Review Article

Melatonin as a potential biomarker in diabetic retinopathy

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ABSTRACT

Background: Diabetic retinopathy (DR) is a major complication of diabetes mellitus (DM). Melatonin protects against inflammation and oxidative stress. This review focuses on the literature comparing melatonin levels in patients with and without DR.

Methods: A thorough search of the PubMed/MEDLINE, Web of Science, and Embase databases was performed for articles published until April 2025. The inclusion criteria were studies reporting melatonin levels in patients with DR and control groups; studies involving human participants of any age, gender, or ethnicity; and investigations documented in scholarly publications. The exclusion criteria were as follows: animal studies; review articles; case reports; editorials; and conference abstracts; studies not available in English or lacking an English translation; and studies focusing on interventions altering melatonin levels rather than comparing levels between patients with DR and controls. Furthermore, we manually checked the reference lists of the included papers to identify any earlier series that were not initially found in our core search. The Newcastle-Ottawa Scale was used to evaluate study quality.

Results: Eight studies with 1004 participants published from 2011 to 2022 were included. The mean age of participants ranged from 39.9 to 72 years. Three studies assessed urinary melatonin excretion, three examined blood melatonin concentrations, one evaluated melatonin concentration in the aqueous humor, and one measured salivary melatonin levels. All samples were collected at night, except for three studies. All studies utilized enzyme-linked immunosorbent assay to measure melatonin concentration, except for the one study, which employed high-performance liquid chromatography. Numerous studies have indicated that patients with DM exhibit reduced melatonin levels relative to healthy controls, and that individuals with DR show lower levels than those without DR. Patients with proliferative DR exhibit reduced nocturnal urinary excretion of 6-sulfatoxymelatonin. Melatonin levels in the aqueous humor were elevated in patients with proliferative DR. Melatonin levels were negatively correlated with both the duration of DM and glycated hemoglobin levels.

Conclusions: The findings of this review suggest that patients with DM, particularly those with DR, exhibit altered melatonin production. Reduced systemic melatonin levels may correlate with increased risk and severity of DR. However, the majority of included studies had a case-control design, which hinders the ability to draw causal conclusions regarding the association between melatonin levels and DR. Moreover, confounding factors, including age, duration of DM, medication use, and lifestyle characteristics of participants, were not uniformly considered, and the limited sample sizes restrict the applicability of the results. Future investigations should emphasize longitudinal studies to clarify the temporal dynamics between melatonin levels and DR progression Additional investigations are required to clarify the function of melatonin in the pathogenesis of DR and its viability as a therapeutic target.

KEYWORDS

diabetic retinopathies, melatonin, chronobiology phenomenon, eyes, pineal-retinal relationships, retina-SCN-pineal pathway, retina-SCN-pineal axis, suprachiasmatic nucleus (SCN)

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How to cite this article: Abounoori M, Sajjadifar SP, Daneshvar K, Pourazizi M. Melatonin as a potential biomarker in diabetic retinopathy. Med Hypothesis Discov Innov Optom. 2025 Summer; 6(2): 74-82. DOI: https://doi.org/10.51329/mehdioptometry225

Received: 01 July 2025; Accepted: 30 July 2025

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia caused by a persistent or relative lack of insulin. Numerous comorbidities, complications, and high mortality rates are associated with DM. Nephropathy, retinopathy, and neuropathy are the primary adverse effects of DM [1]. Diabetic retinopathy (DR) is categorized into two distinct types: non-proliferative DR (NPDR), marked by the occurrence of microaneurysms, intraretinal hemorrhage, hard exudates, and cotton wool spots; and proliferative DR (PDR), defined by the development of new blood vessels in the fundus and iris, with or without vitreous hemorrhage [2]. It is a significant and prevalent microvascular complication of DM and is the primary cause of blindness globally. The onset of DR is characterized by the generation of pro-inflammatory cytokines and attachment of leukocytes to capillaries in the retina. Inflammation, endoplasmic reticulum stress, oxidative stress, and autophagy play crucial roles in the progression of DR [3-6].

Melatonin, scientifically referred to as N-acetyl-5-methoxytryptamine, a compound synthesized by the pineal gland [7]. Additionally, melatonin production in the retina predominantly occurs at night, while its levels remain low throughout the day [8]. Melatonin and its metabolites play protective roles by mitigating inflammation, oxidative stress, and endoplasmic reticulum stress. They can directly scavenge free radicals and function as antioxidants by promoting the activity of antioxidant enzymes such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase [9, 10]. Furthermore, melatonin acts as a cell survival agent by modulating autophagy across different cell types and conditions, which in turn diminishes inflammation, oxidative stress, and endoplasmic reticulum stress [11].

Studies investigating the effects of DM on the pineal gland have revealed a progressive reduction in both the overall size of the pineal gland and the nuclear diameter of pinealocytes during the fourth week after DM induction [12-14]. Furthermore, in nerve fibers containing the 9.5 protein gene product, a widely recognized marker for nerve fibers, the presence of this marker was significantly diminished in the pineal glands of diabetic animals, suggesting the development of neuropathy. Six months after the onset of DM, alterations in glial cells resulting from the thickening of the axon-Schwann cell units were also recorded [12-14]. This review focuses on the literature comparing melatonin levels in patients with and without DR.

METHODS

An extensive search strategy was employed to retrieve studies reporting melatonin levels in patients with DR, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework as a guide. Additionally, this review was registered in the PROSPERO database under ID CRD42024507765.

The review team establishes a search strategy using the PICoS framework. In this logical grid, “P” represents the population of patients with DR, “I” represents the interest in the eye, “Co” represents the context of melatonin level, and “S” represents the study type of original publications.

A comprehensive search was conducted in the PubMed/MEDLINE, Web of Science, and Embase databases from their inception until April 1, 2025. The search technique comprised the keywords “Melatonin,” “Diabetic Retinopathy,” and other similar MeSH terms. Furthermore, we manually checked the reference lists of the included papers to identify any earlier series that were not initially found in our core search.

The inclusion criteria were studies reporting melatonin levels in patients with DR and control groups; studies involving human participants of any age, gender, or ethnicity; and investigations documented in scholarly publications. The exclusion criteria were as follows: animal studies; review articles; case reports; editorials; and conference abstracts; studies not available in English or lacking an English translation; and studies focusing on interventions altering melatonin levels rather than comparing levels between patients with DR and controls.

Evaluation of methodological excellence: To assess irrelevant publications based on the inclusion and exclusion criteria, two authors (M.A. and S.P.S.) reviewed the titles and abstracts of potential studies. Subsequently, they conducted a thorough review of the entire text on two separate occasions to determine the definitive inclusion criteria. The corresponding author (M.P.) has made the full text of the non-open-access articles available upon request. Duplicate experiments were eliminated using the EndNote software (version X8). To reach a final consensus, disagreements between the authors were resolved by adding a third author (M.P.).

Employing the Newcastle–Ottawa Scale [15], the quality of the included studies was independently assessed by two authors (M.A. and S.P.S.), with any discrepancies resolved by a third author (M.P.). A higher rating was considered a sign of enhanced quality. The main outcome was a comparison of melatonin levels between patients with and without DR.

The collected data included the first author's name, publication year, study design, sample size, age, sex distribution, DR status (presence/absence, severity), methods for measuring melatonin (e.g., serum and urinary levels), timing of melatonin measurement (e.g., diurnal variation), melatonin levels in the control group, melatonin levels in patients with DR, and outcomes observed

RESULTS

A total of 167 articles were identified using the search strategy. During the deduplication process, 73 duplicate articles were identified and excluded, leaving 94 articles. Subsequent title and abstract screening 35 records excluded and resulted in 59 candidate articles for full-text evaluation. Through full-text assessment, 44 papers were excluded owing to the use of experimental models, three articles that did not report melatonin levels, two conference abstracts, and two non-English articles. After full-text evaluation, eight records [16-23] were deemed eligible and met the inclusion criteria.

Table 1 summarizes the key characteristics of the included studies. This review encompassed eight studies with 1004 participants published from 2011 to 2022 and was carried out in Asia [16, 18-23] and Europe [17]. The mean age of participants ranged from 39.9 to 72 years. Three studies assessed urinary melatonin excretion [18, 19, 21], three examined blood melatonin concentrations [16, 20, 22], one evaluated melatonin concentration in the aqueous humor [23], and one measured salivary melatonin levels [17]. All samples were collected at night, except for three studies [16, 21, 22]. All studies utilized enzyme-linked immunosorbent assay to measure melatonin concentration [16-19, 21-23], except for the study by Hikichi et al. [20], which employed high-performance liquid chromatography (Table 1). The Newcastle-Ottawa Scale Overall, scores suggested that all studies were of adequate to high quality, with scores ranging from 6 to 8, reflecting varying degrees of adherence to the scale's criteria (Table 2).

Melatonin concentration in aqueous humor

In addition to the pineal gland, recognized as the main internal source of melatonin, ocular tissues have been identified as having the ability to synthesize melatonin and express melatonin receptors [8]. Aydin and Sahin [23] observed that individuals with PDR exhibited significantly elevated levels of melatonin in the aqueous humor compared with the control group. Nonetheless, no significant increase was observed in non-PDR patients compared with the control group. Furthermore, a positive correlation was observed between melatonin levels in the aqueous humor and the duration of DM and glycated hemoglobin (HbA1c) levels, indicating that increased melatonin levels in the aqueous humor may be linked to the severity of DR [23].

Melatonin concentration in blood

Serum melatonin levels are approximately three times higher than those found in the saliva, and plasma sampling has demonstrated enhanced sensitivity in evaluating melatonin concentrations [24].

Daytime blood melatonin concentration: Wan et al. [16] assessed serum melatonin concentrations at 8:00 AM in a cohort of 182 hospitalized patients with DM (57 without DR, 64 without PDR, and 61 with PDR) and 118 healthy controls. These findings indicated a gradual decline in plasma melatonin concentrations among the study groups, with the highest levels recorded in the healthy control cohort (Table 1). They identified plasma melatonin level as a potential diagnostic biomarker for DR, showing an impressive area under the curve of 0.893. Additionally, plasma melatonin levels in individuals with DR were negatively associated with DM duration and HbA1c levels. A significant positive correlation was identified between melatonin and total bilirubin contents [16].

Saeed et al. [22] carried out an investigation to analyze daytime serum melatonin levels in female patients with DM and compared them with healthy females. The findings revealed that daytime melatonin levels were markedly reduced in the females with DM compared with healthy controls. Daytime melatonin levels were lower in individuals with DR than in those without DR. Furthermore, a significant negative correlation was observed between serum melatonin levels and fasting glucose, insulin levels, and insulin resistance [22].

Night-time blood melatonin concentration: Hikichi et al. [20] conducted a hospital-based case-control study to assess nocturnal serum melatonin levels in individuals without DM, patients with non-PDR scheduled for cataract surgery, and those with PDR undergoing combined vitrectomy and cataract surgery because of severe complications, such as vitreous hemorrhage, tractional retinal detachment, or both. Nocturnal melatonin levels were significantly lower in patients with DM than in non-DM controls, and within the case group in those with PDR compared to individuals without PDR [20]. Aydin and Sahin observed a decrease in mean nighttime plasma melatonin levels in patients with PDR compared to those without PDR and non-DR; however, the differences did not reach statistical significance [23].

Melatonin concentration in saliva

Measuring melatonin in saliva is a preferred noninvasive technique for outpatient evaluation compared to blood sampling methods. Ba-Ali et al. [17] carried out an investigation to evaluate salivary melatonin concentrations in individuals with DM and healthy controls. The findings indicated that both the peak melatonin level and the mean nocturnal melatonin concentration were significantly lower in patients with DM than in healthy controls, regardless of ambient light exposure. The mean peak diurnal melatonin concentration was significantly lower in patients with and without DR than in healthy controls. However, no significant differences in nocturnal or peak diurnal salivary melatonin levels were observed between DM patients with and without DR. Melatonin concentrations were comparable between diabetic patients regardless of retinopathy status. They did not find significant differences in nocturnal light exposure between patients with and without DR versus healthy individuals [17].

Melatonin concentration in urine

Approximately 85% of melatonin undergoes conversion to 6-hydroxymelatonin through liver enzymes, which are subsequently conjugated with sulfate and eliminated in the urine as water-soluble compounds referred to as 6-

sulfatoxymelatonin (aMT6s) [25]. Urinary aMT6s levels show a strong positive correlation with serum melatonin concentrations, establishing it as a reliable and accepted biomarker for assessing melatonin production and circadian rhythmicity [25]. Tanaka et al. [21] evaluated urinary aMT6s levels in patients with DM and healthy controls. This study examined the relationship between urinary aMT6s concentrations and the occurrence of diabetic vascular complications. The findings indicated that the natural logarithmically scaled urinary 6-sulfatoxymelatonin/creatinine ratio was significantly lower in patients with DM than in healthy controls. Furthermore, after adjusting for other confounding factors, a lower natural logarithmically scaled urinary 6-sulfatoxymelatonin/creatinine ratio was found to be an independent risk factor for DR development [21].

Chen et al. [19] found that nighttime urinary excretion of aMT6s was markedly reduced in patients with PDR compared to healthy controls, as well as in those with DM but without DR and non-PDR. Nonetheless, there was no observed difference in aMT6s excretion among healthy controls, non-DR patients, and non-PDR patients. After adjusting for various confounding factors, a significant association was identified between reduced overnight aMT6s output and elevated risk of PDR in individuals with DM [19]. Reutrakul et al. [18] found a significant association between DR and reduced nocturnal urinary aMT6s excretion. Moreover, reduced nocturnal aMT6s output was significantly associated with a 1.013% increase in HbA1c levels. The authors suggested that DR may indirectly contribute to poor glycemic control by impairing melatonin production and lowering nocturnal urinary aMT6s output [18].

Table 1. Characteristics of the studies that were included

Author (Year)	Study design	Sample size (n)	Age (year), Mean ± SD	Sex (n) Male/ Female	Sample	Melatonin measurement method	Timing of sampling	Melatonin levels (pg/mL), Mean ± SD
Aydin and Sahin (2016) [23]	Case-control	Non-PDR: 13 PDR: 13 Control: 14	67.5 ± 6.5 63.1± 9.9 66.6 ± 8.9	5/8 5/8 3/11	Aqueous humor	ELISA	Night (6:00 PM)	Non-PDR: 13.79 ± 2.56 PDR: 18.57 ± 2.67 Control: 13.63 ± 2.71
Wan et al. (2021) [16]	Case-control	Non-DR: 57 Non-PDR: 64 PDR: 61 Control:118	58.21 ± 7.75 60.89 ± 9.93 65.72 ± 8.36 59.84 ± 9.60	27/30 26/38 29/32 56/62	Blood	ELISA	Morning (8:00 AM)	Non-DR: 60.38 ± 13.43 Non-PDR: 44.48 ± 10.30 PDR: 44.69 ± 8.95 Control: 72.83 ± 16.25
Tanaka et al. (2021) [21]	Case-control	DM: 167 No DM: 27	58.6 ± 12.3 57.8 ± 15.7	99/68 15/12	Urine	ELISA	First morning urine sample	DM: 13.3 ± 21.0 ng/mL (aMT6s) No DM: 32.7 ± 40.7 ng/mL (aMT6s)
Saeed et al. (2022) [22]	Case-control	DM: 100 (DR/Non-DR:40/60) Control: 100	49.5 ± 12.83 39.9 ± 10.49	0/100 0/100	Blood	ELISA	Morning (10:00 to 12:00 AM)	DM: 0.7 ± 0.4 (DR: 0.4 and Non-DR: 1.2) Control: 3.4 ± 1.8
Reutrakul et al. (2017) [18]	Cross-sectional	DM: 56 (with DR: 14)	52.4 ± 11.7	17/39	Urine	ELISA	Night: Voids collected from post-bedtime to first morning void, excluding the final pre-bedtime void.	Median nocturnal urinary aMT6s, a major melatonin metabolite, was 12.3 ng/mg (range: 0.6–36.5 ng/mg)
Ba-Ali et al. (2018) [17]	Case-control	Moderate DR: 25 Non-DR: 29 Control: 21	61.6 ± 9.1 63.1 ± 8.3 60.0 ± 10.0	14/11 19/10 6/15	Saliva	ELISA	Average nocturnal (from 20:00 to 06:00)	DR: 3.2 ± 3.8 Non-DR: 1.7 ± 1.4 Control: 5.5 ± 4.0
Chen et al. (2014) [19]	Case-control	Non-DR: 10 Non-PDR: 19 PDR: 38 Control: 16	63.10 ± 5.567 65.84 ± 9.884 63.00 ± 5.327 63.00 ± 8.595	4/6 7/12 16/22 6/10	Urine	ELISA	Night: Urine collected from 7:00 PM to 7:00 AM, excluding the final void at 7:00 PM.	Non-DR: 9.90 ± 2.28 Non-PDR: 8.40 ± 1.84 PDR: 5.58 ± 1.33 Control: 9.95 ± 2.42
Hikichi et al. (2011) [20]	Case-control	PDR: 14 Non-PDR: 16 Control: 26	56 ± 12 72 ± 8 66 ± 11	6/8 5/11 10/16	Blood	HPLC	At 12:00–12:30 AM and 3:00–3:30 PM	**Night time:** PDR: 10.9 ± 11.4 Non-PDR: 31.1 ± 26.5 Control: 37.5 ± 30.8 **Daytime:** PDR: 0.4 ± 0.7 Non-PDR: 1.1 ± 0.6 Control: 2.4 ± 4.1

Abbreviations: n, number of participants; SD, standard deviation; pg/mL, picograms per milliliter; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ELISA, enzyme-linked immunosorbent assay; DR, diabetic retinopathy; DM, diabetes mellitus; aMT6s, 6-sulfatoxymelatonin; HPLC, high-performance liquid chromatography.

Table 2. Evaluation of the quality of included studies

Case control studies	Aydin and Sahin (2016) [23]	Ba-Ali et al. (2019) [17]	Chen et al. (2014) [19]	Saeed et al. (2022) [22]	Tanaka et al. (2021) [21]	Wan et al. (2021) [16]	Hikichi et al. (2011) [20]	Cross sectional study	Reutrakul et al. (2017) [18]
Selection								**Selection**	
Is the case definition sufficient?	*	*	*	*	*	*	*	Is the case definition sufficient?	*
Case representativeness	*	*	*	-	*	*	*	Sample	-
Choosing Controls	-	*	-	-	-	-	-	Non-respondents	*
Explanation of Controls	*	*	*	*	*	*	*	Determination of the exposure	*
Comparability								**Comparability**	
The alignment of cases and controls based on the design or analytical approach	**	*	*	*	*	-	*	The subjects in various outcome groups are comparable, according to the study design or analysis. Confounding factors are managed effectively.	*
Exposure								**Outcome**	
Determination of exposure	*	*	*	*	*	*	*	Determination of results	*
Consistent approach for identifying cases and controls	*	*	*	*	*	*	*	Statistical test	*
Rate of Non-Response	*	*	*	*	*	*	*	**Overall**	6
Overall	8	8	7	6	7	6	7		

DISCUSSION

This review indicates that individuals with DR show changes in melatonin production, which may correlate with a heightened risk of developing DR. These findings indicate a potential link between melatonin system disruptions and DR risk in individuals with DM, independent of light exposure. Blood sampling research has consistently demonstrated lower serum melatonin levels in individuals with DM and PDR than in those without DR and healthy controls.

The literature indicates a trend of reduced nocturnal blood melatonin levels in these populations [20]; however, the findings regarding daytime melatonin levels are contradictory, with reports of both decreased [16, 22] and unaltered concentrations [20]. In patients with DM, nocturnal salivary melatonin levels are diminished compared to healthy controls, regardless of the DR status [17]. Additionally, various investigations have reported a reduction in the nocturnal urinary excretion of aMT6s in individuals with DM. The association of reduced aMT6s levels with the development of PDR is noteworthy [18, 19, 21]. Melatonin levels in the aqueous humor were significantly higher in patients with PDR than in healthy controls, in contrast to the concentrations found in the serum, saliva, and urine [23]. Studies have shown that melatonin levels are inversely related to glycemic indices and the duration of DM [16, 18, 22].

The role of melatonin in facilitating glucose transport into mouse skeletal muscles via the insulin receptor substrate-1/phosphoinositide 3-kinase pathway highlights its significance in the regulation of glucose homeostasis [26]. Moreover, the elimination of melatonin receptor-1 (MT-1) markedly disrupts glucose metabolism, underscoring the critical importance of MT-1 in the development of DM [27]. A recent study indicated that single nucleotide polymorphisms in human melatonin receptor-2 (MT-2) could play a role in increasing the risk of developing type 2 DM [28]. Recent research has indicated that individuals with lower levels of urinary aMT6s excretion, a major metabolite of melatonin, are approximately twice more likely to develop DM than those with higher urinary aMT6s levels [29]. Concerning the possible impacts of melatonin on glycemic indices, a clinical trial revealed that the administration of exogenous melatonin can significantly improve glucose tolerance and insulin sensitivity [30]. The extended administration of prolonged-release melatonin in individuals with type 2 DM leads to a significant decrease in mean HbA1c levels [31].

Melatonin protects against diabetic neuropathy [32] and nephropathy [33], potentially by increasing the total antioxidant capacity.

In light of the established synthesis of melatonin in ocular tissues and the identification of melatonin receptors in the retina [34], local ocular production of melatonin does not seem to significantly influence changes in plasma melatonin levels, and reductions in melatonin concentrations do not appear to be directly linked to retinal lesions. In patients with DM and

DR, changes in melatonin levels and disruptions in circadian rhythms occur regardless of light exposure [17]. Recent findings indicate that retinal photoreceptors are essential for the regulation of circadian rhythms [35].

Retinal light perception is transmitted via the autonomic nervous system to the pineal glands. Research has shown that Individuals with type 2 DM, especially those who display signs of autonomic neuropathy, often experience significantly reduced melatonin secretion and disturbances in their circadian rhythms [36]. Consequently, it can be hypothesized that damage to the retinohypothalamic neuronal pathway and diminished retinal light detection associated with DR may disrupt the circadian alignment. Given that circadian rhythm misalignment is associated with diminished glucose tolerance and hyperinsulinemia, it has been proposed that circadian disturbances and alterations in melatonin, which functions as an antioxidant, may lead to deterioration of glycemic control and progression of DR, creating a vicious cycle [37-39]. Melatonin is recognized as a significant antioxidant molecule and its protective effects have been thoroughly validated through extensive research. Melatonin and its metabolites can scavenge reactive oxygen and nitrogen species, while promoting the expression of a range of antioxidant enzymes [40, 41]. Studies have explored the protective effects of melatonin against oxidative stress in the retinal pigment epithelial cells [42, 43] and photoreceptors [44, 45]. Based on these findings, it was reasonable to explore the possible involvement of melatonin deficiency in the development of DR.

Experimental models have indicated that melatonin may help preserve the integrity of the inner blood-retinal barrier, possibly through the deactivation of microglial cells [46]. The outcomes of stem cell transplantation in DR indicate that melatonin may serve as a valuable supportive therapeutic agent because of its potential to significantly decrease retinal inflammatory mediators when used alongside stem cell-based treatments [47]. Moreover, melatonin has demonstrated therapeutic effects in DR by inhibiting pathological angiogenesis [48]. These findings highlight the promising therapeutic implications of melatonin in the management of DR.

Existing evidence regarding the association between melatonin levels and other anti-oxidants and molecules that promote oxidative stress in individuals with retinopathy highlights the contributory role of reduced melatonin in the progression of DR. Serum bilirubin, known for its cytoprotective and antioxidant properties, was observed to be significantly lower in patients with DR [49]. A significant correlation was observed between melatonin and total bilirubin concentrations in patients with DM, PDR or non-PDR [16]. A significant negative correlation between total homocysteine levels and urinary aMT6s excretion in individuals with DR underscores the antioxidative properties of melatonin, particularly its ability to suppress homocysteine production [21].

Our review indicates that patients with diabetes and DR exhibit significantly lower melatonin levels than those without retinopathic complications. This observation suggests two possible explanations: first, lower levels of melatonin could be a risk factor for developing DR Second, the impaired neuroretinal pathways and reduced retinal light perception in these patients may significantly interfere with their circadian rhythms and melatonin production. Importantly, this reduction in melatonin production can significantly impair glycemic control, thereby creating a harmful cycle that ultimately exacerbates the progression of DR. The limitations of this study include considerable variability in the study design, population characteristics, and methods of melatonin measurement, which complicates the integration of findings. The majority of investigations had a case-control design, which hinders the ability to draw causal conclusions regarding the association between melatonin levels and DR. Moreover, confounding factors, including age, duration of DM, medication use, and lifestyle characteristics of participants, were not uniformly considered, and the limited sample sizes restrict the applicability of the results. Future investigations should emphasize longitudinal studies to clarify the temporal dynamics between melatonin levels and DR progression, standardize melatonin measurement techniques, and explore the potential therapeutic effects of melatonin through well-structured randomized controlled trials and comprehensive mechanistic studies.

CONCLUSIONS

This review highlights the potential association between altered melatonin levels and DR. Despite the observed heterogeneity and methodological limitations across the included studies, the findings suggest that reduced melatonin levels might be implicated in the pathogenesis of DR. Future research, particularly longitudinal and interventional studies with standardized measurement methods, is necessary to verify the causal relationship and therapeutic potential of melatonin in the management of DR. These findings may lead to innovative preventive and therapeutic approaches aimed at melatonin pathways in DR.

ETHICAL DECLARATIONS

Ethical approval: Not required.

Conflict of interests: None.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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