Review Article

Retinal Diabetopathy? Sleep Disorders, Retinal Changes, and Insulin Resistance: A Synthesized Systematic Review

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Abstract

Sleep disturbances, particularly prevalent in modern lifestyles, have been increasingly associated with metabolic disorders such as insulin resistance and type 2 diabetes mellitus (DM) (T2DM). Epidemiological evidence underscores the link between impaired sleep and elevated risks of cardiovascular diseases and mortality rates, alongside the emergence of metabolic dysregulation. Notably, conditions such as obstructive sleep apnea syndrome contribute to disrupted sleep architecture and exacerbate insulin resistance through repeated drops in blood oxygen levels during sleep. Furthermore, chronic sleep deprivation, irregular sleep schedules, and shift work disrupt circadian rhythms, amplifying the risk of metabolic disorders. A comprehensive search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for articles from January 2010 to October 2023 using terms such as "sleep disturbances," "Type 2 Diabetes Mellitus," and "retinal receptors." Inclusion criteria covered studies on human and animal participants, comparative analyses, and reviews. Exclusion criteria ruled out nonpeer-reviewed works and those with limited population sizes. Data extraction focused on study design, populations, types of sleep disorders, metabolic effects, and retinal health impacts. Results emphasized the bidirectional relationship among these variables. The critical analytical research and review highlights the bidirectional relationship between retinal receptor dysfunction and DM, emphasizing how metabolic disturbances associated with diabetes impact retinal health, while dysfunctional retinal receptors contribute to the progression of diabetes-related complications. Insights into the role of insulin receptors in the retina and the blood–retinal barrier underscore the mechanisms through which insulin resistance compromises retinal integrity, leading to neuroinflammation, oxidative stress, and photoreceptor damage. The disturbed sleep can also affect the melatonin secretion, thereby affecting insulin resistance. We preliminarily have named the nexus as retinal diabetopathy. By elucidating the impact of intermittent hypoxia and sleep fragmentation on cellular signaling and metabolism, particularly in vital organs such as muscles, liver, fat, and pancreas, the article provides a comprehensive understanding of how prevalent sleep disturbances and retinal changes contribute to the development and progression of T2DM. Overall, this research underscores the importance of addressing sleep disorders in the prevention and management of metabolic disorders.

Keywords: *Diabetes mellitus, eye changes, hyperglycemia, retina*

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Introduction

Sleeping is perhaps one of the most important natural functions of human beings and has tremendous influence on people's health conditions. However, in the contemporary society, sleep is not as regular as it used

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to be in the past, thus exposing many physiological processes to potential danger. One of the interesting links is that irregular sleep alters the structure of cones and rods, which are the two components of the eye's retina responsible for vision. This article aims at understanding the connection between disrupted sleep patterns and change in retinal receptors as well as the impact of disrupted sleep on the overall health of the eyes, thus worsening the effects of diabetes mellitus (DM).

Diabetes and retinal receptor problems are closely linked. When diabetes gets worse, retinal receptors suffer more, and when retinal receptors are damaged, diabetes complications can also worsen. For example, metabolic disorders in diabetic patients can harm retinal receptors significantly. At the same time, damaged retinal receptors can make not only the vision worse and may even lead to more serious metabolic issues like impaired glucose tolerance.[1,2]

Methodology of Search

In order to provide a detailed analysis of the complex relationship between sleep disorders, alterations in the density of retinal receptors, and changes in insulin sensitivity, a strict approach to the search for articles was used using PubMed, Scopus, Web of Science, and Google Scholar databases. The electronic search technique aimed at retrieving articles published in indexed journals in the period of January 2010 to October 2023. The first search terms were "sleep disturbances" and "Type 2 Diabetes Mellitus," "insulin resistance," "retinal receptors," "obstructive sleep apnoea syndrome," "circadian rhythms," and "intermittent hypoxia;" AND, OR were used to link terms effectively.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. Analyzes the works that investigate human and animal participants
2. Comparative empirical studies, review papers, and meta-analytic papers
3. Research focusing on whether there is a correlation between sleep-related disorders and metabolic control, especially of insulin and ocular health in such patients.

The exclusion criteria were as follows:

1. Not peer reviewed
2. Research work with fewer populations or inadequate methodological descriptions.

Data extraction and synthesis

The articles from each trial were used to abstract the titles and assess the relevance of the selection. Based on the titles and abstracts of the identified articles, full-text articles of possibly relevant research were assessed next. The analysis of the data collected involved capturing specifics regarding the study design, the population under consideration, the types of sleep disorders, the metabolic effects, and the impact of sleep disorders on retinal health. According to the nature and types of identified associations, the results were presented narratively to emphasize the bidirectional interactions and processes that connect sleep disturbances, insulin resistance, and retina health.

This systematic and rather formal approach allowed providing a vast and, at the same time, unprejudiced view of the state of the art in this truly interdisciplinary field.

The Importance of Sleep for Health

Sleep is not merely a state of rest; it is a complex physiological process that serves various vital functions. Adequate and regular sleep is crucial for physical health, cognitive function, and emotional well-being. The recommended amount of sleep varies across age groups, with adults generally needing 7–9 h per night. Disrupting this delicate balance can have far-reaching consequences, affecting both systemic and ocular health.[3]

The Circadian Rhythm and Its Role in Sleep

The human body operates on a circadian rhythm, a natural, internal process that regulates the sleep–wake cycle and repeats roughly every 24 h. This rhythm is influenced by external cues, primarily light and darkness, which are detected by the eyes and transmitted to the brain. The suprachiasmatic nucleus in the brain's hypothalamus[4] acts as the body's master clock, synchronizing various physiological processes, including sleep.

Retinal Receptors: The Gateway to Vision

The retina, located at the back of the eye, is a crucial component of the visual system. It contains specialized cells called photoreceptors, namely rods and cones, which convert light into electrical signals that the brain interprets as vision. Rods are responsible for vision in low-light conditions, while cones contribute to color vision and visual acuity in bright light. Disruptions in the circadian rhythm,[5,6] such as those caused by irregular sleep patterns, can impact the functioning of these retinal receptors.

Melatonin and Its Connection to Sleep

Melatonin, often referred to as the sleep hormone, is a key player in regulating the sleep–wake cycle. Its production is influenced by the circadian rhythm and is triggered by darkness. The pineal gland releases

melatonin into the bloodstream, signaling the body that it is time to sleep. Exposure to light, particularly blue light, suppresses melatonin production, making it difficult for individuals with irregular sleep patterns, especially those exposed to artificial light during the night, to achieve restful sleep. Melatonin regulates insulin secretion via the melatonin receptors (MT1 and MT2). It decreases insulin release[7,8] by blocking the cyclic adenosine monophosphate and cyclic guanosine monophosphate pathways while activating the phospholipase C/IP3 pathway, which mobilizes Ca2+ from organelles and hence increases insulin secretion [Figure 1].

Impact of Irregular Sleep on Retinal Receptors

Research suggests a bidirectional relationship between irregular sleep patterns and retinal receptor changes. Prolonged exposure to artificial light during the night can disrupt the circadian rhythm, leading to altered melatonin production and subsequent changes in retinal receptors. Studies have shown that sleep deprivation can affect the function of both rods and cones, potentially leading to visual disturbances and an increased risk of ocular diseases.[9]

The Blue Light Conundrum

One of the challenges that are becoming widespread in the contemporary society is exposure to blue light from the screens of devices. Blue light has a wavelength similar to natural sunlight and has a higher ability to affect the sleep-regulating hormone melatonin than other wavelengths.[10] Exposure to screens before going to bed affects sleep patterns disrupts the structure and function of receptors in the retina, could speed up Age related Macular Degeneration and there by affecting insulin resistance.

Age-related Changes in Sleep and Vision

The characteristic of both sleep and vision also changes as people grow old, although these changes are gradual. It can be said that aging is accompanied by alterations of the circadian rhythm and a shift to an earlier bedtime and earlier morning rise. Furthermore, there are changes in the structure and functionality of the retina as a person ages, and hence, elderly people are more sensitive to the impact of irregular sleep on receptors found in the retina.

Protective Measures and Potential Interventions

Recognizing the interconnectedness of sleep and ocular health, it becomes imperative to adopt strategies that promote healthy sleep patterns and protect retinal receptors. These measures may include creating a sleep-friendly environment, limiting screen time before bedtime, and incorporating blue light filters on electronic devices. Additionally, maintaining a regular sleep schedule and seeking professional advice for sleep-related disorders can contribute to both overall well-being and ocular health. In conclusion, the intricate relationship between irregular sleep patterns and retinal receptor changes underscores the importance

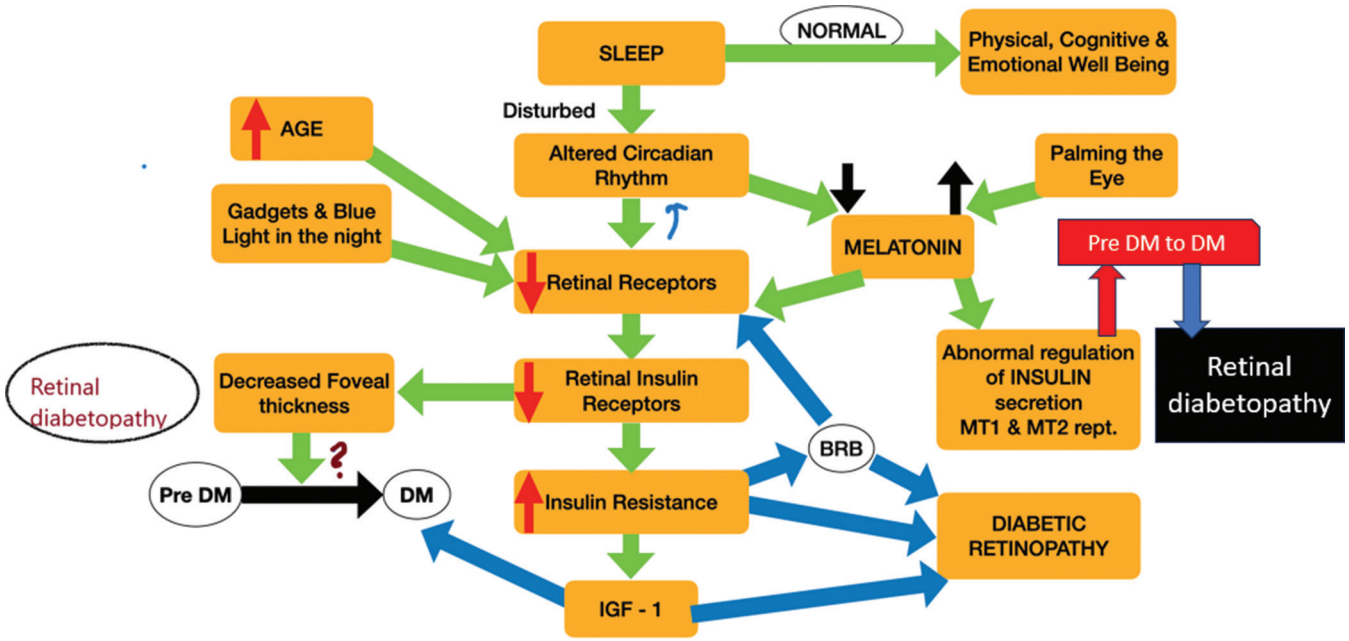

Figure 1: The possible links between retinal changes and diabetic status

of prioritizing healthy sleep habits. Disruptions in the circadian rhythm and exposure to artificial light, particularly blue light, can have profound effects on the structure and function of retinal receptors. As society continues to navigate the challenges of a digitally dominated world, understanding and addressing the consequences of irregular sleep on ocular health become crucial for maintaining overall well-being. By adopting preventive measures and promoting healthy sleep practices, individuals can mitigate potential risks and safeguard both their sleep quality and visual acuity [Figure 1].

The intricate web of connections within the human body often reveals unexpected links between seemingly unrelated physiological processes. In recent years, research has shed light on the interplay between insulin resistance, a condition often associated with metabolic disorders such as diabetes, and retinal receptor changes, the intricacies of which are crucial for vision. This following stanza delves into the fascinating connections between insulin resistance and alterations in retinal receptors, unraveling the implications of these associations for ocular health.

Insulin and Its Role in Metabolism

Insulin, a hormone produced by the pancreas, plays a central role in regulating glucose metabolism. Its primary function is to facilitate the uptake of glucose by cells, promoting energy storage and utilization. Insulin resistance occurs when cells become less responsive to the hormone, leading to elevated levels of glucose in the bloodstream. This phenomenon is a hallmark of metabolic disorders such as type 2 diabetes.

Insulin Receptors in the Retina

Surprisingly, insulin receptors are not exclusive to metabolic tissues; they are also present in various nonmetabolic tissues, including the retina. The retina, being a highly metabolically active tissue, relies on insulin signaling for proper functioning. Insulin receptors in the retina contribute to the maintenance of retinal health, and disruptions in this signaling pathway have been implicated in retinal disorders.[11]

The Blood–Retinal Barrier and Insulin Resistance

The retina is shielded by a complex barrier system known as the blood–retinal barrier (BRB), akin to the blood–brain barrier. Insulin resistance can compromise the integrity of the BRB, leading to increased permeability and allowing harmful substances to penetrate the retina. This breach may trigger inflammatory responses and oxidative stress, contributing to retinal receptor changes and the progression of retinal diseases.

Neuroinflammation and Retinal Receptor Dysfunction

Insulin resistance is closely linked to chronic low-grade inflammation, a state known as neuroinflammation. In the retina, neuroinflammation can lead to the activation of microglial cells and the release of inflammatory mediators, negatively impacting retinal cells, including photoreceptors.[12,13] This inflammatory milieu contributes to changes in the structure and function of retinal receptors, potentially exacerbating vision-related complications.

Oxidative Stress and Photoreceptor Damage

Insulin resistance is often accompanied by increased oxidative stress, an imbalance between the production of reactive oxygen species and the body's ability to neutralize them. The retina, with its high metabolic activity and exposure to light, is particularly susceptible to oxidative damage. Photoreceptors, crucial components of retinal receptors, can suffer from oxidative stress, leading to structural alterations and functional impairment.

Combining structure and function can create an associative framework for tracking pre-DM (DM) or type 2 DM (T2DM) progression in patients. In this multivariate model, N1 in the electroretinogram exhibits a robust correlation with both pre-DM and T2DM. Furthermore, the presence of N1 findings alongside decreasing foveal thickness provides additional insights into ocular health in pre-DM.[14,15] Longitudinal studies are necessary to comprehensively grasp the dynamic alterations in function and structure associated with pre-DM and T2DM.

The Role of Insulin-like Growth Factor-1

Insulin and insulin-like growth factor-1 (IGF-1) share structural similarities and signaling pathways. IGF-1 receptors are also present in the retina, influencing cell survival, differentiation, and function. Changes in insulin and IGF-1 signaling associated with insulin resistance[16] may affect the delicate balance of retinal homeostasis, impacting the viability and function of retinal receptors.

Sleep Disorders, Retinal Receptors, and Insulin Resistance

The modern lifestyle has significantly altered our sleep patterns, with a notable decrease in sleep duration from an average of 8 h to 6.5 h per night, leading to

chronic sleep deprivation. Factors such as irregular sleep schedules, shift work, and frequent travel across time zones disrupt our natural circadian rhythms, causing a mismatch between our internal body clocks and peripheral tissues. Moreover, conditions such as obstructive sleep apnea (OSA) syndrome, affecting 4%–15% of the population, not only disrupt sleep architecture but also lead to repeated drops in blood oxygen levels during sleep.

Epidemiological studies have revealed that impaired sleep is not only associated with an increased risk of overall mortality but also with higher rates of cardiovascular diseases. More recently, research has uncovered a causal link between sleep disturbances and metabolic disorders such as insulin resistance, impaired glucose tolerance, and T2DM. There are intricate endocrine and molecular mechanisms that underlie these associations, including the impact on the hypothalamic–pituitary–adrenal axis, circadian rhythms in peripheral tissues, adipose tissue metabolism, sympathetic nervous system activity, oxidative stress, and inflammation throughout the body.[5]

Metabolic illness, diabetes, has an impact on millions of people in the global society. The clinical targets are mainly focused on insulin resistance and enhanced pharmacodynamics of the drugs. Thus, conventional herbal medicines may be useful as adjuvant therapy for diabetes. Some of the plants that show effects on blood sugar control are bitter melon, fenugreek,[17,18] and cinnamon. Their mechanisms include increasing the efficacy of insulin and decreasing the ineffectiveness of the same.

Evaluations in this article have clearly demonstrated that retinal changes are frequent in patients with diabetes but that changes in vision cannot be directly pinned on diabetes. Retinal changes, commonly referred to as diabetic retinopathy, occur due to high blood sugar levels' impact on retinal blood vessels in patients with diabetes. However, diabetes is mainly a metabolic disease, with insulin dysfunctions, genetic factors, and the customers' habits being the primary causes. As for the retina, the change may serve to worsen the complications of diabetic patients; however, the changes are not capable of initiating the disease. This knowledge is significant to the management and treatment of diabetic retinopathy and the disease itself.

Therefore, we also have to explore how IH (intermittent hypoxia) , that are inherent to OSA (obstructive sleep apnea) syndrome , impact on cellular signaling and metabolism in critical organs – skeletal muscles, liver, adipose tissue, and pancreas. Failing to accomplish this, it may not explain how sleep disturbances and changes in the retina aid in the manifestation and advancement of T2DM.

Limitations

While the progression of retinal damage due to uncontrolled DM is well-documented, understanding the reciprocal relationship of worsening insulin resistance following retinal changes remains in its early stages. Research is ongoing to elucidate the intricate interplay between retinal pathology and systemic metabolic dysregulation in diabetic individuals.

Conclusion

Thus, improvement of knowledge concerning the relationship between sleep disturbances in the course of metabolic disorders such as T2DM, alteration of the density of retinal receptors, and insulin resistance is crucial for dealing with the complex problems that characterize the mentioned disease. Understanding the link between insufficient sleep, retinal disorders, and poor insulin sensitivity is crucial. Finding effective treatments and strategies for these conditions can greatly improve health outcomes. In our view, emphasis should be placed on the need to ensure that a proper night sleep is made in order to reduce the extent of diabetes. We still lack knowledge about how sleep disturbances affect cellular signaling and metabolism in the body's major organs related to T2DM pathogenesis and therapy. Sleep disturbances affect the receptors of the retinal, secretion of melatonin, and insulin sensitivity and improve that labeling this condition as "retinal diabetopathy" might not be advanced, but it is basic. Sleeping well may control the body's clock and advance the internal clock of rhythms, which can be effective to arrest the alteration of insulin situation and slow down the development of diabetes.

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Conflicts of interest

There are no conflicts of interest.

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