaining the occurrence of depressive symptoms. However, there was no significant relationship between change in visual acuity and change in GDS scores in our population. Therefore, we believe that cataract most likely did not have a significant impact in explaining the relationships found in our study.

It could be argued that the change in depressive symptoms for some patients in our study may have occurred simply from the fact that they may have been informed by the attending physician of the progression or stability of their visual fields. However, it is likely that our study replicated what usually happens in clinical practice, and the reported associations likely are to be of clinical relevance. However, the report of depressive symptoms by patients might have been affected by the timing of application of the GDS questionnaires. For example, if in a discussion with the physician a patient was told about visual field progression and the GDS questionnaire happened to be applied shortly thereafter, this patient might have reported a higher prevalence of depressive symptoms at that point than he or she would report if questioned at a later point in time. Unfortunately, we were not able to control the timing of questionnaire application in relation to patient–physician interactions. Future studies should attempt to clarify this issue.

In conclusion, fast visual field loss was significantly associated with the incidence of depressive symptoms in patients with glaucoma. Our findings suggest that rates of change may be indicative of the risk for developing depressive symptoms in patients with glaucoma, and they emphasize the need for an accurate and precise assessment of rates of change in monitoring this disease.

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Abbreviations and Acronyms:

**BVF** = binocular visual field; **dB** = decibel; **GDS** = Geriatric Depression Scale; **MD** = mean deviation; **MoCA** = Montreal Cognitive Assessment; **MS** = mean sensitivity; **SAP** = standard automated perimetry.

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