DERMIS

Review Article 2025; 5(6):57

Circadian Rhythms and Sebaceous Gland Function: The Impact of Disrupted Sleep Patterns on Acne Severity

*Hafsa Hassan[1], Donia Javidi[2], Janine Aguirre[3], Ashley Brudzinski[4], Radina Khalid[5], Tyarah Trias[6], Behzad Maher[7], Kelly Frasier[8]**

[1]Northeast Ohio Medical University, Rootstown, OH, USA

[2]California Health Sciences University College of Osteopathic Medicine, Clovis, CA, USA

[3]Arizona College of Osteopathic Medicine, Glendale, AZ, USA

[4]Arizona College of Osteopathic Medicine, Glendale, AZ, USA

[5]University of Texas at Tyler School of Medicine, Tyler, Texas, USA

[6]California Health Sciences University College of Osteopathic Medicine, Clovis, CA, USA

[7]California Health Sciences University College of Osteopathic Medicine, Clovis, CA, USA

[8]Department of Dermatology, Northwell Health, New Hyde Park, NY, USA

Corresponding author:

Kelly Frasier, DO, MS
Department of Dermatology, Northwell Health, New Hyde Park, NY, United States, Phone: 3105956882

Received : July 14, 2025
Published : December 29, 2025

ABSTRACT

Disruptions in circadian rhythms alter sebaceous gland function and contribute to acne severity through hormonal dysregulation, increased lipid peroxidation, and heightened inflammatory responses. The sebaceous gland operates under a distinct circadian cycle, regulated by peripheral clock genes such as *PER1, BMAL1,* and *CLOCK*, which synchronize lipid synthesis, sebum excretion, and immune homeostasis with the body's internal biological clock. Sleep disturbances and circadian misalignment, including irregular sleep-wake cycles and insufficient sleep duration, lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, triggering elevated cortisol levels that stimulate sebocyte proliferation and sebum overproduction. Concurrently, sleep deprivation reduces nocturnal melatonin secretion, impairing antioxidant defenses and promoting oxidative stress, which exacerbates lipid peroxidation within sebaceous glands, leading to comedogenesis and increased susceptibility to *Cutibacterium acnes*-mediated inflammation. Disruptions in circadian-regulated inflammatory pathways, including altered nuclear factor kappa B (NF-κB) signaling and pro-inflammatory cytokine release (IL-1β, IL-6, TNF-α), further amplify acne severity by enhancing follicular hyperkeratinization and immune cell infiltration. Epidemiological data indicate a correlation between poor sleep quality and higher acne lesion counts, particularly in individuals experiencing chronic sleep deprivation, shift

DOI: https://doi.org/10.35702/Derm.10057

work, or irregular sleep schedules. Additionally, circadian misalignment influences the pharmacokinetics of acne treatments, potentially reducing the efficacy of retinoids and anti-inflammatory agents administered at suboptimal times. Targeted interventions, including sleep hygiene optimization, chronopharmacological approaches to acne therapy, and circadian-based lifestyle modifications, help regulate sebaceous gland function and reduce the impact of disrupted sleep patterns on acne pathogenesis.

Keywords: Circadian Rhythm, Acne Vulgaris, Sebaceous Gland Function, Sleep Disruption, Hormonal Dysregulation, Oxidative Stress

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, affecting the face, chest, and back regions, where sebaceous glands are most abundant [1]. It is among the most common dermatologic conditions in the world, with a reported global prevalence of about 9.4% [1]. The condition usually starts in adolescence and results from a multifactorial interaction of elevated sebum production, follicular hyperkeratinization, colonization with Cutibacterium acnes (*C. acnes*), and subsequent inflammation [1]. Androgens are primarily responsible for triggering the activity of sebaceous glands, leading to the development of non-inflammatory lesions (open and closed comedones) and inflammatory lesions (papules, pustules, nodules, and cysts), especially during the pubertal period [2]. *C. acnes* proliferation in blocked follicles induces an immune response, generating a flux of proinflammatory mediators that promote lesion formation and result in scarring [2]. Despite not being a life-threatening condition, acne has the potential to cause severe long-term physical and psychological complications, including disfigurement, anxiety and depression [1]. Acne vulgaris is a complex disease involving the interplay of many factors, including dysregulated hormonal, microbial, and immune systems, and manifests with substantial clinical severity and chronicity.

Central to the pathogenesis of acne is the sebaceous gland, which is responsible for regulating sebum production and the activity of sebocytes. Sebocytes that make up the gland synthesize and store lipid-rich sebum consisting of triglycerides, wax esters, squalene, and cholesterol that is released onto the skin surface via holocrine secretion [3]. This secretion process is tightly controlled by hormonal and signaling pathways, particularly androgens like testosterone and dihydrotestosterone, which stimulate sebocyte proliferation and lipid production through androgen receptor activation [4]. Excessive sebum not only provides the lipid-rich environment needed for proliferation of lipophilic bacteria such as Cutibacterium acnes, it also disrupts follicular keratinization and promotes pore blockage, causing comedogenesis [4]. Moreover, changes to the composition of sebum, such as an increase in monounsaturated fatty acids and squalene peroxides, worsen inflammation via the activation of the toll-like receptors, resulting in the induction of pro-inflammatory cytokines including IL-1 and IL-8 [3,4]. Over all, the contribution of the sebaceous gland to the pathogenesis of acne involves the modulation of sebum quantity and quality, and consequently the modulation of microbial colonization, keratinocyte behavior and immune responses.

Circadian rhythms are endogenous, self-sustaining biological processes, following an approximately 24 hour cycle, that regulate an extensive array of physiological and behavioral functions in sync with external cues/environmental factors [5]. These rhythms are generated by the hierarchical system of clocks, with the central circadian pacemaker present in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [5]. The SCN synchronizes with external signals such as the light–dark cycle via direct input from photosensitive retinal ganglion cells, thereby coordinating sleep-wake behavior, hormonal release, and metabolism [5]. To echo beyond the central clock, almost all peripheral tissues, such as the liver, skin and sebaceous glands, have their own molecular clocks that govern local physiological processes via tissue-specific gene expression [5]. These peripheral clocks receive entraining signals from the SCN via autonomic innervation, endocrine signaling, or behavioral cues such as feeding and activity [5]. Altogether this synchronized circadian system preserves systemic and cellular homeostasis throughout the organism.

Sleep is essential for the regulation of critical skin physiology, such as barrier function, hydration, and cellular turnover. Chronic sleep deprivation can cause individuals to have increased transepidermal water loss (TEWL), decreased skin hydration, impaired elasticity, and increased wrinkling, suggesting a damaged skin barrier [6]. These effects are compounded by sleep-induced alterations in collagen production and delayed wound healing, which are mediated by stress-related hormonal changes that suppress fibroblast

activity and growth factor expression [7]. Circadian rhythms also help shape the skin's barrier, whose parameters (eg, transepidermal water loss [TEWL], skin pH, and temperature) are subject to predictable variability over a 24-hour cycle [8]. These findings imply that sleep quantity and timing are both important for maintaining healthy skin structure and capacity for repair.

At the cellular level, sleep encourages a hormonal and immune environment that allows skin to restore and protect itself. During slow wave sleep, levels of growth hormone, prolactin, and melatonin elevate, while cortisol and catecholamines decrease, creating a pro-inflammatory environment that stimulates immune cells and tissue regeneration [9,10]. These changes are tightly linked to the function of peripheral circadian clocks located in skin cells—including keratinocytes, melanocytes, and fibroblasts—which regulate proliferation, differentiation, and barrier repair in a time-of-day-dependent manner [11,12]. Internally, disruption of these rhythms through poor sleep or circadian misalignment leads to a breakdown in cellular coordination, compromised immune responses, and increased susceptibility to inflammation and skin disease [7,10]. To summarize, sleep acts as an important modulator of skin health due to its effects on barrier function, immune competence, and hormonal homeostasis.

Circadian Regulation of Sebaceous Gland Function

Like many other tissues in the body, sebaceous glands follow an internal clock that aligns with human sleep/wake patterns. The sebaceous gland secretes an oil called sebum, which typically increases its secretion during the night or evening [13]. Currently, there have been 3 "clock" genes that have been identified: Period 1 (PER1), Brain and Muscle ARNT-Like 1 (BMAL1), and Circadian Locomotor Output Cycles Kaput (CLOCK). These genes are said to be the core of the circadian clock and regulate the 24-hour cycle of the gland's function. The circadian rhythm is described to be a transcription/translation feedback loop with a positive and a negative arm. The positive arm consists of BMAL1 and CLOCK that form heterodimers that bind to a transcription factor to activate transcription of PER1. PER is in the negative arm of the feedback loop that inactivates its own transcription when too much is being made [14]. Together, these findings highlight the critical role of the circadian clock in regulating sebaceous gland function, ensuring that sebum production is synchronized with the body's daily day/wake cycles.

Additionally, clock genes play a key role in maintaining skin homeostasis. Studies indicate that circadian regulation can affect various skin parameters such as skin pH, transepidermal water loss, and stratum corneum hydration levels. The stratum corneum is a layer of skin composed of dead cells, whose hydration levels are dependent on Aquaporins, specifically Aquaporin 3 (AQP3). A recent study by Matsunaga et al. (2014), showed that AQP3 was under the circadian control of Clock genes and a transcription factor called DBP, D-site-binding protein [15]. Interestingly, in clock-mutated knockout mice, levels of AQP3 and stratum corneum hydration were reduced [16]. This finding highlights the importance of the circadian clock with skin barrier function.

In contrast to the central circadian clock that is controlled by light feedback cues through the retina, peripheral tissues, including the skin, are sensitive to additional cues, such as feeding and hormone cycles [17,18]. It has been demonstrated in studies, in mice and human skin models, that disruption of such external cues can result in the misalignment of peripheral clocks and affect the gene expression and metabolic activities in sebocytes. For example, high-fat diet and time-restricted feeding result in altered levels of PER1, CLOCK and BMAL1 with potential disruption of sebaceous gland function, and altered skin barrier [19]. Such results emphasize the importance of circadian regulation in skin biology and pathology.

Mechanisms Linking Circadian Disruption to Acne Pathogenesis

Hormonal Dysregulation and Sebum Overproduction

Sleep has been shown to play an important role in many critical cellular, molecular and whole body functions. This includes maintaining homeostasis, as well as immune function, neural plasticity, memory, etc. There is a key interaction between sleep and the circadian rhythm, which affects when someone typically goes to sleep and the amount of sleep they get. This interaction is primarily driven by the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN interacts with the pineal gland and the Hypothalamic Pituitary Axis (HPA) to regulate sleep-wake patterns through the release of melatonin, cortisol, and androgens, respectively [20]. Research over the past few decades has shown the close relationship between sleep and the HPA axis, where Weitzman et al first determined that sleep had an inhibitory influence on the HPA axis, as well as cortisol secretion [21]. This means that with normal sleep, there is an expected decrease in cortisol throughout the night.

DOI: https://doi.org/10.35702/Derm.10057

The HPA Axis displays a basal rhythm throughout the 24-hour cycle. In the early morning, there is a parallel rise in ACTH and cortisol, followed by a decline throughout the day and low levels at night, until a rapid rise during the second half of the night [22]. Understanding the interconnected relationship between sleep and the HPA axis can help us answer how sleep disruption influences the HPA axis.

The HPA axis regulates cortisol release by responding to stressors in the environment and other homeostatic processes. The hypothalamus secretes corticotropin-releasing hormone (CRH), stimulating the anterior pituitary to release the adrenocorticotropic hormone (ACTH), in order to stimulate the adrenal cortex to release cortisol [23]. Cortisol release is strongly influenced by the circadian rhythm, which is driven by the SCN of the hypothalamus and the HPA axis. A disruption in sleep can act like a physiological stressor, affecting the HPA axis, leading to increased cortisol levels. Wright et al found that one night of sleep deprivation (acute sleep deprivation) increased cortisol levels compared to baseline [24]. This study reported that cortisol levels were higher in the first half of the night, as well as higher during the day following sleep deprivation. These results confirmed that one night of sleep deprivation can affect the HPA axis by disrupting the basal rhythm that would typically secrete low levels of cortisol during the first half of the night. An administration of cortisol also displayed a significant suppression in REM sleep [25]. These findings highlight that insufficient or disrupted sleep leads to abnormal amounts of cortisol, disrupting the HPA axis and circadian rhythm relationship.

The disruption in the HPA axis due to poor sleep increases cortisol, which affects the normal sleep-wake pattern. Low cortisol levels throughout the night have been seen to play a large role in facilitating REM sleep. As a result, an increased amount of cortisol suppresses REM sleep. Steiger et al found that administration of ACTH was associated with decreased sleep time and sleep efficiency, with a marked reduction in REM sleep as they continued administering ACTH [26]. This study tried to replicate a stressor by administering ACTH, followed by a parallel rise in cortisol, to see how sleep can affect cortisol and therefore how cortisol affects sleep. The increased production of cortisol is not just limited to the HPA axis, as research has proved extra-adrenal production of cortisol in the brain, skin, muscle, and fat. These results convey how integrated the relationship between sleep and cortisol are. With increased stressors, such as disruptions in sleep, a rise in cortisol is observed that further disrupts the sleep wake-pattern via the HPA axis.

The local production of cortisol in the skin is due to the 11B-hydroxysteroid dehydrogenase-1 (11B-HSD1) enzyme, which converts cortisone to cortisol. The expression of the 11B-HSD1 enzyme has been found in all layers of the epidermis, as well as dermal fibroblast in healthy human skin [27]. Although the role of 11B-HSD1 has not been extensively studied, it has been found to play a role in inflammation, aging, and cell proliferation [28]. One study demonstrated that increased cortisol treatment had a dose-dependent increase in the 11B-HSD1 mRNA, followed by a positive feedback, further increasing cortisol production [29]. Therefore, an increase in cortisol will further increase 11B-HSD1 activity, leading to potential increases in inflammation and sebocyte proliferation. Another study found that an upregulation of 11B-HSD1 was found in the sebaceous glands in acne lesional skin. This result further shows the close relationship between increased cortisol production and 11B-HSD1 activity. Through enhanced lipid synthesis via sterol regulatory elementary-binding protein 1(SREBP-1), the upregulation of 11B-HSD1 increases sebocyte proliferation and sebum production, [30]. The enhanced production of cortisol further increasing the activity of 11B-HSD1 provides information on how these two factors modulate each other in order to increase sebocytes and sebum production.

The increased production of cortisol is also closely associated with androgen production, as both are released from the androgen gland in response to ACTH stimulation. Androgens have been seen to have a close regulatory relationship to sebocyte proliferation and sebum production [31]. A disruption in the HPA axis due to physiological stressors, such as sleep, can also play a role in increased androgen production, leading to an upregulation in sebum production. Yamamoto et al found that increased androgen levels typically seen during female and male puberty are significantly correlated to the onset of acne [32]. The increased sebocyte proliferation can provide the ideal environment for *C. acnes* proliferation, which has been seen to activate CRH and stimulate further cortisol production [33]. The close relationship between cortisol, androgens, and sebaceous glands, leads to the amplification of the inflammatory response within the sebaceous gland, causing increased sebum production.

Oxidative Stress and Lipid Peroxidation

Sleep deprivation causes circadian rhythm misalignment, affecting downstream neuroendocrine systems and dysregulation of cortisol and melatonin levels. Both cortisol and melatonin secretion are biomarkers for the SCN, which regulates the circadian rhythm [24]. Melatonin is the major hormone being secreted by the pineal gland, but its close relationship to the circadian rhythm makes it vulnerable and prone to disturbances in secretion during times of sleep deprivation. Bhat et al found that sleep deprivation in mice decreased plasma melatonin levels, resulting in a reduction of antioxidants [20]. This study indicated that melatonin is involved in sleep wake patterns, as well as inflammatory responses through its role as an antioxidant. This was further proved by a study done by Castano et al, where they administered melatonin to 33 human participants and reported improved sleep quality and an increase in the antioxidant capacity [34]. Melatonin not only plays a critical role in the circadian rhythm, it can also act like an antioxidant by binding to quinone reductase 2, which protects against oxidative stress [35,36]. Melatonin's role as an antioxidant drives and promotes anti-inflammatory, free-radical scavenging, and immunomodulatory roles in the skin. A sufficient amount of melatonin is needed for its role as an antioxidant. Disrupted sleep suppresses melatonin secretion, thereby leading to increased oxidative stress and activation of a cascade of inflammatory pathways directly affecting sebaceous glands.

Diminished melatonin and higher ROS in the skin initiate inflammatory response. ROS accumulation is known to induce lipid peroxidation in sebaceous glands, which provokes changes in sebum composition and results in comedogenic by-products that lead to follicular plugging [37,38]. These oxidative metabolites stimulate sebocyte inflammation, but they also increase the skin's vulnerability against a colonization with *C. acnes*, a bacterium that in turn activates additional inflammatory signaling [37,39]. Although acne has conventionally been described as an inflammatory disease, recent data identified oxidative stress as a major triggering factor of inflammation and sebogenesis. Elevated ROS combined with hormonal dysregulation, interact to facilitate formation of acne lesions. Such findings provide the basis for antioxidant therapies as potential supplements to standard acne therapies.

Inflammatory Pathway Dysregulation

Circadian regulation profoundly influences immune system activity, with intrinsic clocks in immune tissues such as the spleen, lymph nodes, and peritoneal macrophages. These local clocks function independently of systemic cues and orchestrate rhythmic inflammatory responses. For example, isolated spleen cells exposed to bacterial endotoxins at different times exhibit significant circadian variation in the secretion of TNF-α and IL-6. These rhythms are not driven by fluctuations in glucocorticoid levels or changes in immune cell populations, but by cell-autonomous circadian mechanisms within splenic macrophages. At the molecular level, over 8% of the macrophage transcriptome, including genes involved in pathogen sensing, NF-κB signaling, and cytokine production, oscillates time-dependently. These findings underscore the importance of circadian control in regulating innate immune responses and highlight potential implications for the timing of immunotherapies and anti-inflammatory treatments [40]. Complementing these findings, Toll-like receptor 9, a key pattern recognition receptor, is regulated by the circadian clock, with expression peaking during the early active phase, thereby enhancing pathogen detection time-dependently. This temporal regulation extends to downstream MAPK and NF-κB signaling pathways, resulting in diurnal variation in cytokines such as IL-1β, IL-6, and TNF-α. Significantly, the circadian patterns of these immune events vary by cell type, supporting a coordinated and time-specific immune defense [41]. At a molecular level, the nuclear receptor REV-ERBα is a central link between the circadian clock and inflammatory regulation. It rhythmically suppresses the transcription of pro-inflammatory genes like IL-1β and CCL2 in macrophages, inhibits NLRP3 inflammasome activation, and thereby dampens caspase–1–mediated IL-1β production. Disruption of REV-ERBα leads to exaggerated inflammatory responses, underscoring its essential role in maintaining immune homeostasis and restraining both acute and chronic inflammation [41]. Therefore, these findings suggest that REV-ERBα maintains baseline immune homeostasis and may serve as a potential target for modulating inflammation in time-dependent therapies. Its rhythmic control over cytokine production reinforces that aligning treatment with the circadian clock could enhance therapeutic efficacy.

Circadian rhythms play a pivotal role in modulating immune responses and disease outcomes, with disruptions leading

to heightened inflammation and increased susceptibility to chronic conditions. Immune responses vary depending on the time of day, as demonstrated by worsened viral outcomes in mice infected during their late active phase, driven by elevated cytokine release and immune cell infiltration. Disruptions of the circadian cycle, be it sleep-wake disruption, shift work, or misalignment of light-dark cycles, outweigh this fine-tuned regulation. Circadian disruption enhances macrophage-induced inflammation, NF-κB activity, and the pro-inflammatory mediators even under basal conditions without exogenous stimuli [42,43]. In the skin, this results in defective barrier repair, infiltrated immune cells and disordered keratinocyte shedding, which are features found in the causation of acne [44]. In particular, disruption of inflammatory signaling promotes follicular hyperkeratinization and chronic inflammation of the sebaceous gland, thereby establishing a microenvironment that favors overgrowth of *C. acnes*. This immune activation in turn drives cytokine release presence, perpetuating an inflammatory loop. These findings indicate that the circadian control of immunity is closely associated with acne pathogenesis. Collectively, it can be said that maintaining circadian alignment is essential for immune homeostasis and skin health. Understanding circadian pathways may offer innovative strategies to prevent or treat inflammation-driven diseases, such as acne, particularly those exacerbated by lifestyle-induced circadian disruption.

Clinical and Epidemiological Evidence

Populations experiencing sleep deprivation may be more susceptible to increased acne flare-ups. The Pittsburgh Sleep Quality Index (PSQI) is a widely used tool for assessing sleep, measuring factors such as perceived sleep quality, sleep latency, total sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction [45]. Studies utilizing the PSQI have examined various populations to explore the relationship between sleep quality and acne development. For instance, at the Faculty of Dentistry, Prima University, students aged 17–21 who reported poor sleep quality had a 33-fold increased risk of developing acne vulgaris [46]. The rigorous academic demands in this population often leads to prolonged late-night study sessions, placing them at high risk for irregular sleep patterns and sleep deprivation. Disruptions in sleep quality have been linked to physiological consequences, as evidenced by findings involving PSQI scores and the development of oxidative stress. A positive correlation was observed between PSQI scores and malondialdehyde (a marker of oxidative stress), while an inverse relationship was noted between PSQI scores and glutathione peroxidase, an important antioxidant enzyme [47]. Overall, these findings indicate a link between chronic sleep deprivation and the development of acne development through mechanisms of oxidative stress.

Implications for Acne Treatment and Management

Chronopharmacology of Acne Therapies

Chronopharmacology, the study of how biological rhythms influence drug pharmacokinetics and pharmacodynamics, is an emerging field that offers important implications for acne management. Circadian rhythms govern key physiological processes involved in drug absorption, distribution, metabolism, and elimination. Enzyme activity, gastrointestinal motility, hepatic clearance, and renal excretion all exhibit time-of-day fluctuations, meaning that medication efficacy and side effect profiles may vary depending on the timing of administration [48,49]. Circadian misalignment can significantly impact the efficacy of dermatologic treatments by disrupting the skin's natural rhythms in repair, inflammation, and barrier function. DNA repair in skin cells peaks at night, meaning treatments like retinoids and DNA-repair creams may be most effective in the evening. Anti-inflammatory agents and antibiotics may perform differently depending on the time of day, as skin permeability, immune activity, and cell turnover vary across the circadian cycle. Disrupted rhythms, such as inadequate sleep or irregular light exposure, can impair melatonin production, delay DNA repair, and reduce therapeutic response. This time-of-day dependency is especially relevant for medications like topical retinoids, which may cause increased irritation if applied when skin barrier function is at its lowest. Likewise, antibiotics targeting skin infections could benefit from timing that aligns with peak immune responsiveness, enhancing antimicrobial efficacy while minimizing resistance development [50]. Recognizing these time-sensitive dynamics enables dermatologists to optimize treatment schedules and improve clinical outcomes in patients with inflammatory or photodamaged skin. Overall, aligning drug administration with circadian rhythms can enhance efficacy, minimize side effects, and optimize personalized treatment outcomes.

This time-of-day concept is especially pertinent in relation to acne treatments that are directed at pathways in which circadian physiology has an impact. For instance, retinoids,

agents that enhance keratinocyte turnover and assist with DNA repair, may function optimally when used at night, when skin barrier repair and cell regeneration are maximal. On the other hand, benzoyl peroxide (BP) has antimicrobial activity against *C. acnes* and may be more advantageous for morning application, when the activity of the sebaceous gland is higher [51]. Altered sleep patterns or circadian desynchrony could disrupt these natural rhythms, with possible consequences on the efficacy of the treatment or on local irritation. These approaches are supported by clinical investigation. In one study of 33 participants with mild to moderate acne, use of benzoyl peroxide, 2.5% twice daily, and topical retinol in the evening for 12 weeks significantly reduced total acne lesions and improved acne severity and inflammatory and non-inflammatory lesion counts. Surface roughness, blotchiness, uneven tone, and clarity also improved, with high tolerability and no significant irritation or adverse events reported [51]. Liver enzyme activity varies as it's dependent on the time of day, therefore also impacting liver metabolism of oral retinoids and antibiotics. This warrants further exploration of the best regimen schedule for systemic drug use in acne treatment [52]. Chronotherapy, the delivery of medications to match human circadian biology, has also been demonstrated to lead to lower side effects and greater tolerability, especially in the case of retinoids, which result in photosensitivity and irritation if taken during the day. Finally, the gradual introduction of chronopharmacology into therapeutic schedules for acne could lead to better outcomes in patients, treatment efficacy, diminished side effects, and better outcomes relevant to the patient's circadian profile for the individual.

Lifestyle and Behavioral Interventions

Lifestyle and behavioral interventions, particularly those targeting sleep hygiene, are crucial in managing acne by supporting circadian alignment and reducing inflammation through improved sleep quality. A case-control study by Zhu et al. (2023) investigated the relationship between acne and factors such as sleep quality, circadian preference, and mood [53]. Eighty-one acne patients and 76 age- and sex-matched healthy controls were assessed using standardized tools to measure acne severity, sleep patterns, and psychological well-being. Compared to controls, individuals with acne reported significantly poorer sleep quality and higher anxiety levels. Acne severity was positively associated with poor sleep, evening chronotype, depression, and anxiety, even after adjusting for education and family history of acne [53]. Thus, these findings suggest that sleep disturbances and mood disorders are closely linked to acne, highlighting the importance of a holistic treatment approach that addresses both psychological and dermatological factors.

Furthermore, poor sleep quality affects nearly one-third of U.S. adults and is associated with increased risks of chronic diseases, psychiatric disorders, and higher all-cause mortality. Emerging evidence suggests that sleep disturbances may contribute to skin conditions, including acne. Schrom et al. (2019) explored the relationship between sleep quality and acne severity in 40 adult patients from dermatology clinics in Cleveland, OH [54]. Acne was assessed using the Global Acne Grading Scale, while sleep quality was measured via the Pittsburgh Sleep Quality Index and a 7-day sleep journal. Participants also completed the Dermatology Life Quality Index and the PHQ-2 for depression screening. Findings indicate a potential link between poor sleep and increased acne severity, underscoring the need for targeted sleep hygiene interventions in acne management. Evidence-based strategies to improve sleep and support circadian alignment include maintaining a consistent sleep schedule, reducing evening screen time and blue light exposure, limiting caffeine intake, and creating a dark, calm, and quiet sleep environment [54]. Thus, improving sleep quality may enhance skin outcomes, overall mental health, and treatment response for acne patients.

Additionally, light is a key regulator of sleep–wake cycles, acting through the circadian system to influence melatonin secretion and alertness. Bright light therapy, a low-cost and non-pharmacological treatment, has shown promise for sleep disorders, though past research has produced mixed results. One meta-analysis by Van Maanen et al. (2016) systematically reviewed and found that light therapy has minor to moderate effects on improving sleep overall, with specific benefits for circadian rhythm sleep disorders, insomnia, and sleep disturbances related to Alzheimer's disease and dementia [55]. Effectiveness varied based on study design, light intensity, and participant demographics, and some publication bias was detected. Despite modest effect sizes, findings support light therapy as an effective intervention for sleep problems, especially those tied to circadian misalignment.

The skin is constantly exposed to environmental stressors such as UV radiation, pollutants, physical injuries, and pathogens, requiring robust defense mechanisms. Melatonin, an evolutionarily conserved molecule, is critical in skin

protection and repair. Human skin not only contains functional melatonin receptors but also synthesizes and regulates its own melatonin, making it both a target and a source of this hormone. Topical melatonin, alongside endogenous production, shows promise in enhancing the skin's resilience. Additionally, melatonin supplementation and circadian light therapy may help regulate sebaceous gland activity and inflammatory pathways, offering novel strategies for managing conditions like acne and dermatitis [56]. As a result, these approaches support skin homeostasis by aligning with natural circadian rhythms and strengthening the skin's barrier against environmental insults.

Epidemiological data further support the impact of lifestyle behaviors on acne. Khormi et al. (2024) conducted a cross-sectional study that examined the prevalence and lifestyle risk factors of acne vulgaris in Saudi Arabia [57]. Results showed that 72% of participants reported a history of acne, mainly mild to moderate and affecting the face, with most cases beginning between the ages of 16 and 20. Lifestyle patterns revealed low water intake, short sleep duration of around only 5–7 hours, frequent fast food consumption, and minimal physical activity, all associated with acne occurrence [57]. Therefore, this study demonstrated that modifiable lifestyle factors play a significant role in acne development and supports incorporating lifestyle counseling into acne treatment for improved management. Similarly, a meta-analysis by Wong et al. (2023) evaluates the effects of multicomponent lifestyle medicine interventions on sleep quality, such as consistent sleep schedules, reduced screen time, and healthy daily habits [58]. Analyzing randomized controlled trials, lifestyle medicine interventions significantly improved subjective sleep quality compared to inactive controls both post-intervention and at short-term follow-up, with more tremendous benefits seen in those with clinically significant sleep disturbances. However, no significant differences were found compared to active controls, and long-term effects remain unclear due to limited data [58]. Therefore, these findings highlight the importance of non-pharmacologic, lifestyle-based strategies for improving sleep, especially given the growing evidence linking poor sleep to acne through hormonal dysregulation, inflammation, and impaired skin barrier function. Targeted lifestyle medicine interventions may enhance sleep quality and help mitigate acne symptoms, though additional high-quality, long-term studies are still needed to optimize their role in acne management.

Future Directions and Challenges

Current research supports a potential relationship between sleep quality and acne, but significant gaps remain in fully understanding this connection. There are a lack of longitudinal studies and interventional trials specifically designed to investigate the causal and temporal nature of this relationship [59]. Future investigations should prioritize longitudinal designs to establish causality and explore the dynamics of acne development and its interplay with sleep patterns over time. Investigating time-dependent gene expression within sebaceous glands in response to sleep variations could offer mechanistic insights into acne pathogenesis [60,61]. Circadian rhythms of clock gene activity possibly regulate lipid biosynthesis, immune signaling, and proliferation of sebocytes, which are central to acne pathogenesis. However, the precise genomic and proteomic changes induced by sleep loss are largely unknown and need to be further explored [60,61]. Another area for further inquiry is the potential of melatonin-based therapies for acne, given melatonin's role in circadian rhythms, potential anti-inflammatory and antioxidant properties, as well as its role in regulating skin homeostasis [62]. Additionally, further focus on the development of circadian-specific drug formulations for acne could optimize treatment efficacy by aligning with the skin's intrinsic biological clocks [62]. Current studies face limitations such as small sample sizes and a lack of controlled, objective sleep assessments like polysomnography [61]. Many studies rely on self-reported data, which may introduce bias, and often does not adequately account for confounding lifestyle factors [63]. Addressing these limitations through larger, well-controlled studies employing objective sleep measures is recommended. Finally, given the likely interplay of psychiatric and pathophysiologic factors and the involvement of the circadian clock and skin microbiome, interdisciplinary approaches are encouraged. Collaboration between dermatologists, chronobiologists, sleep researchers, and potentially psychologists and microbiologists will be vital to comprehensively understand the intricate relationship between sleep and acne in order to develop more effective management strategies.

CONCLUSION

Disturbed circadian rhythms and poor quality of sleep can largely contribute to acne development via hormonal dysregulation, oxidative stress, immune dysfunction, and

DOI: https://doi.org/10.35702/Derm.10057

abnormal sebaceous gland function. The increasing evidence highlights the importance of circadian biology in acne prevention and therapy. Chronopharmacology, melatonin-based treatment, and life-style changes, including sleep hygiene, may optimize results in acne patients. Further studies need to be performed in order to investigate longitudinal and mechanistic studies to elucidate causal pathways and facilitate the development of time-targeted, personalized acne treatments. An interdisciplinary effort is required to better understand the complex relationship between sleep, circadian health, and skin disease.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Leung AK, Barankin B, Lam JM, Leong KF, Hon KL. (2021). Dermatology: how to manage acne vulgaris. Drugs Context. 10:2021-8-6.
2. Vasam M, Korutla S, Bohara RA. (2023). Acne vulgaris: A review of the pathophysiology, treatment, and recent nanotechnology based advances. Biochem Biophys Rep. 36:101578.
3. Makrantonaki E, Ganceviciene R, Zouboulis C. (2011). An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinol. 3(1):41-49.
4. Del Rosso JQ, Kircik L. (2024). The primary role of sebum in the pathophysiology of acne vulgaris and its therapeutic relevance in acne management. J Dermatolog Treat. 35(1):2296855.
5. Ayyar VS, Sukumaran S. (2021). Circadian rhythms: influence on physiology, pharmacology, and therapeutic interventions. J Pharmacokinet Pharmacodyn. 48(3):321-338.
6. Shao L, Jiang S, Li Y, Shi Y, Wang M, Liu T, et al. (2022). Regular Late Bedtime Significantly Affects the Skin Physiological Characteristics and Skin Bacterial Microbiome. Clin Cosmet Investig Dermatol. 15:1051-1063.
7. Kahan V, Andersen ML, Tomimori J, Tufik S. (2010). Can poor sleep affect skin integrity? Med Hypotheses. 75(6):535-537.
8. Yosipovitch G, Xiong GL, Haus E, Sackett-Lundeen L, Ashkenazi I, Maibach HI. (1998). Time-dependent variations of the skin barrier function in humans: transepidermal water loss, stratum corneum hydration, skin surface pH, and skin temperature. J Invest Dermatol. 110(1):20-23.
9. Besedovsky L, Lange T, Born J. (2012). Sleep and immune function. Pflugers Arch. 463(1):121-137.
10. Ibarra-Coronado EG, Pantaleón-Martínez AM, Velazquéz-Moctezuma J, Prospéro-García O, Méndez-Díaz M, Pérez-Tapia M, et al. (2015). The Bidirectional Relationship between Sleep and Immunity against Infections. J Immunol Res. 2015:678164.
11. Geyfman M, Andersen B. (2009). How the skin can tell time. J Invest Dermatol. 129(5):1063-1066.
12. Sandu C, Dumas M, Malan A, Sambakhe D, Marteau C, Nizard C, et al. (2012). Human skin keratinocytes, melanocytes, and fibroblasts contain distinct circadian clock machineries. Cell Mol Life Sci. 69(19):3329-3339.
13. Verschoore M, Poncet M, Krebs B, Ortonne JP. (1993). Circadian variations in the number of actively secreting sebaceous follicles and androgen circadian rhythms. Chronobiol Int. 10(5):349-359.
14. Duan J, Greenberg EN, Karri SS, Andersen B. (2021). The circadian clock and diseases of the skin. FEBS Lett. 595(19):2413-2436.
15. Matsunaga N, Itcho K, Hamamura K, Ikeda E, Ikeyama H, Furuichi Y, et al. (2014). 24-hour rhythm of aquaporin-3 function in the epidermis is regulated by molecular clocks. J Invest Dermatol. 134(6):1636-1644.
16. Hara-Chikuma M, Verkman AS. (2008). Roles of aquaporin-3 in the epidermis. J Invest Dermatol. 128(9):2145-2151.
17. Geyfman M, Andersen B. (2009). How the skin can tell time. J Invest Dermatol. 129(5):1063-1066.

18. Spörl F, Korge S, Jürchott K, Wunderskirchner M, Schellenberg K, Heins S, et al. (2012). Krüppel-like factor 9 is a circadian transcription factor in human epidermis that controls proliferation of keratinocytes. Proc Natl Acad Sci U S A. 109(27):10903-10908.

19. Matsui MS, Pelle E, Dong K, Pernodet N. (2016). Biological Rhythms in the Skin. Int J Mol Sci. 17(6):801.

20. Bhat A, Pires AS, Tan V, Babu Chidambaram S, Guillemin GJ. (2020). Effects of Sleep Deprivation on the Tryptophan Metabolism. Int J Tryptophan Res. 13:1178646920970902.

21. Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. (1983). Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab. 56(2):352-358.

22. Balbo M, Leproult R, Van Cauter E. (2010). Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. Int J Endocrinol. 2010:759234.

23. Nicolaides NC, Vgontzas AN, Kritikou I, Chrousos G. (2020). HPA Axis and Sleep. In: Feingold KR, (Eds.) et. al., Endotext. MDText.com, Inc.

24. Wright KP Jr, Drake AL, Frey DJ, Fleshner M, Desouza CA, Gronfier C, et al. (2015). Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. Brain Behav Immun. 47:24-34.

25. Lo Martire V, Caruso D, Palagini L, Zoccoli G, Bastianini S. (2019). Stress & sleep: A relationship lasting a lifetime. Neurosci Biobehav Rev. 117:65-77.

26. Steiger A, Holsboer F. (1997). Neuropeptides and human sleep. Sleep. 20(11):1038-1052.

27. Terao M, Murota H, Kimura A, Kato A, Ishikawa A, Igawa K, et al. (2011). 11β-Hydroxysteroid dehydrogenase-1 is a novel regulator of skin homeostasis and a candidate target for promoting tissue repair. PLoS One. 6(9):e25039.

28. Terao M, Katayama I. (2016). Local cortisol/corticosterone activation in skin physiology and pathology. J Dermatol Sci. 84(1):11-16.

29. Tiganescu A, Walker EA, Hardy RS, Mayes AE, Stewart PM. (2011). Localization, age- and site-dependent expression, and regulation of 11β-hydroxysteroid dehydrogenase type 1 in skin. J Invest Dermatol. 131(1):30-36.

30. Lee SE, Kim JM, Jeong MK, Zouboulis CC, Lee SH. (2013). 11β-hydroxysteroid dehydrogenase type 1 is expressed in human sebaceous glands and regulates glucocorticoid-induced lipid synthesis and toll-like receptor 2 expression in SZ95 sebocytes. Br J Dermatol. 168(1):47-55.

31. Del Rosso JQ, Kircik LH, Stein Gold L, Thiboutot D. (2020). Androgens, Androgen Receptors, and the Skin: From the Laboratory to the Clinic With Emphasis on Clinical and Therapeutic Implications. J Drugs Dermatol. 19(3):30-35.

32. Yamamoto A, Ito M. (1992). Sebaceous gland activity and urinary androgen levels in children. J Dermatol Sci. 4(2):98-104.

33. Borrel V, Gannesen AV, Barreau M, Gaviard C, Duclairoir-Poc C, Hardouin J, et al. (2019). Adaptation of acneic and non acneic strains of Cutibacterium acnes to sebum-like environment. Microbiologyopen. 8(9):e00841.

34. Castaño MY, Garrido M, Delgado-Adámez J, Martillanes S, Gómez M, Rodríguez AB. (2018). Oral melatonin administration improves the objective and subjective sleep quality, increases 6-sulfatoxymelatonin levels and total antioxidant capacity in patients with fibromyalgia. J Appl Biomed. 16:186-191.

35. Murali R, Thanikaivelan P, Cheirmadurai K. (2016). Melatonin in functionalized biomimetic constructs promotes rapid tissue regeneration in Wistar albino rats. Journal of materials chemistry B. 4(35):5850-5862.

36. Boutin JA. (2016). Quinone reductase 2 as a promising target of melatonin therapeutic actions. Expert Opin Ther Targets. 20(3):303-317.

37. Kardeh S, Moein SA, Namazi MR, Kardeh B. (2019). Evidence for the Important Role of Oxidative Stress in the Pathogenesis of Acne. Galen Med J. 8:e1291.

38. Briganti S, Picardo M. (2003). Antioxidant activity, lipid peroxidation and skin diseases. What's new. J Eur Acad Dermatol Venereol. 17(6):663-669.

39. Zouboulis CC, Xia L, Akamatsu H, Seltmann H, Fritsch M, Hornemann S, et al. (1998). The human sebocyte culture model provides new insights into development and management of seborrhoea and acne. Dermatology. 196(1):21-31.

40. Keller M, Mazuch J, Abraham U, Eom GD, Herzog ED, Volk HD, et al. (2009). A circadian clock in macrophages controls inflammatory immune responses. Proc Natl Acad Sci U S A. 106(50):21407-21412.

41. Ding J, Chen P, Qi C. (2024). Circadian rhythm regulation in the immune system. Immunology. 171(4):525-533.

42. Jerigova V, Zeman M, Okuliarova M. (2022). Circadian Disruption and Consequences on Innate Immunity and Inflammatory Response. Int J Mol Sci. 23(22):13722.

43. Castanon-Cervantes O, Wu M, Ehlen JC, Paul K, Gamble KL, Johnson RL, et al. (2010). Dysregulation of inflammatory responses by chronic circadian disruption. J Immunol. 185(10):5796-5805.

44. Duan J, Greenberg EN, Karri SS, Andersen B. (2021). The circadian clock and diseases of the skin. FEBS Lett. 595(19):2413-2436.

45. Khosravi A, Emamian MH, Hashemi H, Fotouhi A. (2021). Components of Pittsburgh Sleep Quality Index in Iranian adult population: an item response theory model. Sleep Med X. 3:100038.

46. Rajagukguk M. (2024). The Relationship of Sleep Quality with Severity Level Acne Vulgaris in Students Aged 17-21 Years Faculty of Dentistry Prima Indonesia University. Journal of Community Health Provision. 4(1):18-27.

47. Gulec M, Ozkol H, Selvi Y, Tuluce Y, Aydin A, Besiroglu L, et al. (2012). Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 37(2):247-251.

48. Piedras ALR, Sánchez UB, Hernández EGO, Romero AC. (2024). Chronopharmacokinetics: A brief analysis of the influence of circadian rhythm on the absorption, distribution, metabolism, and elimination of drugs. Biomedicine and Pharmacotherapy Journal. 17(3):2011-2017.

49. Erkekoglu P, Baydar T. (2012). Chronopharmacokinetics of drugs in toxicological aspects: A short review for pharmacy practitioners. J Res Pharm Pract. 1(1):3-9.

50. Lyons AB, Moy L, Moy R, Tung R. (2019). Circadian Rhythm and the Skin: A Review of the Literature. J Clin Aesthet Dermatol. 12(9):42-45.

51. Kosmoski G, Miller D, Coret C, Atillasoy E. (2022). A Topical Combination Regimen of Benzoyl Peroxide and Retinol Moisturizer for Mild to Moderate Acne. J Drugs Dermatol. 21(12):1340-1346.

52. Dobrek L. (2021). Chronopharmacology in Therapeutic Drug Monitoring-Dependencies between the Rhythmics of Pharmacokinetic Processes and Drug Concentration in Blood. Pharmaceutics. 13(11):1915.

53. Zhu J, Peng K, Zhang Y, Bai X, Zhong C, Ye J, et al. (2023). Sleep quality, circadian preferences, and mood among patients with acne vulgaris: a case-control study. Sleep Breath. 27(5):1997-2003.

54. Schrom KP, Ahsanuddin S, Baechtold M, Tripathi R, Ramser A, Baron E. (2019). Acne Severity and Sleep Quality in Adults. Clocks Sleep. 1(4):510-516.

55. van Maanen A, Meijer AM, van der Heijden KB, Oort FJ. (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev. 29:52-62.

56. Rusanova I, Martínez-Ruiz L, Florido J, Rodríguez-Santana C, Guerra-Librero A, Acuña-Castroviejo D, et al. (2019). Protective Effects of Melatonin on the Skin: Future Perspectives. Int J Mol Sci. 20(19):4948.

57. Khormi G, Aldubayyan N, Hakami M, Daghriri S, Aqeel S. (2024). Impact of Lifestyle and Dietary Habits on the Prevalence of Acne Vulgaris: A Cross-Sectional Study From Saudi Arabia. Cureus. 16(3):e57200.

58. Wong VW, Ho FY, Wong YS, Chung KF, Yeung WF, Ng CH, et al. (2023). Efficacy of lifestyle medicine on sleep quality: A meta-analysis of randomized controlled trials. J Affect Disord. 330:125-138.

59. Khormi G, Aldubayyan N, Hakami M, Daghriri S, Aqeel S. (2024). Impact of Lifestyle and Dietary Habits on the Prevalence of Acne Vulgaris: A Cross-Sectional Study From Saudi Arabia. Cureus. 16(3):e57200.

60. Matsui MS, Pelle E, Dong K, Pernodet N. (2016). Biological Rhythms in the Skin. Int J Mol Sci. 17(6):801.

61. Schrom KP, Ahsanuddin S, Baechtold M, Tripathi R, Ramser A, Baron E. (2019). Acne Severity and Sleep Quality in Adults. Clocks Sleep. 1(4):510-516.

62. Xin M, Bi F, Wang C, Huang Y, Xu Y, Liang S, et al. (2025). The circadian rhythm: A new target of natural products that can protect against diseases of the metabolic system, cardiovascular system, and nervous system. J Adv Res. 69:495-514.

63. Rosenman R, Tennekoon V, Hill LG. (2011). Measuring bias in self-reported data. Int J Behav Healthc Res. 2(4):320-332.

DOI: https://doi.org/10.35702/Derm.10057