**The Relationship Between Sleep Quality and Structural Changes in Patients with Glaucoma**

**ABSTRACT**

**Aims:** The aim of our study was to evaluate the quality of sleep in glaucoma patients, and to determine its correlations with structural changes .

**Study design:** This is a case-control study.

**Place and Duration of Study:** Ufuk University Faculty of Medicine Department of Ophthalmology, Ankara between March 2023 and September 2023.

**Methodology:** Forty three patients with the diagnosis of primary open angle glaucoma (POAG) and 27 healthy control subjects were enrolled. Participants completed the Pittsburgh Sleep Quality Index Questionnaire (PSQI). Their mean retinal nerve fiber layer thickness (RNFL) and ganglion cell layer thickness (GCL) were measured. PSQI scores were compared, and the association between PSQI and RNFL, GCL were analyzed.

**Results:** Subjects with PSQI score of >=5 were significantly more in the glaucoma group than the control group (26 (60.47%) vs 7 (25.93%) (P=.005). The mean RNFL (72.79± 10.65µm) and the mean GCL (65.69± 10.45µm) of the glaucoma group were significantly less than the control group (89,35±6,85 and 75,14±4,27 respectively) (*P*< .001and *P*< .001, respectively). By using multiple linear regression analyses, correlation coefficients in relation with PSQI for age, mean RNFL and mean GCL showed low or non-significant correlation (0.07, 0.12, and 0.04, respectively, and all had *P* values > .05) in the glaucoma group.

**Conclusions:** The current study implied that the glaucoma patients had significantly impaired sleep quality. However, the presence of structural damage to the RNFL and GCL thickness were not significantly associated with sleep quality in patients with glaucoma.

**Keywords**

Sleep quality; glaucoma; intrinsically photosensitive retinal ganglion cell; circadian rhythm; retinal nerve fiber layer thickness.

**Introduction**

“Glaucoma is a progressive optic neuropathy and the second leading cause of preventable blindness worldwide” [1]. By 2020, 76 million cases of glaucoma had been diagnosed worldwide and is projected to increase to 111.8 million by 2040 [2]. Although the etiology of it is multifactorial, elevated intraocular pressure (IOP) is the main risk factor for glaucoma.

“Glaucoma is characterized by progressive degeneration of retinal ganglion cells (RGC) and visual field loss which is irreversible. In glaucoma, ganglion cell damage might result in death of many kinds of neurons. One of them is intrinsically photosensitive retinal ganglion cells (ipRGCs), these cells have been shown to be sensitive to light wave lengths (460-480 nm) and they mediate non–visual response to light and circadian rhythm” [3]. “Several animal studies reported that RGC degeneration was not cell type-specific in glaucoma, which indicated that ipRGCs might also be damaged in glaucoma” [4]. “Studies showed that post-illumination pupil response to blue light could be a specific feature for testing activity of ipRGCs” [5,6].

Sleep is an important physiological function of the human body and regulated by the circadian rhythm. Light perception is considered to be one of the most important factors influencing the circadian rhythm which regulates body temperature, sleep duration, hormonal levels and other physiological variables. Light stimuli detected by the photoreceptor cells are transmitted via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN). The SCN is responsible for signaling the release of melatonin by the pineal gland and cortisol by the adrenal gland. The SCN monitors the release of these two hormones based on the visual stimuli [7,8].

Several previous studies have demonstrated degeneration of ipRGCs and sleep disorders in glaucoma patients [9-11]. These results suggest that distruption of ipRGCs could lead to the dysfunction of the circadian rhythm.

The aim of our study was to evaluate the quality of sleep in glaucoma patients, and to determine its correlations with structural changes in retinal nerve fiber layer and ganglion cell layer (RNFL thickness and GCL thickness).

**Materials and methods**

This is a case-control study conducted from March 2023 to September 2023. A total of 43 patients with the diagnosis of bilateral primary open angle glaucoma (POAG) and 27 healthy control subjects were enrolled in this study. All patients were in the age interval of 60-80 years.

All subjects underwent a complete ophthalmic examination. The participants with ocular pathology including mature cataract, optic neuritis, retinal pathology, central nervous system pathology, psychiatric illness, obstructive sleep apnea, and the participants using sleep medicine and anti-depressants were excluded from the study.

Participants were asked to complete the Pittsburgh Sleep Quality Index (PSQI) Questionnaire. This questionnaire is widely used for assessing sleep quality, which is subjectively completed by patients. It assesses the sleep quality during the preceding one month. The PSQI evaluates seven components of sleep; the subjective quality of sleep, sleep latency, duration, habitual efficiency, sleep disturbances, the use of sleep medication and day-time dysfunction. Each component is rated on scale from 0 to 3. The total score of seven components gives the overall scale score. The total score ranges from 0 to 21. The total score greater than 5 indicates poor sleep quality.

All participants’ retinal nerve fiber layer thickness (RNFL) and ganglion cell layer thickness (GCL) were measured using spectral–domain optical coherence tomography (Cirrus HD-OCT Model 400; Carl Zeiss Meditec, Jena, Germany). The peripapillary RNFL thickness was obtained around a 3.4 mm diameter circle centered around the optic disc, and only the measurements beyond signal strength 7 (˃ 7) were studied.

The PSQI scores, the RNFL and GCL thicknesses were compared between groups. Also the association between PSQI scores and structural parameters (RNFL thickness and GCL thickness) were analyzed.

*Statistical Analyses*

Statistical analyses were performed using the SPSS software version 15. The variables were investigated using analytical methods (Shapiro-Wilk’s test) to determine whether or not they are normally distributed. The sex and PSQI score subgroups were compared between the groups by using Chi-square test. The parameters affecting PSQI were investigated using Spearman/Pearson correlation and t-test wherever appropriate. A multiple linear regression model was used to identify independent predictors of PSQI. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A p-value of less than 0.05 was considered to show a statistically significant result.

**Results**

The study included 140 eyes from 70 participants; 86 eyes were from 43 patients with glaucoma and 54 eyes were from 27 control cases. The mean ages of the glaucoma group and of the control group were 70.72±5.84 years and 68.11±5.46 year, respectively. There was no statistically significant difference between the two groups in relation to age (*P*= .06; t-test). Twenty-seven patients (62.80%) in the glaucoma group and 13 patients (48.15%) in the control group were female. There were no significant differences between groups in relalation to sex (*P*= .22; Chi-square test). (Table 1).

**Table 1. Comparison of parameters between glaucoma and control groups.**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters | GlaucomaGroup | Control Group | P |
| N=43 | N=27 |
| Age | Mean± Standard deviation | 70,72±5,84 | 68,11±5,46 | .06a |
| Sex | Male  | 16 (37.20%) | 14 (51.85%) | .22b |
| Female | 27 (62.80%) | 13 (48.15%) |
| PSQI subgroups | 5 or more | 26 (60.47%) | 7 (25.93%) | .005b\* |
| Less than 5 | 17 (39.53%) | 20 (74.07%) |
| RNFL thickness | Mean±Standard deviation | 72,79±10,65 | 89,35±6,85 | .0001a\* |
| GCL thickness | Mean±Standard deviation | 65,69±10,40 | 75,14±4,27 | .0001a\* |

PSQI: Pittsburgh Sleep Quality Index scores

RNFL: Retinal Nerve Fiber Layer thickness

GCL: Ganglion Cell Layer thickness

\* Statistically significant difference

a t-test

b Chi-square test

When we evaluated the sleep quality between groups; the glaucoma group showed significantly worse PSQI scores than the control group. In the glaucoma group; the PSQI scores of 26 subjects (60.47%) were 5 or more. In the control group; the PSQI scores of only 7 subjects (25.93%) were 5 or more. This difference was statistically significant (*P*= .005; Chi-square test).

The mean RNFL thickness (72.79± 10.65µm) and the mean GCL thickness (65.69± 10.45µm) measurements of the glaucoma group were significantly less than the control group (89,35±6,85 and 75,14±4,27 respectively; *P*< .001; t-test).

We also investigated whether the variables, the mean RNFL thickness and the mean GCL thickness, had effect on the sleep quality by using multiple linear regression analyses. In the glaucoma group, correlation coefficients in relation with PSQI for age, mean RNFL and mean GCL showed low or non-significant correlation (0.07, 0.12, and 0.04, respectively, and all had *P* values> .05) (Figure 1 and 2).

**Figure 1.** Linear regression analyses of mean retinal nerve fiber layer thickness (RNFL) and Pittsburgh sleep quality index (PSQI) in patients within the glaucoma and the control groups.



**Figure 2.** Linear regression analyses of mean ganglion cell layer thickness (GCL) and Pittsburgh sleep quality index (PSQI) in patients within the glaucoma and the control groups.



In the control group, correlation coefficients for age (-0.17), sex (0.11), mean GCL (-0.04) showed nonsignificant correlation with PSQI. However, mean RNFL showed significant (*P*< .001) and very good negative correlation (-0.73) with PSQI. According to the regression model; mean RNFL could predict 53 percent (0.53) of PSQI (Figure 1 and 2).

**Discussion**

In the present study we evaluated the sleep quality and the association between sleep quality and structural changes in glaucoma patients.

We found that the patients in the glaucoma group were more likely to have poorer sleep quality than the control group in the age interval of 60-80 years. The difference was statistically significant. The magnitude of PSQI ≥5 were 60.47% and 25.93% among the glaucoma and the control group, respectively. These findings are consistent with several previous reports (61.3%, 66.36%, 75.5%) [12-14]. Tegegne et al, reported higher level of poor sleep quality in Ethiopian glaucoma patients( 82.5%) [15]. This variation may be due to the difference in demographic features of study population [15].

It is currently accepted that sleep and glaucoma have a bidirectional relationship; patients with poor sleep are more likely to develop glaucoma, likewise patients with glaucoma are more susceptible to sleep disorders than healthy people [16-18]. The progressive nature of the disease and the burden of life-long medication use might contribute to sleep disturbance in patients with glaucoma.

The possible reasons for poor quality of sleep among glaucoma patients may be due to biological and psychological changes. Although how the mechanism of glaucoma may induce sleep disorders is not obvious, one possibility is that the ipRGC loss decreases light inputs to the SCN and desynchronizes the circadian rhythm [19]. The circadian system regulates the sleep and wake phases, and the light plays an important role in regulating it. “The primary circadian pacemaker is the suprachiasmatic nucleus (SCN) in the human brain. It receives photic input from ipRGCs which contain the melanopsin. Several previous studies reported that loss of RGCs including the loss of ipRGCs in glaucoma patients compromises the circadian rhythms” [9,20]. The characteristic of ipRGCs is that they express melanopsin. “Light transmission to SCN is only regulated by the ipRGC. The major eye disease that induces degeneration of ipRGC is glaucoma” [9,20].

Old age and various eye diseases are important causes affecting the photic input via decreased light transmission (e.g., cataract, retinal and macular diseases, optic neuropathy and glaucoma). Because age would affect sleep quality, we limited the ages of study population between 60-80 years for the alleviation of this factor. The participants with ocular pathology including mature cataract, optic neuritis, retinal pathology and central nervous system pathology, obstructive sleep apnea and the participants using sleep medications and antidepressants were excluded from the study.

Some studies revealed that vision loss due to glaucoma may result in depression, and depression results in development of sleep disorders [21,22]. Although we excluded the people using antidepressants in our study, we did not apply a test that measures depression.This limitation restricted our interpretation of findings in relation to depression. Future studies incorporating depression scales could provide a more comprehensive understanding of the result.

In the present study; the mean RNFL thickness and the mean GCL thickness measurements of the glaucoma group were significantly less than the control group. We investigated whether the variables, mean RNFL thickness and mean GCL thickness, had effect on the sleep quality by using multiple linear regression analyses. In the glaucoma group, correlation coefficients in relation with PSQI for age, mean RNFL and mean GCL showed low or non-significant correlation. Therefore, our results did not indicate a significant correlation between sleep quality and structural damage to the RGC layer.

There are several studies which evaluated sleep and glaucoma relationships. Gracitelli et al. demonstrated low sleep quality which was evaluated by polysomnography in 32 glaucoma patients. Currently, “polysomnography is the most commonly used test for assessing sleep disorders, and it is considered to be a nonsubjective test. They observed that sleep efficiency was worse in patients with glaucoma but they reported no correlation between the mean RNFL thickness and polysomnography parameters except the oxygen desaturation index” [23].

Although polysomnography is an objective test for sleep analysis, it does not directly show ipRGCs activity. In studies directly measuring ipRGC activity, such as post-illumination pupil reflex (PIPR) response, a relationship with RNFL thickness has been demonstrated [24,25]. “One study evaluated the correlation between the RNFL thickness and the response to blue flashes during the pupillary light reflex which could be a specific feature for the testing activity of ipRGCs. That study demonstrated a significant correlation between the RNFL thickness and the sustained response to blue flashes with a luminance of 250 cd/m2 during the pupillary light reflex. Furthermore, a significant correlation was noted between the severity of glaucoma and the sustained pupillary response to the blue flash with a luminance of 250 cd/m2”[24]. Additionally, Yoshikawa et al. reported a significant association between functional and structural glaucoma severity and impaired ipRGC function which was assessed by postillumination pupil response. Their multivariable linear regression analyses indicated that worsening in visual field median deviation and thinner RNFL thickness were significantly associated with higher blue six second post illumination pupil response ( PIPR ) amplitude [25].

The different results of the studies may be due to the different stages of glaucoma and different history of intraocular pressure fluctutation,which may cause different ranges of damage to the whole retina (including rods) and lower input to the ipRGCs in glaucoma patients.

Some studies reported type-specific changes in ipRGC population and the variability duration of IOP elevation in different glaucoma models [26,11]. It is possible that a higher IOP elevation is required to cause marked damage to ipGCLs. The duration of high IOP levels may also affect the loss of ipGCLs in different glaucoma models.

Altough some previous studies reported that glaucoma patients tended to have sleep disorders [23,22], Ra et al. revealed no statistically significant difference between the glaucomatous patients and the control patients according to sleep quality [27]. The researchers suggested that this result might be due to the absence of severe glaucoma cases among the study participants and the well-regulated nature of their glaucoma [27].

There are some limitations of our study. Primarily, our study sample was small, and sleep behaviours were measured by self-reported questionnaires. Studies using objective measurements of sleep patterns and larger sample sizes are warranted to validate our findings. Another limitation of our study is that we did not administer a test that measures depression. Due to the relationship between sleep disorders and depression, future studies incorporating depression scales could provide a more comprehensive understanding of the results.

**Conclusion**

The current study implied that glaucoma patients had significantly impaired sleep quality in addition to the main disease**.** According to our results, structural damage to the RGCs was not significantly associated with sleep quality. Because different issues could influence these complex systems, further studies with larger cohorts of patients and objective methods should be performed to evaluate the glaucoma and sleep relationship.

When evaluating glaucoma patients,multidisciplinary treatment focusing also on sleep quality and circadian rhythms might be useful for these patients.

**ETHICAL APPROVAL AND CONSENT:**

The Institutional Review Board and Ethics Committees of Ufuk University approved this study (Date: 28.02.2023, Number: 12024861-28), and the study was performed in accordance with the principles of the Declaration of Helsinki. All participants gave informed consent to participate, prior to the study.

**Disclaimer (Artificial intelligence)**

Authors hereby declare that NO generative AI Technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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