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ORIGINAL RESEARCH

Age-Related Macular Degeneration and Circadian Preference

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Purpose: Age-related macular degeneration (AMD) is the leading cause of blindness in developed nations. Within the retina, a subset of cells, called *melanopsin-containing intrinsically photosensitive retinal ganglion cells*, are implicated in circadian rhythms, prompting a search for a potential connection between circadian behavior and AMD. Our objective was to compare the chronotype (ie, preference for morning or evening activity) of individuals with AMD to that of those without ocular conditions.
Patients and Methods: The Horne-Östberg Morningness-Eveningness questionnaire was administered to previously screened patients with wet AMD who received bilateral anti–vascular endothelial growth factor eye injections (study participants) as well as those without eye pathology (controls). Thirty-one study participants and 19 controls completed the survey and were included in the analysis. We used Wilcoxon rank sum test and Fisher exact test for continuous and categorical variables respectively.
Results: Study participants had a higher median age compared to controls (83 vs 75, $P<0.001$). No significant difference in body mass index was observed between respondents. While the disparity in survey responses between study participants and controls was generally not statistically significant, more study participants struggled with attending exercises between 7:00 and 8:00 in the morning compared to controls (45% vs 21%, $P=0.02$). Additionally, fewer study participants expressed the need to sleep before 10:15 PM compared to controls (55% vs 63%, $P=0.04$). Study participants tended to have a delayed sleep-wake cycle.
Conclusion: In this pilot study, study participants encountered greater challenges with morning exercise compared to controls. Nonetheless, there was no significant difference in chronotype between study participants and controls. The study could serve as a foundation for more extensive research exploring the interplay between vision loss and circadian rhythms.

Plain Language Summary: Age-related macular degeneration (AMD) is a leading cause of blindness in developed nations. Researchers are exploring connections between AMD and circadian rhythms, particularly focusing on certain cells in the eye. This study aimed to compare the daily activity preferences (chronotypes) of individuals with AMD to those without eye conditions. In this study, participants with AMD and controls without eye pathology completed the Horne-Östberg Morningness-Eveningness questionnaire to identify their circadian preference. Findings indicated that individuals with AMD experienced more challenges with morning exercise and tended to prefer later bedtimes compared to controls. Despite these trends, there was no significant difference in chronotype between the groups. This pilot study suggests that participants with AMD may exhibit a preference for a delayed sleep-wake cycle and encounter difficulties with morning activities. However, further research is necessary to fully understand the relationship between AMD and circadian rhythms.

Keywords: chronotypes, circadian rhythm, maculopathy, retinal ganglion cells, pilot study, surveys and questionnaires

Introduction/Background

Advanced age-related macular degeneration (AMD) leads to deterioration of central visual acuity, resulting in permanent visual impairment, ultimately leading to legal blindness. With approximately 8.7% of the global population affected,

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AMD is the leading cause of legal blindness in developed nations.[1] The prevalence of AMD increases with age from 2% among people aged 40 to 44 to 46.6% among those older than 85. [2] It is projected that the number of individuals with AMD in the US will almost double from 9.1 million in 2010 to 17.8 million in 2050. [2]

AMD results from the deposition of extracellular debris between the basement membrane of the retinal pigment epithelium and adjacent membranes. The pathogenesis of these deposits is only partially understood, but multiple factors have been suggested, including genetic predisposition, local inflammation, protein buildup, and damage from exposure to light.[3] Fortunately, several lifestyle modifications have been shown to reduce the risk of AMD, including making healthy dietary choices, reducing alcohol intake, quitting smoking, and treating obesity.[4–6] Furthermore, evidence suggests that circadian rhythm dysregulation exacerbates aberrant activation of cellular regulatory pathways, leading to neurodegenerative conditions, including AMD.[7–11] Conversly, damage of intrinsic photosensitive retinal ganglion cells (ipRGCs) in AMD may disrupt circadian rhythms.[7,12–15] This bidirectional relationship provides a strong biological basis for the connection between AMD and circadian rhythm disruptions, highlighting the importance of healthy sleep as a potential preventive intervention.

Furthermore, sleep disorders are linked to health conditions beyond neurodegenerative diseases, including coronary artery disease, hypertension, and stroke, all of which impose substantial burdens on the health care system due to their high economic and social costs.[16–18]

This pilot study sought to elucidate circadian preference (chronotype) in patients with AMD and those without ocular pathology. Our goal was to add evidence to the existing literature and increase awareness of the link between sleep and AMD.

Methods

Study Population and Data Acquisition

The Horne-Östberg Morningness-Eveningness questionnaire,[19] a validated survey to establish circadian rhythm type, was sent to prescreened patients with wet AMD receiving bilateral anti–vascular endothelial growth factor (VEGF) eye injections in our ophthalmology clinic and a control group composed of patients without macular disease (ascertained from the electronic health record) with visual acuity of at least 20/30 bilaterally on their most recent eye examination. Exclusion criteria for both groups included severe mental illness or dementia, severe corneal opacities, glaucoma with visual field deficit of more than 14 dB (Humphrey perimeter), vitreous hemorrhage, and proliferative diabetic retinopathy. Patients with severe AMD were chosen as more advanced macular disease would have a higher likelihood of damage to ipRGCs. Patient demographics are summarized in Table 1. Survey scores and individual survey answers were compared between the two groups. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All participants provided informed consent prior to their inclusion in the study, and the research protocol was reviewed and approved by the Mayo Clinic Institutional Review Board (approval #19-009991).

Table 1 Patient Demographics

	Cases (n=31)	Control (n=19)	Total (N=50)	*P* value
Age, median (range)	84.5 (54.0–99.0)	75.0 (62.0–83.0)	78.0 (54.0–99.0)	<0.001
Sex, No. (%)				0.75
Female	20 (64.5)	12 (63.2)	32 (64.0)	
Male	8 (25.8)	6 (31.6)	14 (28.0)	
Unreported	3 (9.6)	1 (5.2)	4 (8.0)	

Statistical Analysis

Continuous variables were summarized as mean (range) and compared between groups using Wilcoxon rank sum test. Categorical variables were reported as frequency (percentage) and compared using Fisher exact test. All tests were 2-sided with α level set at 0.05 for statistical significance.

Results

Our analysis included 31 patients with AMD (study participants) and 19 patients without ocular pathology (controls). Study participants were generally older than controls (median age, 83 vs 75 years; *P*=0.003). No significant difference in body mass index was observed between respondents. Although there was no statistically significant difference in circadian rhythm scores between study participants and controls (median 59.5 vs 62.0), a higher proportion of study participants reported difficulty in attending exercises between 7:00 and 8:00 in the morning compared to controls (46.7% vs 16.7%; *P*=0.02). Additionally, a smaller percentage of study participants expressed the need to sleep earlier in the night (before 10:15 PM) compared to controls (56.6% vs 66.6%; *P*=0.03). Table 2 presents the statistical analysis of answers from study participants and controls to questions from the Horne-Östberg Morningness-Eveningness questionnaire.

Table 2 Survey Results

	Case (n=31)[a]	**Control (n=19)[a]**	**Total (N=50)[a]**	***P* value**
Question asking participants about the time of day when they feel the need for sleep.				0.038
8:00 PM–8:59 PM	1 (3.2)	4 (21.1)	5 (10.0)	
9:00 PM–10:14 PM	16 (51.6)	8 (42.1)	24 (48.0)	
10:15 PM–12:44 AM	12 (38.7)	3 (15.8)	15 (30.0)	
12:45 AM–1:59 AM	2 (6.5)	2 (10.5)	4 (8.0)	
2:00 AM–3:00 AM	0 (0.0)	2 (10.5)	2 (4.0)	
Question asking participants about their ability to perform physical exercise at 7:00–8:00 am.				0.024
Good form	5 (16.1)	11 (57.9)	16 (32.0)	
Reasonable form	12 (38.7)	4 (21.1)	16 (32.0)	
Difficult	9 (29.0)	2 (10.5)	11 (22.0)	
Very difficult	5 (16.1)	2 (10.5)	7 (14.0)	
Question asking participants about their peak time of day.				0.146
5:00 AM–7:59 AM	2 (6.5)	0 (0.0)	2 (4.0)	
8:00 AM–9:59 AM	7 (22.6)	10 (52.6)	17 (34.0)	
10:00 AM–4:59 PM	20 (64.5)	8 (42.1)	28 (56.0)	
5:00 PM-9:59 PM	2 (6.5)	1 (5.3)	3 (6.0)	

(*Continued*)

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Table 2 (Continued).

	Case (n=31)[a]	Control (n=19)[a]	Total (N=50)[a]	*P* value
Question asking participants to identify with their circadian "type".				0.741
Morning type	12 (38.7)	6 (31.6)	18 (36.0)	
Likely morning type	13 (41.9)	10 (52.6)	23 (46.0)	
Likely evening type	6 (19.4)	3 (15.8)	9 (18.0)	
Evening type	0 (0.0)	0 (0.0)	0 (0.0)	

Note: [a]Results are reported as No. (%).

Discussion

This pilot study sought to elucidate the circadian preference of patients with and without AMD. There was no significant difference in morningness and eveningness scores between study participants and controls. However, a higher proportion of study participants found it difficult or very difficult to attend exercises between 7:00 and 8:00 in the morning compared to controls (46.7% vs 16.7%; *P*=0.02). Additionally, a lower percentage of study participants felt the need to go to sleep before 10:15 pm compared to controls (56.6% vs 66.6%; *P*=0.03). These indicators are typical of individuals with a late-night bedtime preference, who struggle to participate in physical or cognitive activities during the morning hours and must alter their natural sleep-wake patterns to accommodate societal obligations occurring earlier in the day.

Our study was limited by the small population size, which may impact the generalizability of our findings. It is also possible that the circadian rhythm survey used may not have been sensitive enough to detect subtle differences between the 2 groups. It is worth noting that the group with AMD demonstrated low baseline visual function, potentially constraining their ability to engage in physical activity. Additionally, studies have shown that patients with AMD are generally less likely to engage in physical activity, which could introduce confounding biases.[20] We were unable to account for factors such as the duration of AMD, baseline vision, and other factors not captured by the survey which may influence circadian rhythm in individuals with AMD. Furthermore, these patients were undergoing active anti-VEGF treatments, introducing a potential confounding factor that could influence the condition under investigation. Moreover, we lacked circadian preference data prior to AMD development, precluding our ability to determine if patients experienced a shift in their baseline circadian rhythm at disease onset or later during disease progression.

Studies that investigated the association between sleep and AMD are heterogenous and therefore difficult to compare with one another; however, there is enough evidence to support the presence of a relationship between sleep and AMD. In 2 large population analyses using a Mendelian randomization, Zhu et al[13] and Lei et al[12] independently found that longer sleep duration plays a small protective role in AMD and likewise, a shorter sleep duration increases the risk of early AMD. Tsai et al[9] found a positive association between sleeplessness and AMD, and in Perez-Canales et al's[21] case control study using self-reported sleep duration, patients with AMD showed an increased prevalence of short sleep duration (less than 6 hours) compared to those who slept more than 6 hours. Conversely, Khurana et al[22] found that increased sleep duration was associated with geographic atrophy secondary to AMD and, contrary to our findings, Grover et al[7] observed a significant causal effect between morning preference and genetic predisposition to AMD. Some studies failing to show a significant relationship between sleep duration and AMD had considerably smaller sample sizes than the studies mentioned previously. Additionally, the magnitude of the effect of sleep duration is thought to be rather small, and the impact of sleep on AMD may be dependent on the stage and severity of the disease.[7,13]

Several authors have explored the cellular and molecular alterations that occur under the influence of environmental factors, including an altered sleep cycle. In a regression analysis, Sharma et al[10] revealed that sleeping patterns can contribute to the progression of AMD by altered expression of cellular regulatory proteins. Vallee et al[11] found that dysregulation of circadian rhythms enhances aberrant activation of the Wnt/β-catenin pathway, which is associated with

focal retinal degeneration and exudative AMD. These findings underscore the impact of sleep on cellular damage and highlight the importance of addressing circadian rhythm dysregulation.

Stepicheva et al[14] have delineated melatonin's role in coordinating the timing of waste material phagocytosis by the retinal pigment epithelium, which peaks after the onset of light. Changes in sleep patterns disrupt the secretion of melatonin, thereby interfering with this process. Additionally, Schmid-Kubista et al[23] discovered that individuals with AMD exhibited notably elevated levels of daytime melatonin compared to those without the condition. This incongruity may stem from diminished light perception in ipRGCs, leading to an inability to suppress melatonin production in the pineal gland. Consequently, the daytime melatonin secretion pattern could disrupt circadian rhythm, resulting in buildup of waste products that lead to AMD (ie, deposition of extracellular debris between the basement membrane of the retinal pigment epithelium and adjacent membranes).[23]

Furthermore, patients with AMD may develop a dependence on artificial light exposure during evening hours, thus introducing an additional risk of photochemical damage.[4] Constant light exposure leads to oxidative stress within the retinal pigment epithelium, thus disturbing the circadian-mediated phagocytosis of waste material, causing more inflammation, which induces VEGF secretion and leads to choroidal neovascularization.[24]

It is worth noting that there are several similarities between neurodegenerative disorders (eg, Alzheimer disease) and certain eye pathologies, particularly AMD and chronic open-angle glaucoma. This relationship launched an area of research focused on the role of the glymphatic system in preserving neuronal function. This perivascular network system facilitates solute exchange between cerebrospinal fluid and aqueous humour with the interstitial fluid, thus clearing waste products from the brain and the eye, respectively.[25] This exchange follows a circadian pattern and accomplishes more waste elimination during sleep. Therefore, any factor contributing to interrupted or insufficient sleep or damage to ipRGCs which mediate the synchronization between internal circadian clocks and the natural day-night cycle controlled by the suprachiasmatic nucleus (SCN), may lead to decreased aqueous humour circulation and suboptimal waste disposal.[26–28]

This theory is based on animal studies that have demonstrated that the destruction of ipRGCs results in disruption of the process by which an organism's biological clock adjusts to the daily cycles of light and darkness in its environment, also known as the *circadian photoentrainment*.[15,29] The exact number of viable melanopsin-containing ipRGCs required to maintain proper SCN photic entrainment in humans remains unknown, highlighting a gap in our understanding of circadian regulation in the context of AMD. Based on the findings of this study, the circadian rhythm of patients with AMD shifts toward a delayed phase, which contrasts with observations in the general older population, who typically exhibit a shift toward an advanced circadian phase and earlier wake times.[30,31] This raises the question of whether sleep disorders contribute to the development of AMD or if AMD leads to sleep disorders. Studies have shown that short sleep duration increases the risk of early AMD, and patients with AMD are at an increased risk of experiencing short sleep duration.[12,32] However, further research is needed to establish causality.

Environmental factors also help maintain circadian rhythm. One example is physical activity, which is recognized for its ability to act as a nonphotic circadian entrainer that speeds up adjustment of the sleep-wake pattern, although it does not impact the melatonin cycle.[33] Aging leads to deterioration of the SCN and gradual reduction of evening secretion of melatonin.[31,34,35] Exercise may help to compensate for the loss of SCN function, it serves as a useful approach to counteract age-related disruptions in circadian rhythm, and has been proven to lower odds of early and late AMD.[36,37]

Despite the uncertainties, understanding the potential link between circadian rhythm disturbances and AMD could have important clinical implications. Strategies to maintain a healthy circadian rhythm, such as promoting regular sleep patterns and exercise and minimizing exposure to artificial light at night, may be beneficial for overall eye health and potentially reduce the risk or progression of AMD. However, more research, including well-designed clinical studies, are necessary to validate these strategies and determine their effectiveness in preventing or managing AMD.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics Approval and Informed Consent

The study was approved by the Mayo Clinic Institutional Review Board (approval #19-009991).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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