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REVIEW

The Association Between Dry Eye and Sleep Disorders: The Evidence and Possible Mechanisms

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Abstract: Dry eye is a disease that severely affects patients' quality of life, increasing the global burden on public health and finance. There is growing evidence that a poor lifestyle is a significant risk factor for dry eye. Along with the development of society, sleep, as a way of life, is also constantly changing. The main manifestations of sleep disorders are reduced sleep time, circadian rhythm disturbances, and sleep breathing disturbances. Sleep disorders and their secondary systemic diseases have attracted wide attention in recent years. This review mainly explored the correlation between sleep disorders and dry eye, and found that sleep-related problems and other factors potentially leading from sleep disorders could be critical factors for dry eye. These results suggest that ophthalmologists should pay attention to the sleep health problems in patients with dry eye, and we hope that this paper can provide help for future research in this field.

Keywords: circadian rhythm, sleep, sleep disorders, dry eye

Introduction

Dry Eye and Sleep Disorders

The etiology of dry eye is multifactorial, affecting the ocular surface and tear film condition. Patients present with symptoms including dryness, itching, coarseness, pain, light sensitivity and blurred vision that can significantly affect the life quality of the patients.[1] A clinical survey of dry eye epidemiology in China found that the prevalence of dry eye was up to 57.6% among 31,124 volunteers.[2] Dry eye is a substantial global public health and financial burden.[1] Growing evidence shows that lifestyle is a significant factor in dry eye.[3]

Sleep, as a lifestyle modality, also changes with the development of society. As a universal function of living species, sleep accounts for one-third of human life. While Sleep disorders mainly include insomnia, circadian rhythm disturbances, and sleep-disordered breathing.[4] Sleep cycle is classically divided into two distinct phases: rapid-eye-movement (REM) and non-rapid eye movement sleep (NREM).[5] This review aims to analyze the relationship between essential manifestations of sleep disorders and dry eye, and to explore deeper mechanisms for future research in this field.

Sleep Disorders are Risk Factors for Dry Eye

Sleep disorder is positively associated with the incidence and severity of dry eye,[6,7] and various risk factors that connected with sleep disorder are also related to dry eye. A cross-sectional study found that among 79,866 Dutch people aged 20–94, the prevalence of dry eye was particularly prevalent among those aged 20–30, associated with risk factors including psychiatry, sleep apnea, depression, etc.[8] Magno et al[9] found that 8.9% of the 71,761 participants had dry eye and 36.4% had poor sleep quality. Dry eye was significantly associated with poor sleep quality, and this association was presented in all ages and genders. Yu et al[10] conducted a community-based study involving 3070 people in Hangzhou, and similar results were obtained that sleep quality and sleep dysfunction correlated significantly with the severity of dry eye. Subjective sleep quality, sleep latency, sleep duration, sleep efficiency, and difficulty falling asleep are all influencing factors of dry eye. A large-sample prospective cross-sectional study conducted by Lim[11] found that

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6.4% of the 3303 participants were excessive sleepiness, 20.5% were at high risk for sleep apnea, 2.7% had clinical insomnia, and 7.8% <5 hours of sleep. Sleep apnea, insomnia, and reduced sleep duration are all independently associated with symptoms of dry eye. Sleep disorders are particularly pronounced in patients with Sjögren's syndrome, and are more common in patients with primary Sjögren's syndrome (pSS).[12,13] Wang et al[14] found an 81.7% prevalence of sleep disorders in patients with primary Sjögren syndrome, with 52.7% of patients suffering from moderate or severe sleep disorders, which led to their mood disorders[15] and affected their quality of life. Studying the relationship between sleep disorders and dry eye is of great significance for the occurrence, development, and treatment of dry eye.

Search Methodology

Articles were acquired via PubMed, Web of Science and Google Scholar, and papers published between January 1980 and August 2022 were extracted. This article made a series of literature searches using the keywords: Dry eye, Meibomian gland dysfunction, Sleep problems, Sleep disorders, Insomnia, sleep deprivation, Obstructive sleep apnea, mood disorder, and Circadian rhythm. All keywords were used in all possible permutations and abstracts from the results of searches were assessed. In addition, the following journals were hand-searched for articles that met the eligibility criteria: Sleep, Sleep Medicine, Behavioral Sleep Medicine, Nature and Science of Sleep Journal, Sleep Medicine Reviews, Ocular Surface, Ophthalmology, Jama Ophthalmology and Investigative Ophthalmology & Visual Science. After an inspection of the full texts, 83 papers from 202 were selected. And the older articles were identified through hand searching the reference lists of articles that met the inclusion criteria. Secondary documents from the reference lists of the primary designated papers were searched, assessed for suitability, and included.

Study on the Mechanism of Sleep Disorders Leading to Dry Eye

Sleep Loss

The blood pressure, heart rate, hormone secretion, immune defense function, cellular repair, temperature control, memory retrieval and cognition will all change during sleep.[16] Multiple health problems associated with sleep deprivation can reduce the quality of life and increase mortality.[17] Sleep loss and sleep deprivation have become a widely recognized health problem. The National Institutes of Health recommends that adults need sleep at least 7 hours a day.[18] Compared to those who slept 8 hours a day, people who slept shorter had an increased prevalence of DED.[19] In a cross-sectional study of 15,878 people, Lee et al[20] found that those who slept less than 5 hours had a 20% increased risk of dry eye compared to people who slept longer than 6 hours. A cross-sectional study proposed that shortened sleep time could be an independent risk factor for water-deficient dry eye, and the long-time use of video terminals and excessive pressure are risk factors for evaporative dry eye.[3]

Sleep deprivation has been linked to dry eye. Lack of sleep has been shown to worsen the signs and symptoms of dry eye by leading to hypertonic tears, shortened TBUT, and reduced tear secretion.[21] Li et al[22] found that sleep deprivation impaired the function of the lacrimal gland system and induced dry eye. Sleep deprivation can reduce tear secretion, resulting in corneal epithelial cell defects, increased corneal sensitivity, increased apoptosis, and induce corneal epithelial squamous metaplasia. As sleep deprivation persists, the lacrimal glands become hypertrophied, and abnormal lipid metabolites, secreted proteins and free amino acid profiles change significantly. Changes in the ocular surface caused by ten consecutive days of sleep deprivation were largely reversed after 14 days of rest.[22]

Metabolic disorder may be the cause of dry eye contributed by sleep deprivation. Sleep deprivation disrupts the levels of circulating leptin and ghrelin,[23,24] leading to improved appetite, increased calorie intake and reduced energy expenditure, which may contribute to insulin resistance, poor glycemic control, and obesity.[25,26] Effects of diabetes on the ocular surface include decreased corneal sensitivity, shorter tear membrane rupture time, decreased Schirmer test results, epithelial metaplasia, squamous metaplasia, goblet cell loss, and changes in tear protein. The worse the controlled blood glucose, the more pronounced these adverse effects become.[27–29] There is growing evidence of a link between short sleep duration and obesity.[30] Floppy eyelid syndrome (FES) can cause secondary dry eye,[31,32] and FES patients exhibit elevated plasma leptin levels and elevated leptin levels have higher BMI,[33] which could be a potential cause of secondary dry eye in patients with sleep disorders.

Tang et al[34] found that corneal epithelial lipid accumulation, microvilli morphology changes, and decreased tear secretion in a sleep-deprived mouse model were associated with significant decreases in expression levels of PPARα, carnitine palmitoyltransferase 1α(CPT1α), transient receptor potential vanillic acid 6 (TRPV6), and Ezrin phosphorylation status. Therefore, they proposed that sleep deprivation induces dry eye via abnormal microvilli morphology of corneal epithelial cells, caused by the expression of PPARα, TRPV6 and sequential downregulation of Ezrin phosphorylation states. Chen et al[35] found that sleep deprivation reduced the expression of endogenous lipid palmitoylethanolamide (PEA) in the lacrimal glands, resulting in lipid accumulation, lacrimal gland hypertrophy and dysfunction, in which lead to abnormal lipid metabolism. Exogenous PEA therapy can restore local lipid metabolism homeostasis of the lacrimal gland, prevent corneal barrier function impairment, and relieve dry eye symptoms caused by sleep deprivation, which may be related to the influence of nuclear receptor peroxisome proliferators-activated receptor -α (PPAR-α).

Circadian Rhythm Disturbances

The human circadian rhythms are manifested as complex phenotypes that exhibit many physiological processes, among which the most prominent circadian rhythm in mammals is sleep-wake.[36] Although the circadian rhythm types are often considered as individual traits with a genetic basis, they are also influenced by external factors and changes throughout the life cycle, reflecting the temporal biology phenotypes that arise due to individual differences in circadian rhythms.[37] Circadian rhythm sleep-wake disorders(CRSD) are very common.[38] Delayed sleep-wake disorder, which accounts for 10% of patients with chronic insomnia, is particularly common in adolescents, with an incidence of 7% to 16%.[38] There are three temporal patterns included in the concept of circadian rhythm preference: early morning (M-Types), intermediate (N-Types), and night (E-Types).[39] About 60% of the adult population is of the intermediate type, and 40% is one of these two extreme types.[37]

Various age stages show different circadian rhythms, and abnormal circadian rhythms in the elderly can increase sleep problems.[40] Aging affects sleep parameters such as reducing slow-wave sleep and actual sleep time, decreasing sleep efficiency, increasing the number of nighttime awakenings, and prolonging sleep latency.[41,42] A study of student populations found that adolescents have different biorhythms, such as when they get up, when they fall asleep, and when they feel physically and mentally optimal.[37,43] In general, young people are more inclined to the nocturnal type, and adolescents tend to stay up late gradually, sleep later in the morning, and sleep longer on weekends than they did before puberty.[44]

The quality of sleep varies between morning and night. People with type E have difficulty falling and maintaining asleep.[45] Research shows that E-types people experience nightmares and insomnia symptoms more frequently than M-Types.[46] There are differences in sleep efficiency among young people of M and E Types, Lehnkering et al[47] found that M-Types(87.9%, SD = 1.3) had better sleep efficiency than E-Types(84.3%, SD = 0.87%; p = 0.007). A study by Vitale et al on college students showed that the sleep quality and sleep duration of E-type was lower than that of M-type during weekdays, while on weekends, E-type's sleep quality and quantity reached the same level as others,[48] The possible explanation is that the school's fixed learning schedule is out of sync with students' daily cycle types.[49] Type E accumulates insufficient sleep on weekdays and recovers from this deficiency in "free days". This can also be verified by the poor sleep quality of Type E employees who are forced to work early.[50]

Compared with M-type college students, the typical characteristics of E-type college students are not only poor sleep quality, but also high levels of anxiety,[51] Type E is at increased risk of psychiatric disorders compared to type M.[52] The prevalence of sleep disorders and mood disorders is significantly higher in patients with DED.[53] There is a correlation between depression, mood disorders, anxiety symptoms, and the severity of DED symptoms.[53–55] Nocturnal people tend to have more depressive symptoms, as well as cognitive and behavioral disorders, hyperactivity, attention deficits, and impulsivity.[56,57] Circadian rhythm preferences are associated with emotional stability and affective disorders, and this relationship is particularly pronounced among medical students.[58]

Explanations of the association between dry eye and the type of daily cycle could be related to the neurotransmitters, 5-hydroxytryptamine (5-HT) is closely related to the regulation of circadian rhythm preferences,[59] and is also related to metabolic abnormalities and depression associated with abnormal rhythms.[60,61] 5-HT is a neurotransmitter known to be involved in the sensitization process of nociceptors and is present in human tears. The level of 5-HT is associated with

signs and symptoms of dry eye. Compared to the dry eye disease patients with normal tear secretion, the level of 5-HT in tears was higher in those with symptomatic water-deficient dry eye disease.[62]

Changes in circadian rhythms can affect metabolic diseases such as obesity and diabetes.[63] Yu et al[64] studied 1620 people aged 47–59 years and found that night sleep types are independently associated with diabetes mellitus (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.01–2.95), metabolic syndrome (OR, 1.74; 95% CI, 1.05–2.87) supporting the viewpoint that circadian rhythms play an important role in metabolic regulation, and metabolic diseases may further cause the occurrence of dry eye.

A large cross-sectional study of 3920 first-year high school students aged 16 to 17 by Saxvig IW found that the time of people with E-Types used electronic media in bed was longer than that of other circadian rhythm types.[65] Prolonged use of video terminals can shorten the time for tear film breakup, causing or aggravating dry eye.[66] Personality traits of evening and early morning type individuals led to their different susceptibility to risky behaviors such as smoking, drug use, and alcohol abuse, the daily cycle type and smoking were most significantly associated, and the night type showed a strong correlation with smoking.[67] Tobacco smoke contains many kinds of oxides and toxic substances, and when the tear film is exposed to tobacco smoke, it leads to elevated levels of caproyl lysine (a marker of oxidative stress of lipid peroxidation reactions) in the tear fluid[68], which can lead to tear film dysfunction.[69,70]

Milić et al[71] surveyed 712 students majoring in medical-related fields with circadian rhythm preferences and personality dimensions and found that early-rising students scored higher on responsibility and emotional stability. They proposed that medical students should improve their understanding of common personality traits and adhere to certain circadian rhythm preferences in order to choose a more appropriate schedule of classes and work in the future, and avoid sleep deprivation and emotional disorders caused by disturbing circadian rhythm preferences.

Other Factors Potentially Lead from Sleep Disorders to Dry Eye

Hormone Metabolism Disorder

At present, the relationship between sleep disorders and hormone metabolism disorders has received widespread attention. Chronic sleep deprivation caused by sleep deprivation can lead to insulin resistance as well as increased cortisol levels.[72,73] The prevalence of dry eye also shows a trend of increasing with age, and an increase in insulin resistance associations may be expected with growing age.[74,75] The mechanism by which insulin resistance leads to dry eye may be associated with increased oxidative stress, degeneration of lacrimal glands, decreased secretion of tear fluid, and increased expression of pro-inflammatory cytokines.[76–78] Adrenocorticotropic hormones (ACTH) and cortisol (CORT) may play a role in the development of dry eye. The hypothalamic-pituitary-adrenal axis (HPA axis) is associated with various stress physiological responses, and its main physiological functions are: the hypothalamus releases corticotropin-releasing hormone (CRH), CRH acts on the pituitary gland to release adrenocorticotropic hormone (ACTH), after which ACTH acts on the adrenal cortex to release cortisol (CORT),[79] dysfunction of the HPA axis can cause sleep disorders.[80]

When stress and other factors lead to hyperfunction of the HPA axis, the body experiences a change in sleep structure: NREM sleep decreases, REM sleep increases,[81] which is very similar to the conversion in sleep structure of insomnia in depressed patients,[82] Extensive studies have confirmed the widespread presence of dry eye in depressed patients.[83–85] The correlation between the occurrence of dry eye and changes in sleep structure after HPA axis activation needs to be further investigated. ACTH expression may be associated with dry eye, and clinically ACTH insensitive syndromes (eg, Allgrove) may present with tear-free symptoms.[86–89] The effect of ACTH synthesis on tear fluid and the mechanism by which tear production decreases in Allgrove syndrome require further study. CORT, as a type of glucocorticoid (GC), is involved in maintaining homeostasis in the body's environment and also plays an important role in sleep regulation. People with long-term insomnia are in a state of chronic stress, which activates the amygdala and thus activates the HPA axis, showing an increase in CRH and CORT.[90] During normal sleep cycles, high concentrations of CORT decrease sleep efficiency, while low concentrations increase slow-wave sleep time.[79] CORT may affect the function of the lacrimal gland, and according to current research, the specific receptor mRNA of GC has been identified in human lacrimal gland tissues.[91] On the other hand, high concentrations of CORT will increase the concentration of adrenaline in the blood,

exerting a diuretic effect, resulting in dehydration and decreased secretion of tear fluid,[92] This phenomenon may be related to the activation of the renin-angiotensin-aldosterone system, thereby exerting the function of sodium excretion and diuretics.

Chronic sleep deprivation can lead to a decline in thyroid hormone circulation, damaging the body's defense systems.[93–96] Thyroid hormones (TH), including triiodothyronine (T3) and thyroxine (T4), have the function of promoting the synthesis of lipids and proteins and accelerating tissue growth and differentiation.[97,98] TH nuclear receptors are distributed in the lacrimal glands and ocular epithelium. The decrease in T3 and T4 levels can cause lacrimal gland atrophy, corneal metaplasia, and decreased tear fluid volume.[97] TH deficiency may also lead to hypercholesterolemia and decreased lipid secretion from sebaceous glands, which may affect meibomian gland function.[99] Gelir et al found that rapid eye movement (REM) sleep deprivation rats had reduced T3 and T4 levels in their blood.[100] Since dry eye caused by sleep disorders might be related to TH expression level, the specific mechanism needs further investigation.

Obstructive Sleep Apnea Hypopnea Syndrome, OSAHS

Patients with OSAHS often present with increased ocular irritation, tear film abnormalities, and eyelid laxity.[101] Ong et al[102] conducted a longitudinal study of 120 veterans evaluating risk factors associated with severe symptoms in dry eye progression and found that OSAHS was the most significantly associated risk factor. The study of Lim et al also concluded that OSAHS is an independent factor influencing the incidence of dry eye.[20] Muhafiz et al[103] evaluated 32 OSAHS patients and 27 controls, and the results showed that the median f-NTBUT was 2.1 seconds and 5.7 seconds, and the median meibomian gland loss was 20.10% and 14.70%, respectively (P=0.043). The loss of the meibomian glands and the shortening of f-NTBUT suggest that patients with OSAHS may have a tendency to evaporative dry eye caused by damage to the meibomian glands. Higher severity of apnea hypopnea in OSAS patients, leads to lower the Schirmer and TBUT values, and the higher the OSDI and corneal luciferin sodium staining scores, the more likely they were to have dry eye.[104,105] Positive airway pressure (PAP) can relieve dry eye symptoms while treating OSAS.[105] Karaca et al[106] found that in patients with severe OSAHS, in addition to the shedding of the meibomian glands, morphological changes in the twisting, thinning, and dilation of the meibomian ducts was also pronounced, and they were more likely to develop over-evaporated dry eye.

Continuous positive airway pressure (CPAP) is the mainstay therapy for OSAS. Kadyan et al[101] found that TBUT prolongation in patients with OSAHS treated with CPAP. However, Hayirci et al[107] found that the tear secretion test was elevated and the TBUT was shortened after CPAP treatment, which may be related to the irritation of the ocular surface by the air leakage from the mask during CPAP therapy. This finding suggests that during CPAP treatment, doctors should pay more attention to the eye surface, whether short-term CPAP treatment has clear side effects of damaging the eye surface, or the mechanism by which OSAHS CPAP therapy is used to improve the symptoms of dry eye needs further investigation.

Chronic Pain

The mechanism of chronic pain is complex and affected by biological-psycho-social factors. The physiological system comprising sleep-wake rhythm and the psychological system, including emotion, may play a role in the onset of dry eye.[108] Galor et al[109] divided 187 patients with dry eye into a high-eye pain group and a low-eye pain group in a cross-sectional study, and found that those with high eye pain had more severe sleep disorders. Hakki Onen[110] also found that REM sleep deprivation induced a significant increase in rat response to nociceptive mechanical, thermal and electrical stimulation, which may be responsible for the worsening dry eye symptoms in patients with sleep disorders.

Physiological Emotion

Anxiety and depression are associated with the occurrence of sleep disorders and dry eye.[53,111] Anxiety, depression, stress, sleep and mood disorders are associated with worsening dry eye symptoms, and may be responsible for the incomplete matching between dry eye symptoms and signs.[112] Focusing on mood and sleep has guiding significance for the relief of dry eye symptoms.

It is believed that a positive mental state, including a sense of well-being, can improve all aspects of a person's functioning. The World Health Organization considers "well-being" to be an important part of overall health, and good sleep plays an important role in the attainment of "well-being" and a positive mental state.[113]

Tear Alterations May Be a Potential Factor Linking Sleep Disturbance and Dry Eye

In the study of Bitton et al[114], the condition of the ocular surface was evaluated before bedtime and after awakening, and it was found that after one night's sleep, both normal and dry-eyed patients had elevated tear river heights, and dry-eyed patients had an increased period of NIBUT after awakening. Shen[115] also found that after a night of sleep, the tear meniscus height in patients with dry eye was significantly raised, and remained elevated for 10 minutes after eyes opening. Relieving of dry eye symptoms may be linked to the changes in the composition of tear during sleep.

Tears can be classified into basic, reflexive, emotional and closed-eye tears. Closed-eye tears are collected from the eye surface immediately after sleep, and their composition is different from that of other types. Studies have reported that the secretion of tear fluid decreases when the eyes are closed at night.[116] And a series of changes occur in the ocular surface: the decrease in oxygen partial pressure makes the anterior part of the ocular surface in a hypoxic state, the tissue metabolism shifts to anaerobic metabolism, the PH and osmotic pressure of tear fluid decreases, and the permeability of the corneal epithelium increases.[117–122] Closed-eye tears can serve a defensive and clearance function during prolonged closure of the eye surface. SIgA accounts for 2% of reflex tears, compared with up to 58% of closed-eye tears. Levels of hemolysis enzyme, lactoferrin, and lipid carrier proteins account for 85–88% of total proteins in basal and reflex tears, compared with less than 30% in closed-eye tears. A few hours after eye closure, a large number of activated neutrophils accumulate in the tear fluid, and their degranulation releases a variety of proteases including elastase, metalloproteinase 9 (MMP-9) and urokinase. At the same time, closed-eye tears contains a variety of complement components required by complement to activate the classical pathway and bypass pathway, including complement C3, factor B, C4, and C9.[123] Further study of the closed-eye tear component from the perspective of proteomics, metabolome and other multi-omics, and the analysis of the correlation between sleep structure changes and tear component changes, may be of great significance to dry eye caused by sleep disorders.

Conclusion

Sleep disorders are common in dry eye patients, their etiology is complex and regulated by many factors. Sleep disorders and a range of diseases caused by dry eye have a serious impact on the life quality of sufferers and pose a serious financial burden. Ophthalmologists, however, often ignore their patients' sleep states.

Ophthalmologists should proactively ask dry eye patients about their sleep status, provide sleep-related health information and counseling, at the same time review the patient's current medications and possible causes of sleep changes, and, where appropriate, consider referring patients to sleep specialists. Early intervention to slow the progression of sleep disorders and dry eye in patients by combining medication and non-medication, topical and systemic therapies.

Sleep disorders come in many forms. While the effects and mechanisms of sleep loss and circadian rhythm disturbances on dry eye, as well as disorders that can lead to sleep disorders such as Hormone metabolic disorder, OSAHS, Chronic pain, and Emotional disorder, were described in this paper, the extent to which sleep disorders are risk factors for dry eye occurrence or progression is still unclear. Further studies are needed to determine the interaction between dry eye and sleep rhythms by specialized sleep systems.

In recent years, there has been a boom in multi-group studies and biomarker studies to further tear composition investigation from proteomics, metabolomics and other multi-group perspectives, analyze the correlation between changes in sleep structure and changes in tear composition, and identify markers of sleep disorders and dry eye that may be important for dry eye caused by sleep disorders.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, execution and interpretation, or in all these areas; have drafted or written, or substantially revised or critically reviewed the article; 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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The authors declare that they have no competing interests.

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