Unraveling the interplay between chronobiology, circadian rhythm, and gut microbiome dynamics in human health

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Abstract.
Background: This study investigates the intricate interplay between disrupted circadian rhythms, sleep variations, and gut microbiota dynamics, recognizing their bidirectional influences on human health. The relationships are explored through the brain-gut-microbiota axis, emphasizing the importance of maintaining a harmonious balance for overall well-being.
Methods: A selection criteria was determined after a thorough literature review across search engines and databases. SAMRA guidelines were followed to draft the manuscript.
Objectives: To elicit the interplay between sleep patterns, chronobiology, and circadian rhythm influence the composition and functionality of the gut microbiome in human participants. Results: Disruptions in circadian rhythms impact gut microbiota composition, leading to dysbiosis and pathological mechanisms. Reciprocally, variations in sleep duration and quality influence the diversity and function of the gut microbiome. Identified microbial patterns associated with different circadian phases reveal nuanced connections, highlighting the broader implications of circadian rhythm disruption on human health.

Keywords:
circadian rhythm
sleep variations
gut microbiota
brain-gut-microbiota axis
dysbiosis
microbial patterns
human health
Introduction

Humans operate within a 24-hour internal clock known as the circadian rhythm, intricately influencing various physiological functions. Central to this influence is the gut microbiota, often regarded as the body's largest endocrine organ, playing a pivotal role in digestion, vitamin synthesis, and immune regulation [1].

Dietary habits significantly shape the gut microbiota, and disruptions in the circadian rhythm can lead to dysbiosis, favoring pathological mechanisms. The bidirectional relationship between circadian rhythms and the gut microbiota underscores the importance of understanding their interplay for overall well-being [2]. This manuscript aims to unravel the impact of disrupted circadian rhythms on the diversity and abundance of gut microbiota, exploring the intricate relationships between sleep, circadian rhythm, and the gut microbiome. Additionally, we delve into the correlation between variations in sleep duration and quality, shedding light on their reciprocal influence through the brain-gut-microbiota axis. Furthermore, we identify microbial patterns associated with different phases of the circadian rhythm, emphasizing the relevance of maintaining a healthy circadian rhythm for human health.

METHODOLOGY

A thorough search was conducted across Google Scholar and PubMed. The following criteria were employed to select and screen relevant literature and data.

Inclusion Criteria:
1. Study Type:
   - Include primary research studies such as randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional studies.
   - Include systematic reviews and meta-analyses for an overview of existing evidence.
2. Participants:
   - Include studies involving human participants of any age.
   - Consider studies with participants diagnosed with sleep disorders, those with disrupted circadian rhythms, or those with documented variations in gut microbiome composition.
3. Interventions/Exposures:
   - Include studies exploring interventions related to sleep patterns, chronobiology, and circadian rhythm.
   - Consider studies examining the impact of sleep-related interventions on the gut microbiome.

4. Outcomes:
   - Include studies that report outcomes related to sleep quality, circadian rhythm disturbances, and changes in gut microbiome composition.
   - Focus on studies with measurable and objective outcomes, such as laboratory analyses of microbiome samples.

Exclusion Criteria:
1. Study Design:
   - Exclude studies that are not primary research (e.g., editorials, opinion articles).
   - Exclude studies with insufficient methodological rigor.
2. Interventions/Exposures:
   - Exclude studies that do not specifically address sleep, chronobiology, circadian rhythm, or their impact on the gut microbiome.
3. Outcomes:
   - Exclude studies without relevant outcomes or clear associations between sleep-related factors and gut microbiome changes.

Impact of Disrupted Circadian Rhythms on the Diversity and Abundance of Gut Microbiota

Dietary habits significantly influence gut microbiota, affecting its population and function. Disruption of circadian rhythms can lead to dysbiosis, favoring pathological mechanisms. Studies show that gut microbiota composition fluctuates over 24 hours, influenced by host signals rather than light exposure. Various bacterial metabolites, such as short-chain fatty acids (SCFAs), mediate the synchronizing effect of gut microbiota on the host’s circadian clock. For example, SCFAs regulate hepatic circadian gene expression, impacting the rhythmicity of genes like PER2, PER230, and ARNTL [2].

A bidirectional relationship exists between circadian rhythms and gut microbiota. Disruption of circadian rhythms can lead to dysbiosis, impacting the oscillations of microbiota composition and function. Conversely, gut
microbiota influences the host's circadian clock through bacterial metabolites, emphasizing the importance of maintaining a healthy circadian rhythm for overall well-being.

**Correlation between Variations in Sleep Duration and Quality and Their Impact on Gut Microbiome**

Sleep quality and gut microbiota (GM) have an interdependent relationship through the brain-gut-microbiota axis (BGMA); one variation leads to changes in the other. A change in gut flora can adversely affect sleep quality, efficiency, and duration, and likewise, disrupted sleep patterns can affect the diversity and function of the GM [3].

The possible mechanisms underlie the metabolic processes of the bacteria, which release short-chain fatty acids, which in turn modulate the immune system, circulating cytokines, and local vagal responses [5]. They also influence the bile acid metabolism, local neurotransmitters, neuroendocrine system, and hypothalamic-pituitary-adrenal axis [5, 4].

Sleep parameters are maintained by various 'good bacteria' in the gut, such as *Lactobacillaceae*, *Bifidobacteriaceae*, *Ruminococcaceae*, and *Clostridiales*, and are being utilized for their prospective therapeutic effects [3, 4]. However, exogenous influences such as diet and lifestyle may shift microbial species to pro-inflammatory and anaerobic bacteria (harmful bacteria), which can lead to a dismissal of beneficial compounds, culminating in inadequate, tired, and fragmented sleep [3]. It can lead to insomnia, parasomnias, and various psychiatric disorders such as anxiety, depression, and dementia, which can further deteriorate sleep [5].

The diversity and composition of GM influence multiple sleep parameters such as quality, duration, and efficiency, as depicted in Table. A high gut bacterial diversity results in better sleep and vice-versa. Distinct phyla and genera are implicated in causing many sleep patterns such as Firmicutes, *Verrucomicrobia*, *Pseudomonas*, *Bacteroides*, etc. Similarly, a Firmicutes to Bacteroides ratio (F/B ratio) can be calculated, and a higher ratio corresponds to better sleep parameters [3-5]. Therefore, identifying the distinct gut flora patterns and determining gut dysbiosis is crucial to identifying sleep...
disturbances and detecting incipient cardiometabolic disorders, psychiatric disorders, and dementia affecting the general health of the individuals.

Table 1
Tabulation of the Changes in the Sleep/Circadian Rhythm and consequent Microbial levels and the mechanism.

<table>
<thead>
<tr>
<th>Sleep/Circadian Rhythm Changes</th>
<th>Microbial Involvement (Correlated with Improved Sleep Parameters)</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher Levels</td>
<td>Lower Levels</td>
</tr>
<tr>
<td>1. Sleep Quality</td>
<td>Bacterial diversity</td>
<td>Anaerobes i.e. Bacteroides Phyla (Prevotella) [6]</td>
</tr>
<tr>
<td></td>
<td>Firmicutes (Ruminococcus and Blautia), Verrucomicrobia (Akkermansia muciniphila), and Lentisphaerae Phylum [3, 6]</td>
<td>Firmicutes Phyla: produces metabolite butyrate has anti-inflammatory properties [6]</td>
</tr>
<tr>
<td>3 Sleep Duration</td>
<td>Bifidobacterium genus, Firmicutes, and Blautia genus [8]</td>
<td>Suturella [9]</td>
</tr>
</tbody>
</table>
Table continuation 1

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P. aeruginosa</strong>: leads to gut inflammation with a propensity for low-grade systemic inflammation leading to a catabolic state and cachexia [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>Order Selenomonadales and its class, Negativicutes [10], Modulates melatonin to reduce insomnia risk by enhancing gut neural pathways and epithelial barrier [10]</td>
<td></td>
</tr>
<tr>
<td><strong>Circadian Rhythm: Chronotype (Being able to wake up early or stay up late)</strong></td>
<td>Genus Anaerofilum, order Enterobacteriales, and family Enterobacteriaceae: the ability to stay up late with a heightened risk of obesity and metabolic syndrome [10]</td>
<td>Impact the circadian rhythm genes of the intestinal epithelium leading to impaired metabolism [10]</td>
</tr>
</tbody>
</table>

**Identifiable microbial patterns associated with different phases of Circadian Rhythm**

The body’s internal clock, running in the background to carry out essential functions and processes is the Circadian
Rhythm. It is centrally located in the Suprachiasmatic Nucleus which is known to synchronize the peripheral clocks in the rest of the body. The circadian clock is self-regulated using the feedback loop of a network of genes expressing proteins, BMAL1, CLOCK, Per 1/2/3, and CRY 1/2 [12].

These clock genes maintain homeostasis and coordinate various biological processes such as metabolism, immune function, and behavior. The Human gut microbiome involves a complex and yet a diverse set of micro-organisms. Bacteria are the dominant microbe with common phyla including Firmicutes and Bacteroidetes. They play a vital role in digestion, metabolism, and immunity. In recent years, there has been a growing interest in elucidating the relationship between the gut microbiome and its influence on the circadian rhythm. The GI tract regulates physiological functions such as digestion and absorption of food, and gastric emptying which are activities also regulated by the clock genes, entrained by Light/Dark cycles.

In humans, studies have shown that the levels of butyrate producers, Lachnospira, Roseburia, and Eubacterium, increase during daytime, peaking earlier due to the availability of food and decreasing significantly after microbial utilization. Primary feeders such as those that survive by rapid but incomplete breakdown of the carbohydrate, bile-tolerant groups, and H2S-producing bacteria were also found to have emerged earlier in the day [13].

Decreased daytime food intake led to changes in food intake, and increased production of short-chain fatty acids was seen during overnight fasting. The microbiota restructured its community to forage on host-derived glycans [13].

Despite the fecal samples having not been collected overnight, this study still exhibited the clock time effects on the gut microbial balance in humans. More studies are required to fully understand the identifiable changes in the microbial patterns associated with different phases of circadian rhythm in humans as well as the potential implications of this relationship.

**Relationship of Human Health Associated with the Circadian Rhythm**

Circadian clocks play a crucial role in maintaining the
rhythmicity of internal cycles encompassing behavior, physiology, and metabolism. This orchestration allows organisms to anticipate and adapt to the 24-hour rotation of the Earth. Within mammals, the circadian integration of metabolic systems is pivotal for optimizing energy harvesting and utilization throughout the light/dark cycle, ensuring a harmonious balance [14]. As the Serin & Tek (2019) review highlights, circadian rhythms exert a bidirectional influence on nearly all metabolic processes. The synchronization of peripheral clocks with the central clock is imperative for seamless coordination. However, disruptions leading to chronodisruption have been identified as a key physiological alteration. This disturbance is associated with a spectrum of disorders, including neurologic, psychiatric, cardiometabolic, and immune disorders. [15].

Lunde et al. (2020) conducted a comprehensive three-year investigation into the correlation between shift work and cardiovascular disease, aiming to elucidate the influence of circadian rhythm on heart health. The study unveiled a plausible association between shift work and cardiovascular disease (CVD), attributing it to circadian rhythm disruption that induces hormonal changes and metabolic disturbances. These disruptions manifest in conditions such as high blood pressure, atherosclerosis, diabetes, and overweight status [16]. In parallel, the research by Gale et al. (2011) on rats specifically highlighted an elevated risk of Type 2 Diabetes Mellitus (T2DM) among genetically predisposed individuals due to circadian rhythm disturbances [17]. Furthermore, Garbarino et al. emphasized in their work that sleep deprivation is linked to alterations in both innate and adaptive immune parameters. This association contributes to a chronic inflammatory state, thereby elevating the risk of infectious and inflammatory pathologies [18].

Disrupted sleep also significantly impacts mental health and is associated with multiple psychiatric as well as neurological consequences. Impaired circadian rhythms are commonly observed among individuals with various psychiatric disorders, including major depressive disorder, bipolar disorder, anxiety, schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder[19, 20]. Xu S et
al (2021) explore the impact of circadian rhythms on diverse cognitive functions. They state circadian rhythms to affect several cognitive functions particularly those needed for effort-intensive cognitive tasks, which require considerable top-down executive control. These include inhibitory control, working memory, task switching, and psychomotor vigilance [21]. Disrupted sleep can also lead to an increased number of accidents due to an increase in daytime sleepiness [22].

Circadian rhythm disruption also affects aging. While the precise mechanisms remain unclear, the premature aging observed in certain circadian mutants may be attributed to the engagement of circadian proteins in overseeing metabolism, managing genotoxic stress response, and maintaining homeostasis of reactive oxygen species (ROS) [23].

**DISCUSSIONS**

The correlation between variations in sleep duration and quality and their impact on the gut microbiome highlights a complex interdependence through the brain-gut-microbiota axis. The bidirectional relationship underscores the importance of maintaining a healthy gut microbiome for optimal sleep and vice versa.

The identified microbial patterns associated with different phases of the circadian rhythm further accentuate the intricate connections between the body's internal clock and gut health. Understanding these relationships provides insights into potential therapeutic interventions and preventive strategies for sleep disturbances and associated health conditions. The diversity and composition of gut microbiota play a crucial role in modulating various sleep parameters, including quality, duration, and efficiency. The presented table illustrates the nuanced microbial involvement in different aspects of sleep and circadian rhythm changes.

From the modulation of inflammatory responses to the impact on neurotransmitter activity, the gut microbiota emerges as a key player in maintaining optimal sleep patterns. Moreover, disruptions in circadian rhythms have broader implications for human health, extending beyond sleep disturbances. The orchestration of circadian clocks in maintaining rhythmicity across behavior, physiology, and...
metabolism is crucial for overall well-being. Chronodisruption has been linked to a spectrum of disorders, including neurological, psychiatric, cardiometabolic, and immune disorders.

This disruption, as evidenced by studies on shift work and cardiovascular disease, emphasizes the far-reaching consequences of circadian rhythm disturbances on health [15, 16]. The impact of circadian rhythm disruption extends to mental health, contributing to various psychiatric and neurological consequences. Disrupted sleep patterns are commonly observed in individuals with conditions such as major depressive disorder, bipolar disorder, anxiety, schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder [19, 20]. Understanding the intricate relationships between circadian rhythms, sleep, and health outcomes is crucial for developing comprehensive strategies to promote overall well-being.

CONCLUSION

In conclusion, this manuscript provides a comprehensive exploration of the intricate relationships between disrupted circadian rhythms, sleep variations, and gut microbiota dynamics. The bidirectional influences underscore the importance of maintaining a harmonious balance between circadian rhythms and gut health for optimal sleep and overall well-being.

The identified microbial patterns associated with different phases of the circadian rhythm add granularity to our understanding, highlighting potential avenues for therapeutic interventions. The implications of circadian rhythm disruption extend beyond sleep disturbances to impact various facets of human health. From cardiovascular diseases and metabolic disorders to mental health conditions and cognitive functions, the consequences of disrupted circadian rhythms are profound. Recognizing the multifaceted impact of circadian rhythm disturbances is imperative for developing targeted interventions to mitigate health risks associated with chronodisruption.

This manuscript serves as a foundational exploration, emphasizing the need for further research to elucidate the complex interactions between circadian rhythms, sleep, and...
Continued investigation in this field holds the promise of uncovering novel therapeutic strategies and preventive measures to enhance human health and well-being.

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MEDICINE AND PHARMACY


