Journal of Affective Disorders 333 (2023) 290–296

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Depression scores are associated with retinal ganglion cells loss

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ARTICLE INFO

Keywords:
Beck depression inventory
Retinal ganglion cells
Glaucoma
Sleep
Circadian disruption
GNβ3 rs5443

ABSTRACT

Background: Light is a known factor affecting mood and the circadian system. Light deficit is linked to deteriorated transduction of photic information to the brain, and reduced amplitude of the perceived circadian light signaling. Retinal ganglion cells (RGCs) loss due to advanced glaucoma can be a factor compromising light perception, with consequences for circadian rhythms, sleep and mood. This study aimed to estimate associations of RGCs loss with a depression score by multiple regression, accounting for other features of glaucoma.
Methods: One hundred and fifteen patients diagnosed with primary open-angle glaucoma completed the Beck Depression Inventory II questionnaire. The damage to their RGCs was assessed by high-definition optical coherence tomography (HD-OCT) and their function by pattern electroretinogram (PERG). On fifteen of these patients, 24-h salivary melatonin patterns were determined under light-controlled laboratory conditions, and analysis of eight clock related gene polymorphisms was performed.
Results: Backward stepwise multiple regression revealed that the BDI score was the strongest factor that was most closely associated with the HD-OCT-based percentage of global RGCs loss (standardized coefficient, $b^* = 0.784$, $p < 0.001$), surpassing other related factors, including age, intraocular pressure, visual field loss, and PERG amplitude. A high BDI score was associated with the GNβ3 825C > T polymorphism (dbSNP rs5443).
Limitations: This study did not specifically address damage to intrinsically photoreceptive RGCs. The gene study is based on a limited number of volunteers.
Conclusions: Depression scores are strongly associated with RGCs loss, increasing abruptly above a threshold of 15 %, supporting the hypothesis that RGCs loss in advanced glaucoma may affect non-visual photic transduction and lead to mood disturbances.

1. Introduction

Daytime light is crucial for human circadian rhythms, sleep, and mood. Different types of retinal ganglion cells (RGCs) participate in transducing visual and non-visual photic information to the relevant brain regions. It was recently shown that light can affect mood directly through a SCN-independent pathway linking intrinsically photosensitive RGCs (ipRGCs) to a novel thalamic region, the perihabenular nucleus (Fernandez et al., 2018), through mechanisms that involve the core clock gene *Per1* (Olejniczak et al., 2021). Aberrant ambient light signaling in an experimental animal model induced mood deficits that preceded learning impairments and changes in circadian rhythms (LeGates et al., 2012).

Light perception is compromised when RGCs are affected. Damage to

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https://doi.org/10.1016/j.jad.2023.04.039
Received 25 November 2022; Received in revised form 27 March 2023; Accepted 14 April 2023
Available online 20 April 2023

the retinal cells may occur in certain pathologies, e.g., neurodegenerative diseases, diabetic retinopathy, and glaucoma. Glaucoma is a progressive optic neuropathy that by the year 2020 affected 76 million people. It is estimated to exceed 110 million by 2040 (Allison et al., 2020). Primary open-angle glaucoma (POAG) is the most common form; the current global of POAG population is estimated at 68.56 million people (Zhang et al., 2021). Increasing damage to the RGCs with glaucoma progression impairs light synchronization, thereby affecting circadian rhythms (Gubin et al., 2019, 2021), sleep (Agorastos et al., 2013; Gracitelli et al., 2015; Guo et al., 2017; Gubin et al., 2019), and mood (Agorastos et al., 2013; Zhang et al., 2017; Chen et al., 2018; Shin et al., 2021).

Different subtypes of RGCs have uneven susceptibility to glaucomatous damage and therefore may occur earlier or later during glaucoma progression (Lin and Peng, 2013; Cui et al., 2015; Vidal-Sanz et al., 2017; Yang et al., 2020; Mure, 2021). Since ipRGCs are resistant to mild glaucoma, but are lost in advanced stages (Obara et al., 2016), alterations in circadian rhythms, sleep, and mood are also expected to be more pronounced in advanced glaucoma. A certain threshold of RGCs loss may also exist before deleterious effects on mood, sleep, and circadian rhythms are observed. Indeed, we previously found that RGCs' global loss volume (GLV) above 15 % may trigger circadian deterioration (Gubin et al., 2019, 2021; Neroev et al., 2020; Gubin and Weinert, 2022), affecting systemic variables such as temperature (Gubin et al., 2019, 2021) and melatonin (Gubin et al., 2021; Gubin and Weinert, 2022), or local variables such as intraocular pressure (Neroev et al., 2020; Gubin and Weinert, 2022), as well as sleep, and mood (Gubin et al., 2019, 2021).

Mood alterations are closely linked to glaucoma (Agorastos et al., 2013; Zhang et al., 2017; Chen et al., 2018; Yoshikawa et al., 2019) and the odds ratio of cognitive dysfunction is more than doubled in severe glaucoma (Yoshikawa et al., 2021). Glaucoma is associated with a prevalence of depression assessed by the Beck depression inventory, which was nearly 10 times higher than that in the general population in Mexico (Gamiochipi-Arjona et al., 2021). The odds ratio of depression in North America associated with glaucoma was over 12 (Zhang et al., 2017). A depression score was recently shown to be associated with the visual field mean deviation in glaucoma (Shin et al., 2021). It was concluded that anxiety may increase the risk of glaucoma progression, as most clinical studies had anticipated. Herein, we present results in favor of an alternate concept: the loss of RGCs may provoke depression that intensifies when RGCs loss reaches a threshold of 15 %, a limit above which circadian rhythms and sleep are altered.

2. Materials and methods

2.1. POAG diagnosis and progression criteria

The criteria for selecting patients with POAG were visual acuity 0.5–1.0 (without correction or with correction requiring no more than ±3.0 diopters, and no >1 diopter for astigmatism), a transparent lens and no pathology of the macular region of the retina. The dynamics of visual function were assumed to have stabilized in patients with a change in mean deviation (mD) by no >0.5 dB (dB) per year, and a decrease in GLV by no >2 % per year. These patients were assigned to the stable group, S-POAG. In other cases, the process was considered progressive, and patients were assigned to the advanced group, A-POAG. Data from the worst eye were considered for group assignment. Patients with S-POAG and A-POAG were matched by gender, age and treatment; exclusion criteria are the same as those described previously (Gubin et al., 2019, 2021; Neroev et al., 2020).

2.2. RGC damage assessment

Standard Automated Perimetry (SAP) was performed to assess the visual field (VF) with the Humphrey Field Analyzer (*Carl Zeiss, Jena, Germany*), using the 30-2 SITA-Standard strategy. The following parameters were obtained: total photosensitivity of the central VF, mD, and pattern standard deviation (PSD). Damage to the Retinal Ganglion Cell Complex (RGCC) was measured by means of high-definition optical coherence tomography (HD-OCT) (*RTVue-100, Optovue, 2800 Bayview Dr, Fremont, CA, USA)*. The average amount of GCC loss over the entire GCC map (Global Loss Volume, GLV, %) and the average amount of localized thinning over the entire GCC map (Focal Loss Volume, FLV, %) were estimated. Optic nerve head (ONH) and retinal nerve fiber layer (RNFL) scanning protocols 3.45 were followed, using the *GCC for the RTVue-100* tomograph.

2.3. RGC function assessment

Functional ability of RGCs was assessed by pattern electroretinogram amplitude (PERGA), a useful tool to estimate the risk of glaucoma progression (Porciatti, 2015; Jeon et al., 2019). PERG was assessed at three different times of the 24-h cycle, once per day on 3 consecutive days, at 8:00 on the first day, at 14:00 on the second day, and at 20:00 on the third day. No nightly data were obtained due to the fact that patients had to come to the clinic to have this complex and burdensome procedure performed. PERG was assessed by electroretinography, using "Tomey EP 1000" (*Tomey, Japan-Germany*), with electrode-cups fixed on the lower eyelid. Standard methods were followed in accordance with the recommendations of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Marmor and Zrenner, 1999). Results were evaluated in accordance with the electrophysiological standards of the ISCEV. In this study, three-measurements-mean values of PERG were used in multiple linear regression models.

2.4. Intraocular pressure (IOP) measurements

IOP was measured 7 times a day (at 8:00, 11:00, 14:00, 17:00, 19:00, 23:00 and 3:00 h) for three consecutive days (72 h), as described previously (Neroev et al., 2020; Gubin et al., 2021). In this study, 24-h mean values of IOP were used in multiple linear regression models.

2.5. Mood assessment

The Beck Depression Inventory II (BDI-II), Russian translation (Smarr and Keefer, 2011), was completed by each participant for a quantitative analysis of mood. Depressive symptoms were considered minimal if the total score was 0–13, mild if it was 14–19, moderate if it was 20–28, and severe if it was 29 or higher.

2.6. Sleep assessment

Individual diaries provided information about the time of going to bed and the time of awakening. Mean sleep phase and mean sleep duration over three days were estimated based on diaries, as previously described (Gubin et al., 2019).

2.7. Chronotype assessment

The chronotype score (CS), which reflects individual habitual preferences in 24-h activities, was assessed by the Horne–Ostberg Morningness–Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976). Low scores correspond to morning types, whereas high scores denote evening types.

2.8. Body temperature (Tb) measurements

Axillary body temperature (Tb) was measured 7 times per day (at 8:00, 11:00, 14:00, 17:00, 19:00, 23:00 and 3:00 h) on three concessive days (72 h) with a mercury thermometer (*Amrus AMTD, Amrus Enterprises Ltd., New Jersey, USA*), as described previously (Gubin et al., 2019,

2021). In this study, mean phases of individual Tb measurements and a measure of phase instability (phase standard errors) were used in multiple linear regression models. Both estimates were derived from the cosine curve best fitting Tb data over the whole 72-h time series.

2.9. Salivary melatonin assessment

Fifteen volunteers were engaged in a standardized in-laboratory study (Gubin et al., 2021). Controlled lighting was used with lights on (400 lx) from the start (10 a.m.) until 6.p.m. and lights off (<5 lx) from 6 p.m. to 8 a.m.; a standardized water and food protocol was followed. Precautions were followed according to the Procedures for Dim Light Melatonin Onset (DLMO) measurements in saliva protocol (Pandi-Perumal et al., 2007). Saliva samples were taken around the clock starting at 2 p.m. (at 2 p.m., 5 p.m., 8 p.m., 10 p.m., hourly from 10 p.m. to 4 a.m., at 6 a.m. and 10 a.m.). The protocol was previously described in more detail elsewhere (Gubin et al., 2021).

2.10. Genotyping

The genotyping procedure was always performed by the same operator, who was not aware of the participant's clinical characteristics. Saliva samples were collected according to standard protocols from 15 patients, as described elsewhere (Neroev et al., 2020; Gubin et al., 2021). Polymorphic gene variants were identified by SNP Screen Kit (Syntol; Moscow, Russia) for 8 genes (clock genes: PER2 rs6431590, PER3 VNTR, CLOCK rs 1801260 3111T/C, cryptochrome CRY1 rs12820777; melatonin receptor genes MTNR1A rs34532313, MTNR1B rs10830963, G-protein GNB rs5443; and angiotensin converting enzyme, ACE rs1799752 insertion/deletion).

2.11. Data analysis

Multiple linear regression, and stepwise forward and backward analyses were applied to examine associations between depression scores and factors related to glaucoma progression. One-way analyses of variance (ANOVA) was performed using the software packages Excel, STATISTICA 6 and SPSS 23.0. Shapiro-Wilk's W-test was applied to check for normality of the distribution. When variables were normally distributed (W-test's p-value >0.05), a 1-way ANOVA was used, with Tukey's post hoc correction for multiple testing. Otherwise, the Kruskal-Wallis and the Mann-Whitney post hoc tests were used. Statistical comparison of the strength of correlations between two associations was performed with the free online software *cocor* (Diedenhofen and Musch, 2015). The level of statistical significance was set at 5 %.

3. Results

3.1. BDI score and factors of glaucoma progression

Factors that are considered causal for glaucomatous RGC damage and its progression, or related to it, were all significantly correlated with the BDI score. These factors include IOP, RGCs damage (GLV, FLV, SAP mD), RGCs function (PERG P50 and N95 amplitudes), circadian parameters (Tb rhythm phase and phase instability), chronotype, sleep duration, and age, Table 1. The strength of correlation of these factors with the BDI score did not differ between men and women for all factors, except for circadian phase stability of Tb; this correlation was significant in women ($r = 0.394$; $p = 0.0004$), but not in men ($r = 0.010$; $p = 0.952$). Variables correlating most strongly with the BDI score were the GLV two-eye mean ($r = 0.784$) and FLV of the better eye ($r = 0.763$). These variables were also the same that correlated consistently with the BDI score in both S-POAG and A-POAG patients considered separately, Table 1. In a backward stepwise regression model, GLV also remained the variable that accounted for the strongest association with the BDI score. The BDI score correlated with chronotype, a higher score being associated with an earlier chronotype. This correlation, however, was found to be secondary to age, since only age was significant in a backward stepwise regression model. The BDI score also correlated independently with the circadian parameters: higher BDI scores are associated with a later Tb phase, a greater instability of the circadian parameters, and a shorter sleep duration. No association between the BDI score and the mean sleep phase was found. At the final step of the multiple regression analysis, the overall and forward stepwise regression models kept GLV two-eye mean (standardized coefficient, $b = 0.646$), age ($b = 0.129$), mean sleep duration ($b = -0.150$), and Tb phase stability ($b = 0.127$) as statistically significant predictors of the BDI score. However, only the higher GLV two-eye mean percentage remained

Table 1
Factors linked to glaucoma progression that are associated with an increase in the Beck Depression Inventory (BDI-II) score.

Factor		All POAG n = 115		S-POAG n = 65		A-POAG n = 50	
		r	p	r	p	r	p
Intraocular pressure, mmHg	Worse eye	**0.682**	**<0.001**	0.104	0.409	0.174	0.227
	Better eye	**0.596**	**<0.001**	0.035	0.781	**0.294**	**0.039**
	2-eye mean	**0.668**	**<0.001**	0.055	0.665	**0.296**	**0.037**
SAP mD, dB	Worse eye	**−0.765**	**<0.001**	−0.126	0.317	**−0.558**	**<0.001**
	Better eye	**−0.472**	**<0.001**	−0.044	0.727	−0.269	0.059
	2-eye mean	**−0.734**	**<0.001**	−0.097	0.441	**−0.528**	**<0.001**
GLV, %	Worse eye	**0.775**	**<0.001**	0.175	0.164	**0.311**	**0.028**
	Better eye	**0.733**	**<0.001**	**0.316**	**0.010**	0.175	0.215
	2-eye mean	**0.784**	**<0.001**	**0.258**	**0.038**	**0.312**	**0.028**
FLV, %	Worse eye	**0.737**	**<0.001**	**0.290**	**0.019**	0.254	0.076
	Better eye	**0.763**	**<0.001**	**0.319**	**0.010**	**0.336**	**0.017**
	2-eye mean	**0.727**	**<0.001**	0.215	0.085	0.243	0.089
PERG P50A, μV	Worse eye	**−0.482**	**<0.001**	0.003	0.984	−0.234	0.101
	Better eye	**−0.500**	**<0.001**	−0.215	0.086	−0.117	0.421
	2-eye mean	**−0.689**	**<0.001**	−0.234	0.060	−0.215	0.133
PERG N95A, μV	Worse eye	**−0.641**	**<0.001**	**−0.258**	**0.038**	0.019	0.894
	Better eye	**−0.591**	**<0.001**	−0.240	0.055	−0.240	0.102
	2-eye mean	**−0.662**	**<0.001**	**−0.252**	**0.043**	−0.131	0.366
Tb phase		**−0.389**	**<0.001**	−0.223	0.075	0.021	0.888
Tb phase stability		**0.304**	**0.001**	0.115	0.361	**0.412**	**0.003**
MEQ Score		**0.316**	**<0.001**	**0.264**	**0.037**	0.269	0.059
Sleep duration, h		**−0.490**	**<0.001**	**−0.436**	**<0.001**	−0.102	0.483
Age, years		**0.390**	**<0.001**	**0.427**	**<0.001**	**0.470**	**<0.001**

statistically significant after backward stepwise regression, which predicted a BDI score increase the best. Adding age, Tb phase stability, and mean sleep duration either separately or concomitantly consistently improved the model to predict the BDI score in a forward stepwise regression model, suggesting that light transmission through the eyes and the circadian system itself both contribute synergistically to the BDI score.

Fig. 1 depicts the association of the BDI score with the two-eye mean GLV, the variable best assessing glaucoma progression. Associations become most pronounced after the threshold of approximately 15 % is reached. In our cohort, none of the patients diagnosed with S-POAG had GLV above 10 % and none had severe depression with a BDI score above 30; only 5 % had moderate depression. On the contrary, patients diagnosed with A-POAG all had GLV above 15 %, 38 % reported severe depression, 50 % moderate depression, and only 12 % mild depression (BDI score < 19). Hence, the greatest BDI scores were found in advanced POAG patients with a two-eye mean GLV above the 15 % threshold. Associations between the BDI score and the two-eye mean GLV were similar when considering S-POAG ($r = 0.258$, $p = 0.038$), or A-POAG ($r = 0.312$, $p = 0.028$) patients separately; the null hypothesis of equal correlation strength between these two groups was retained, $p = 0.286$, Fig. 1.

3.2. BDI score, melatonin profiles, and gene polymorphisms

Fifteen patients volunteered to complete a 26-h in-laboratory light- and activity-controlled routine protocol and provided data on 24-h salivary melatonin production, as previously described (Gubin et al., 2021). No significant associations were found between the BDI scores and the 24-h mean, amplitude, or phase of salivary melatonin.

Patients were also genotyped for several genes, as described previously (Neroev et al., 2020; Gubin et al., 2021). No associations were found between the BDI score and polymorphisms in clock genes or melatonin receptor genes. Patients homozygous for the T allele of GNβ3 rs5443 genetic variant had higher BDI scores overall, due to the higher scores of advanced POAG patients, Table 2.

4. Discussion

Herein we demonstrate a strong correlation between the progressive loss of RGCs and an increase in depression score in glaucoma patients over 50 years of age that is independent of gender. Importantly, an abrupt increase in the BDI score was observed when the two-eye mean GLV exceeded 15 %, suggesting the existence of a threshold in RGCs loss above which depression is more likely to occur. This threshold

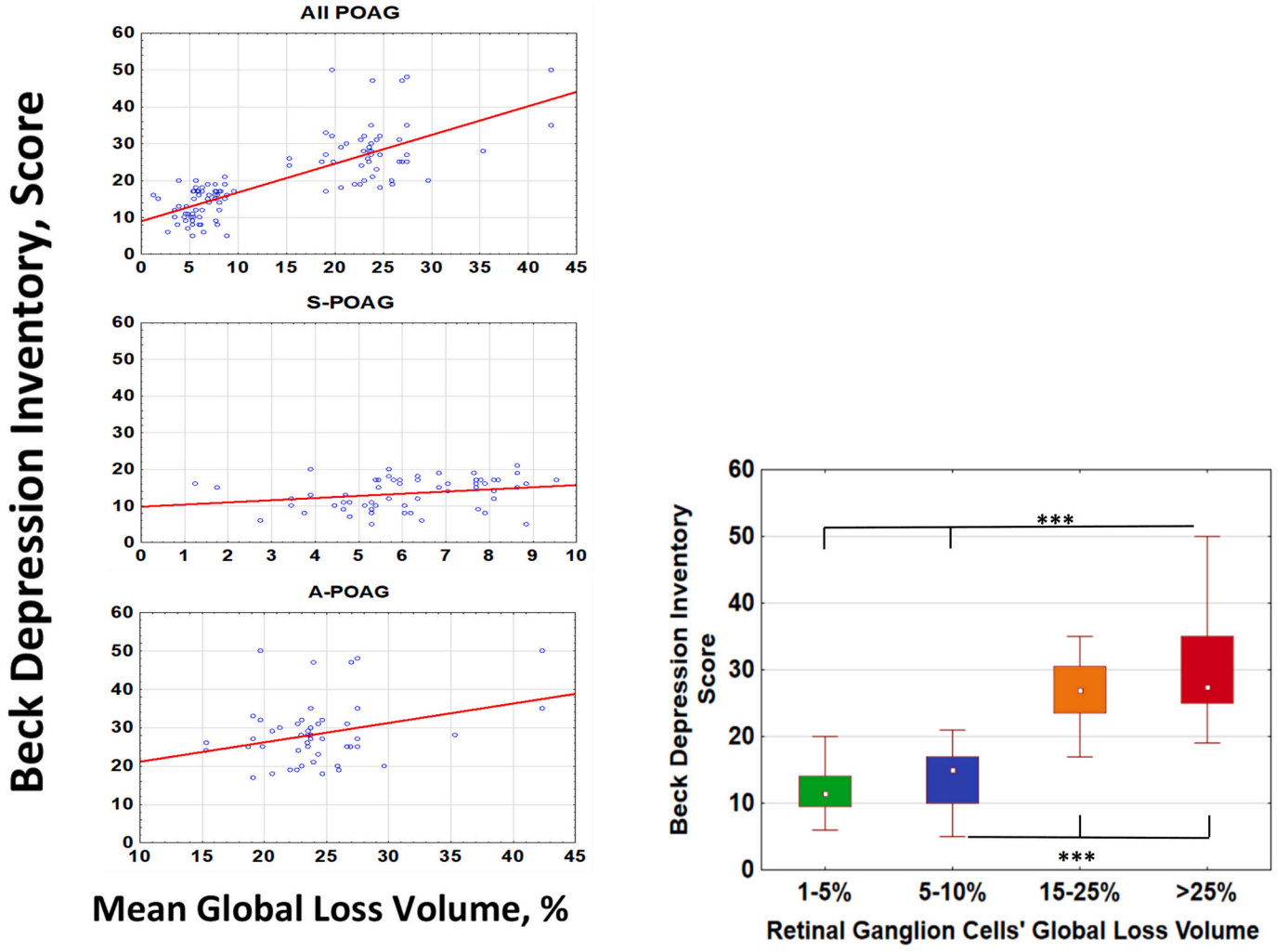

Fig. 1. Beck Depression Inventory (BDI) score is strongly associated with retinal ganglion cells loss. Left: Linear regression between the BDI score and two-eye mean percentage of global loss volume. All POAG: $r = 0.784$, $p < 0.0001$; S-POAG: $r = 0.258$, $p = 0.038$; A-POAG: $r = 0.312$, $p = 0.028$. Right: Corresponding boxplot. Note that associations become most pronounced after the threshold for GLV of approximately 15 % is reached, resembling associations previously found for disrupted circadian rhythm and sleep (Gubin et al., 2019). Boxplot depicts Median (dot); 25 %–75 % Range (colored box), and Non-Outlier Range (bracketed vertical line). Kruskal-Wallis $H (3;115) = 80.41$; *** $p < 0.0001$ between subgroups with different percentages of GLV loss. All-POAG – whole POAG cohort, $n = 115$; S-POAG – stable POAG, $n = 65$; A-POAG – advanced POAG, $n = 50$.

Table 2
Dependence of the Beck depression inventory score on some polymorphic variants of biological clock, melatonin receptors, and G-protein genes in patients with primary-open glaucoma (POAG).

Gene polymorphism	P-value for effect significance; ANOVA / MANOVA	
	BDI	BDI * GROUP
CLOCK rs1801260 3111 T/C	0.321	0.157
PER2 rs6431590	0.733	0.899
PER3 VNTR	0.475	0.605
CRY1 rs12820777	0.721	—*
MTNR1A rs34532313	0.176	0.361
MTNR1B rs10830963	0.725	0.583
GNB rs5443	**0.026**	**0.007**

* The main allele variant prevailed; rare polymorphism carriers were not present in either S-POAG or A-POAG group. MANOVA tested for BDI, S-POAG versus A-POAG group, and their interaction.

corresponds to concomitant alterations in the circadian rhythm of Tb (phase delay and instability) and impaired sleep described earlier (Gubin et al., 2019, 2021). Though early dysfunction in ipRGCs can be discerned already in early glaucoma stages (Adhikari et al., 2016), it was repeatedly shown that ipRGCs are more resistant to glaucomatous high-pressure damage compared to the general RGCs population (Cui et al., 2015; Vidal-Sanz et al., 2017), assuming that changes in the circadian system are not severe, since non-photic signaling is maintained at these stages. Indeed, in mild glaucoma, sleep, circadian rhythm, and melatonin profiles are retained or only minimally altered (Adhikari et al., 2016; Gubin et al., 2019, 2021, 2022). In advanced glaucoma, however, substantial ipRGCs loss becomes evident (Obara et al., 2016). As expected, rhythmic secretion of melatonin becomes severely impaired (Pérez-Rico et al., 2010; Yoshikawa et al., 2020; Gubin et al., 2021, 2022) and circadian disruption is clearly manifested (Gubin et al., 2019, 2021, Neroev et al., 2020).

The intensity and timing of ambient illumination are both associated with mood (Girardin et al., 2005). We hypothesize that gradually reduced light reception caused by RGCs loss in glaucoma may affect mood by a mechanism somewhat similar to that of seasonal affective disorder, which includes impaired circadian rhythms and serotonin metabolism. The diminished amplitude of light signaling weakens circadian synchronization (Roenneberg and Merrow, 2016) and facilitates disruption of circadian rhythms (Gubin et al., 2016). In turn, unstable, less robust circadian rhythms make humans more susceptible to mood disorders (Erren et al., 2011). Vice versa, an increase in the post-illumination pupil response after scheduled daily bright light exposure correlated with an increased circadian amplitude and higher inter-daily stability of the activity rhythm (Kawasaki et al., 2021).

A cross-sectional HEIJO-KYO study in general elderly population found that glaucomatous optic disc was associated with higher prevalence of depression independent of potential confounders, including daily light exposure (Yoshikawa et al., 2019). A more recent work (Shin et al., 2021) reported associations between Beck's depression and anxiety scales and the visual field mean deviation (mD) and retinal nerve fiber layer (RHFL) thickness in glaucoma. The correlation may seem lower than that described herein. However, such a modest correlation becomes very similar to what we reported here considering that the average mD of glaucoma in POAG patients (Shin et al., 2021) was comparable, or only slightly higher (−4.4) than our S-POAG group patients (−3.4). By contrast, our advanced-stage patients had a much greater mD (average for the two-eye mean of −12.0; average for worse eye, −15.9) (Neroev et al., 2020). Therefore, the present work expands our knowledge linking further intensified mood deteriorations with a greater degree of RGCs loss that may correspond to ipRGCs damage, and reduced non-visual photic transduction to brain centers of the circadian system and mood. In accordance with this concept, another recent study (Yoshikawa et al., 2021), which included patients with visual loss comparable to our group of A-POAG patients, found a 2.6-fold increase in cognitive impairment in severe glaucoma compared to the mild stage. On the other hand, a Japanese study (Ayaki et al., 2016) reported associations of higher visual field loss in advanced glaucoma with sleep (assessed by the PSQI), though not with mood, assessed by the Hospital Anxiety and Depression Scale (HADS). Other notable factors include the environment (geography, season), and genetics (ethnicity, definite genetic polymorphisms), which may account for differences in the mood response to RGCs loss.

Individual susceptibility to light-mediated mood disorders may depend on gene polymorphic variants. These include clock genes, melatonin-receptor genes, and neurotransmitter receptors, guanine nucleotide-binding proteins (G proteins), as common anti-depressant targets, e.g., G protein beta3 subunit gene polymorphism (C825T), GNβ3 rs5443. Indeed, depression susceptibility was found to be associated with clock genes (Kennaway, 2010; Gyorik et al., 2021), melatonin receptor genes (Comai and Gobbi, 2014; Liu et al., 2017), and GNβ3 (Fang et al., 2015; Ma et al., 2017; Nam et al., 2018).

Polymorphism of the beta-3 gene of the G-protein subunit (GNβ3) 825C > T (rs5443) can be related both to mood disorders and visual function and retinal diseases. This T-allele is associated with the appearance of the GNB3-s RNA variant (encoding G beta3-s) during splicing, in which the nucleotides of exon 9 498-620 are removed, which causes the G-protein to lose a chain of 41 amino acids, thereby disrupting the signal transduction of G-proteins (Siffert et al., 1998). In the work of Ma et al. (2017), it was reported that the relationship of GNβ3 rs5443 with depression took place when combined with a "negative life event". In our opinion, progression of glaucoma, accompanied by physiological and chronobiological disorders may belong to such negative events. Indeed, in this study, we found a significant association between the homozygous GNβ3 rs5443 TT genotype and higher BDI scores in glaucoma patients. The G-protein gene GNβ3 825C > T had no significant effect on the circadian parameters of the overt physiological variables, Tb, IOP, and salivary melatonin. However, these circadian phenotypes were interrelated with other genes, such as MTNR1b (Gubin et al., 2021) and ACE (Neroev et al., 2020). Of note, compromised light perception with retinal ganglion cell loss in our patients was associated with altered daytime profiles of serum lipids, depending on a polymorphism of the *CLOCK* gene (Gubin et al., 2022), a feature also linked to altered mood and depression (Enko et al., 2018).

Study limitations. The lack of a significant association of depression scores with salivary melatonin (profile, receptor genes) and clock genes in this study can likely be accounted for by the limited number of volunteers. The question should be readdressed in larger and more representative studies. Another limitation of this study is that it did not specifically address damage to ipRGCs. Future research is thus needed to assess associations between ipRGCs damage and features of sleep, mood, and circadian rhythms to determine more accurately the existence of any threshold above which harm occurs.

5. Conclusions

Herein we present results showing that progressive loss of RGCs is positively associated with depression scores and that this association is stronger when RGCs global loss exceeds a threshold of 15 %. RGCs' two-eyes mean GLV correlated most strongly with the depression scores, surpassing all other factors of glaucoma progression in a backward stepwise multiple regression model. An abrupt increase in the strength of this association occurred when alterations in circadian rhythm characteristics and sleep were found. These results support the hypothesis that RGCs loss in advanced glaucoma may affect non-visual photic transduction and lead to mood disturbances. In addition, the GNβ3 825C > T polymorphism was associated with a high BDI score.

Institutional review board statement

The study adhered to the tenets of the Declaration of Helsinki and

was approved by the Institutional Review Board at the Tyumen Scientific Center of the Siberian branch of the Russian Academy of Sciences (Protocol No. 5, 15 May 2013), theme registration number AAAA-A17-117120500038-2.

Informed consent to participate statement

Informed consent was obtained from all individual participants included in the study.

Funding

The work was supported by Government of Tyumen District, Decree of 20.11.2020, No. 928-rp., West- Siberian Science and Education Center. The funding organization had no role in the design or conduct of this research. The author(s) have no proprietary or commercial interest in any materials discussed in this article.

CRediT authorship contribution statement

Conceptualization, D.G., T.M., D.W., and V.N.; methodology, D.G., T. M., D.W., S.K., and V.N.; software, G.C.; validation, V.N., A.V., T.M.; formal analysis, T.M., D.G., D.W., A.V., S.K., G.C.; investigation, D.G., T. M., D.W., S.K., N.Y., A.V., D.G.; resources, D.G., V.N., T.M.; data curation, T.M., A.V., D.G.; writing—original draft preparation, D.G.; writing—review and editing, V.N., T.M., D.W., G.C., S.K.; visualization, D. W., G.C., D.G.; supervision, V.N., T.M.; project administration, V.N., T. M., D.G..; funding acquisition, D.G. All authors have read and agreed to the published version of the manuscript. Funding organization had no any influence on study concept and its outcomes.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and analysed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

Acknowledgments

We would like to thank all participants who took the time to complete this study.

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