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THE CRITICAL INTERPLAY BETWEEN SLEEP AND IMMUNITY

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ABSTRACT

Sleep is a natural state of rest and a restorative process for the mind and body. For ages, it has been believed that someone deprived of sleep is more likely to acquire infections and other pathologies, highlighting its role as an important immune modulator. In recent years, sleep disorders and declining sleep quality have become increasingly prevalent. We also know that immune responses during immune activation affect cytokines that control sleep architecture. Sleepiness and dizziness are common symptoms of fever and infections.

Diseases like autoimmune disorders or chronic infections are associated with disrupted sleep, including fragmented sleep and insomnia. While immune activation affects sleep, poor sleep can also impair immune function, creating a cycle that increases both sleep disturbances and health issues.

This review summarizes information on the reciprocal relationship between sleep and immunity. This area of research has important implications for public health, as lack of sleep can lower immunity in the population. Knowing the value of this relationship is crucial, as it impacts both individual well-being and societal health. By elucidating the complex interactions between sleep and the immune system, this review highlights the importance of addressing sleep issues to improve overall health outcomes.

INTRODUCTION

Sleep and immunity both are essential component of human health. Restorative and regulatory properties of sleep are well known from past researches [1,2]. but that is not the whole picture, sleep also influences immune function of the body. Sleep deprivation is being identified as the cause of abnormal variations in various components of immune system, mostly immune cells and cytokines [3,4,5] . Cytokines are small proteins important for cell signaling, they have substantial role during infections and inflammatory conditions.

Globally in this modern era sleep deprivation is at all time high [6] and increasing day by day, that's why knowing interplay between sleep and immunity is important for regulating financial burden from diseases and infections caused by suboptimal immune system.

When we are sick or there is some disease process or infection in our body, sleep patterns are the component of sleep that change and has noticeable effect on our livelihood [7,8].

Sleep as we know affects various physiological systems memory consolidation, learning, etc [9,10,13]. Some of these affects are so unrelated that various studies are controversial and thus sleep as a whole is still quite unknown field of research. Understanding this bidirectional relationship is important because it tells us how closely connected our body systems are actually. Proper sleep creates powerful immune system which then continues in the form of a healthy cycle for staying healthy

and fast recovery from various diseases and inflammatory conditions. If disrupted this can result in cycle of poor health [11,12].

SLEEP CYCLE, HORMONES AND IMMUNE PARAMETERS

Our body follows a pattern for 24h there is a fixed path that tells our body when to sleep and when to be awake. Everything happens in cyclical and well-organized manner in our body and as sleep is big part of our day-to- day life it plays important role in changes in various physiological parameters in this rhythmic cycle known to all as circadian rhythm. Light and dark has a lot of influence in this and as they are external influencers it is important to note down that body rhythm is not all about self-regulation [13].

Behavioural cues and physiological cycles both are intermingled in influencing the sleep and wake cycle of a person. Various daily activities and habits change the way sleep works and thus is responsible in change of sleep quality and sleep time. In this we must add that hormone influence; part of physiological processes is really necessary to understand as they are important regulators of sleep. Melatonin that is increased by dark stimulation induces sleep and cortisol as supported from studies is at its peak when person awakes from sleep. Suprachiasmatic nucleus of hypothalamus plays an important role in controlling above mentioned hormonal influences thus establishing clearcut involvement of CNS in sleep cycle. Abnormal variations in these hormones are important indicators for presence of some disease or abnormal entities [13,14,15].

Other hormones such as growth hormone, prolactin and leptin along with melatonin have positive effects on immune system of the body, they have pro inflammatory effects on body as they increase mediators such as interleukins, tumour necrosis factors and other cytokines such as interferons [16-22]. The other side of picture however, hormones such as catecholamines including adrenaline and noradrenaline and cortisol supresses immune function by providing anti-inflammatory function [23,24]. Expanding on function of some of the hormones.

Melatonin: Along with regulation of sleep has shown to increase immune response and boost immunity. It enhances the production of certain cytokines and thus improves defence capabilities of our body.

Leptin: this hormone regulates appetite along with hormone ghrelin both of these hormones are produced by neuroendocrine cells in gastrointestinal system of human body and leptin is known for increasing immune response of the body.

Growth hormone and Prolactin: These hormones are responsible for increased production of immune cells that is white blood cells such as lymphocytes and natural killer cells and like others in the list also increase immune mediators like cytokines which include interleukins and tumour necrosis factors.

Cortisol: also known as stress hormone in a general term. It is released in response to stress and anxiety and is an important regulator of metabolism and like others immune responses. It has known anti-inflammatory properties that helps body manage excess inflammation, but increased cortisol for long periods of time that is chronic high levels may supress immune functions and thus increases the chance of body to acquire diseases and infections.

Catecholamines: These are also known as fight or flight hormones and as the name suggest are involved in such situations. These hormones have suppressive effects on immune system of the body as they reduce the levels of cytokines and various immune cells in the body, so these hormones might decrease the infection resisting capabilities of our body.

In addition to the above-mentioned hormones, various dangerous factors also accumulate in the body like reactive oxygen species (ROS), nucleotides and heat shock proteins (HSP). Although their release is endogenous but as we have discussed earlier are also influenced by external factors that result in cellular stress, like heavy physical activity that can result in variable amount of cell injuries. These factors increase in the body during active awake period and act as if any pathogenic antigen stimulation is present in the body like lipopolysaccharide, and as they act in this manner, they also stimulate the immune cells known as Antigen Presenting Cells (APC) to produce pro-inflammatory cytokines, which themselves act as signal for immune response to initiate adaptive immunity [25].

During rest and parts of sleep there is also peak in proinflammatory mediators such as TH1 cytokines these then go on to stimulate various immune cells in various parts of human body such as splenic and peritoneal macrophages [26,27]. This link of sleep with regulating peripheral immune cells like macrophages also links it to complex processes such as phagocytosis, as macrophages are immune cells that play important role in engulfing and digesting the pathogenic and dead cell matter, the process which is phagocytosis, not just that macrophages

themselves increase inflammatory cytokines and aids in tissue repair and defence function of the body.

Along with the natural clock that our body has our immune cells such as macrophages also have their own clock, which just like circadian rhythm has its own rhythm and regulates the inflammatory responses throughout the day. As macrophages are important immune cells linked to inflammation in our body, and as inflammation can affect sleep quality and lead to sleep fragmentation it is important to know this relationship so as to identify how to control this for overall benefit of the body [27,28,29].

This immune activation can alter sleep important cytokine like tumour necrosis factor alpha and interleukin 1 beta are related to increased sleep and disrupted sleep architecture.[30]. Chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, presents with bad quality sleep and increased events of waking up in the middle of night, these features are linked to abnormal levels of interleukin 6 that modulates and fragments sleep. [30,31].

IMPACT OF INFECTION ON SLEEP

Now as we know the impact sleep and immunity on each other it is really important to know the impact of infection on the sleep quality and duration. We think of sleep as being inactive state of body but it is far from it, while we sleep our immune system is still active and fending of various infectious agents in the blood stream and peripheral organs, so sleep is not a passive process but an active process and its disruption must stop.

Molecules such as interleukin 1 beta ,10,12 and tumour necrosis factor alpha which are secreted during sleep influence great increase in immune cells such as

dendritic cells, monocytes. Their increase in serum level is un-related to circadian rhythm of the body their serum level peak during sleep [30]. When sleep patterns are altered due to infections the level of immune mediators and cells also get altered [30,31].

Various researches have described neuroendocrine effects on sleep and immunity as discussed earlier, so we know that Central Nervous System and endocrine system has various direct and indirect impacts on our sleep and immunity [4,9-12]. This means infections can have vast and severe consequences over sleep as even if the pathogen causes systemic infection can lead to highly altered sleep patterns and direct infection of central nervous system will be even more detrimental to sleep and circadian rhythm [32].

Recovery and healing in any disease and infection is most important part of any medical delivery system it dictates amount of time and care dedicated to any patient. Thus, disrupted sleep during any infection can impair recovery and increase time of disease process and hence addressing sleep disturbances in any individual suffering from any infection may improve their health at a faster pace and this will be a great service to overall medical systems in place and their functions.

There must be further research in various topics so that we know how cytokines and immune modulators affect various areas of brain and in turn changes central nervous system and their influence on hormone levels. As very specific areas of the brain and central nervous system are related to sleep regulation and regulation of immune functions hypothalamus responds to cytokines such as interleukins 1 beta and tumour necrosis factor alpha both possessing great role in immune modulation of one system [30]. Infection in areas such as hypothalamus and hippocampus will lead far more detrimental effects on immunity than

abnormal release of these immune modulators. By controlling both cytokine and neuro-endocrine mediators we can achieve normal sleep patterns and which in turn will help in overall health promotion. Managing sleep disturbances can have multiple modalities including pharmacological and non- pharmacological such as cognitive behavioural therapies for insomnia, these procedures are behavioural intervention [33] that changes physiological abnormalities as in such cases treating pathological changes may not be the most optimum process to go for.

During various researches it is found out that an important substance that is related to sleep regulation during the course of infection in the body is known as Factor S. It was first isolated from human urine and the rabbit brain during infections. Factor s is identified as muramyl peptide. The thing is muramyl peptide bears close resemblance with the monomeric muramyl peptide found in bacterial peptidoglycans [35].

In any pathogenic invasion of the body the pathogenic antigens are identified by various receptors in body tissues and immune cells some of the important mechanisms take help of pattern recognition receptors (PRR) these pattern recognition receptors detect another entity known as pathogen associated molecular patterns (PAMP). This evaluation and detection is important to trigger various different immune responses against infections in our body. The thing is Factor S as discussed earlier is recognized by our immune system by these pattern recognition receptors (PRR) this in turn activates Pathogen associated molecular patterns (PAMP). This process then triggers cascades of intermingled responses which then affects immune pathways and sleep patterns and quality [30,31,35].

Now we also know how various pathogens can influence our sleep patterns by doing research in pattern recognition receptors (PRR) and Pathogen Associated

molecular patterns (PAMP). Pathogens can influence sleep by modulating these inflammatory pathways and various cytokines involved in sleep regulation. Usually, the effect of pathogen is increased physiological mechanisms that normally regulate sleep but, in this case, leads to increased sleep cycle and sleepiness including dizziness [35].

There have been various studies indicating various changes in sleep pattern quality and cycle. [35] These researches were done by infecting various organisms with different pathogens and then observing any sleep changes accumulated overtime. In one research, Rabbits were infected with *Staphylococcus aureus* and then observed for various disturbances in sleep quality and duration, it was observed that test animals experienced increased non rapid eye movement (NREM) sleep and decreased rapid eye movement sleep (REM). Various other researches which chose different pathogenic test organisms such as *Pasteurella multocida* and *Escherichia coli* also went on to demonstrate similar results; that is disrupted sleep patterns. Not only the pathogens but their type, time when the infection was initiated, method of infection, time of the day and sleep history of host are some of the important parameters that can influence sleep patterns during various kinds of infections [32,33,35].

It's not just pathogens that can influence the sleep cycle of host even bacterial cell wall components such as lipopolysaccharides (LPS) and killed bacteria can also induce sleep disturbances that increase sleep duration. Lipopolysaccharides LPS, which are part of the outer coat of most gram-negative bacteria, when injected in an organism has shown increased non rapid eye movement sleep (NREM) in both cases of systematic and central injections [36]. Even when high doses of heat killed bacteria were used for experiments it was observed that even the presence of bacterial components independent of live replicating

bacteria can influence sleep. These killed bacteria were also recognized by pattern recognition receptors (PRR) and indicate that pathogen associated molecular patterns (PAMP) are also not so necessary for inducing sleep changes [37].

Considering the above knowledge, we can come to the conclusion that pathogenic components also have similar effects as many immune modulators and cytokines and results in overall increased physiological mechanisms that increase sleep including the Non rapid eye movement portion of it. Cytokines they imitate are interleukin 1 beta and tumour necrosis factor alpha [30,35]. Many studies showing attenuation of enhanced non rapid eye movement [NREM] sleep on use of interleukin 1 receptor antagonists and anti-interleukin 18 antibodies shows the role of pro-inflammatory cytokines in changing sleep during infection [31,35].

IMPACT OF BACTERIAL INFECTION ON SLEEP AND IMMUNITY

Bacterial agents have significant impact on the sleep and immune systems as they are the main pathogens causing disruption in immune inflammatory cells and mediators and they directly have major effects on the central nervous system (CNS). Here we will explore various different ways in which bacteria affects sleep and immunity directly, indirectly, experimental studies and various clinical observations.

Direct effect of bacteria on sleep: there are various molecules that are released by bacterial pathogens that interact and act in a detrimental way for the body as mentioned earlier muramyl peptide, a component of bacterial cell wall increases slow wave sleep (SWS) these results are seen in various animal model experiments in rabbits, rats etc [35,53]. In a similar way, intravenous infusion of

lipopolysaccharides (LPS) which is a major component of bacterial cell wall leads to increase in slow wave sleep (SWS) it also suppresses rapid eye movement sleep (REM) in rabbits [54].

Experimental Studies: several animal studies have provided required knowledge for knowing how bacterial infections influence sleep. One of the examples of such study is the administration of *Staphylococcus aureus* in rabbits which increased the overall slow wave sleep (SWS) including amplitude and duration of slow wave sleep [57,58,59]. This effect was also associated with simultaneous suppression of rapid eye movement sleep (REM) as we already know from various earlier discussions [35]. These effects persist for several hours in test animals, but use of antibiotics such as cephalothin stopped these sleep changes indicating the necessity of ongoing active bacterial infection for abnormal sleep modulation and fragmentation [57-59].

In other infection causing infectious bacterial agents such as *Escherichia coli, Candida albicans and Pasteurella multocida* produced similar sleep disturbances as described earlier with experiments involving *Staphylococcus aureus* [58,59]. Bacterial colonization experiments in rats gave slightly varying results of day time sleepiness and delayed onset abnormal sleep architecture suggesting relationship between sleep and bacterial colonization [60].

Clinical Observations: it is observed that not only the animal tests prove the relationship between sleep and infections but clinical data also supports the findings, as they reveal highly increased abnormal sleep patterns in infected individuals. An important example for instance is Lyme disease caused by *Borrelia burgdorferi*, interesting findings of restless leg syndrome, decreased sleep efficiency and latency, along with sleep disturbances such as insomnia, daytime increased naps and sleepiness and difficulty in normally falling asleep is

observed these patients also report of increased sense of stimulus and arousal [61].

One interesting finding in such patients is the presence of alpha waves in non-rapid eye movement sleep (NREM). This finding can be the reason for the highly disrupted and abnormal sleep architecture in these patients [61].

In patients infected with *Bordetella pertussis*, causing Whooping cough there are various different findings such as choking in sleep, epileptic seizures and sleepwalking. These abnormalities are known to be linked to the infection as after resolution of the disease, these disturbances resolve spontaneously on their own [62].

Respiratory diseases related to sleep disorders: these classes of infection are one of the most important to trigger various different sleep disorders as some of these infections lead to lesions in areas of brain that are responsible for normal respiration which then leads to disruption in sleep quality and duration. Some of the noteworthy examples include bacterial meningitis caused by *Streptococcus pneumoniae* and *Listeria monocytogenes*. These infectious agents have profound complications in sleep architecture. Here in studies, it is shown that Listeria damages reticular formation in brain which then goes on to destroy normal respiratory rhythm which goes on to cause hypoxia and results in changes in both non rapid eye movement sleep (NREM) and rapid eye movement sleep (REM) these changes results in frequent sleep fragmentation and wake periods in between of sleep [63-65]. Systemic granulomatous conditions such as Sarcoidosis is also known to cause apnoea and disrupted sleep wake cycles [67] .

Autoimmune associations: in some bacterial infections there are studies showing that there are increased levels of auto- antibodies against antigens of pathogens like *Streptococcus and Helicobacter pylori* which are responsible for inducing narcolepsy [66]. This abnormal relationship shows the impact of autoimmunity on

sleep cycles but more research must be conducted in this field as it is very unclear how these physiological mechanisms work.

INTERPLAY BETWEEN SLEEP, INFLAMMATION AND CELLULAR AGING

Various researches have shown us the multifaceted relationship between sleep and inflammation. Long term sleep disorders such as insomnia have high potential to initiate complex events that can lead to activation of immune cells and hence immune modulators that lead to activation of inflammatory pathways. These effects not just have detrimental effects on sleep but also affect the complex process of aging and advances its progression this is not on a systemic level but on a cellular level as it affects cellular aging in an organism.

From the above discussion we know that sleep plays an important role in regulation of immune function and inflammatory pathways. Researches have shown that sleep losses and disturbances such as insomnia leads to increased inflammatory markers such as interleukin 6, tumour necrosis factor alpha [68]. These parameters are also abnormal in individual with poor sleep quality. Chronic and long-term activation of these mediators will lead to overstimulation of inflammatory pathways that are linked to chronic illnesses such as cardio vascular diseases, diabetes and arthritis [69].

This interplay between sleep disturbances, inflammatory pathways and aging has various complex cascade of mechanisms working simultaneously to affect the body. One of the abnormal molecular mechanisms include mitochondrial genetic damage and telomere shortening that are known common markers of cellular aging are also exacerbated by sleep disturbances [70].

Mitochondrial damage: occurs due to abnormally high oxidative stress and inflammation this leads to impaired energy production as mitochondria is powerhouse of cell and hence causes increased aging and age-related diseases.[71]

Telomere shortening: telomere is portion of extra non replicative protective segments of chromosomes. These shorten by each cell replication that a cell undergoes as cell division in normal process of continuum of life progressive shortening of these segments leads to cellular senescence. Inflammatory processes increase this shortening and lead to cell death as in the end the cell is unable to replicate in normal fashion [71,72].

Experimental evidence such as Prather et al. (2011) have studied the impact of sleep duration and quality on leukocyte telomere segment length as it is an important biomarker to estimate cellular aging. This experiment shows that there is evident relation between poor sleep and telomere shortening but the sleep duration does not have significant impact on telomeres. These associations were independent of any racial or age-related factors and body mass index (BMI). Chronic and long-term sleep deprivation is predictive of shorter telomeric length and thus highlights importance of sleep quality in managing cellular health and repair [73].

Cribbet et al. (2014) investigated interaction between age and sleep quality in changes in telomeric length using an index known as Pittsburgh Sleep Quality Index (PSQI) and measurements of telomeric length in mononuclear cells. Their results show that in older adults' good sleep quality results in lesser effect of age on telomeric length. This indicates maintaining good sleep helps in mitigation of harmful effects of aging on cellular health [74].

Cell cycle and cell damage are highly influenced by inflammatory responses of the body from above investigation we already know the relationship between

aging and sleep as inflammatory mediators influence sleep patterns It is important to know the intricate relationship between sleep, aging and inflammation. It also a known fact that sleep abnormalities increase with age, so it is of great importance to know various other such factors that influence sleep.

ROLE OF NUTRITON ON SLEEP IMMUNITY BOND

In modern times as the general population is getting more and more aware of the importance of dietary supplements and nutrition in day-to-day life. It is really important to explore the interplay between diet, sleep and immunity. As various researches indicate profound impact of dietary supplements and nutrition on sleep quality and duration. It is important to explore various dietary strategies for improvement of sleep and immune system bond [75].

Some dietary supplements that enhance sleep quality are

Amino Acids

Tryptophan plays an important role in regulation of sleep as it is a precursor molecule to both serotonin and melatonin, both of which have known effects on sleep architecture and maintain normal sleep cycle and circadian rhythm. Tryptophan supplements can boost sleep onset and duration by increasing serotonin and melatonin production in the body. This physiological and biochemical mechanism tells us about the importance of amino acid supplements in promoting sleep.

Melatonin

Supplementation of this hormone is effective in treating various sleep disorders and even disturbances with the circadian rhythm can be regulated by it. Its role

in sleep is well known making it very popular among medical care providers for therapeutic use [76].

Vitamin D

It is one of the fat-soluble vitamins and maintains bone health, studies have shown its role in regulating sleep [77]. These studies have shown that sleep disorders are strongly related with low serum levels of 25- hydroxyvitamin D. Vitamin D supplements have shown to improve sleep in many cases. These effects may be due to Influence over circadian rhythm.

Omega-3 Fatty Acids

Docosahexaenoic acid (DHA) has an important role in reducing inflammatory responses in the nervous system that is neuro-inflammations and thus helps in enhancing sleep quality. It supports neuro chemical balance in the body and contributes to better sleep results. [78]

Phytochemicals and Polyphenols

Phytochemicals includes resveratrol and polyphenols/flavonoids are found in fruits and vegetables. Resveratrol, a substance present in grapes and red wine, is known to reduce sleep abnormalities and improve sleep time and duration. Diet rich in polyphenols and flavonoids, is associated with better sleep duration and quality. These compounds have various antioxidant effects and boost sleep and immunity on regular intake [79].

Specialised dietary patterns like fasting and restricted feeding have been found to be beneficial for the immune system, reducing systemic inflammations and enhancing sleep. Intermittent fasting regimen can influence metabolism and regulate sleep cycle and circadian rhythm [80]. Low carbohydrate diet can help with better sleeping cycles and reduces chronic inflammatory processes in the body. Individuals must avoid high fructose intake as it is detrimental to the sleep

immune bond [81]. Lifestyle modifications such as physical exercises support both immunity and sleep. Exercising also reduces inflammation and improves sleep quality. It also increases immune modulators [82].

DISCUSSION

This review summarizes that sleep is not just a passive state but an active process with loads of impact on immune function. Sleep disorders can lead to abnormal immune response that can increase susceptibility to various different disease processes and infections.

Immunity influences sleep by various molecular patterns like cytokines. And hence, various chronic immune and autoimmune conditions can impact the sleep immune bond [83].

Circadian rhythm and its regulatory hormones like melatonin affect both sleep and immunity. Cortisol suppresses immune function and melatonin enhances it along with sleep but their regulation is important for creating a balanced inflammatory response [13-15,23,24].

Viral and bacterial infections influence sleep and can cause sleep disorders such as increased NREM and decreased REM sleep. This proved that infections produce immune responses that produce significant sleep disturbances [32,33,35].

This relationship is affected by various other factors diet, nutrition, deficiencies, physical activity, obesity and has severe implications as can lead to cardiovascular disorders, diabetes and these factors not just influence body systems but also influence cellular clocks and mechanisms leading to accelerated cellular aging and increased oxidative stresses in cell organelles [70-74,80-82].

There is a need for future studies for understanding precise mechanisms in sleep immune bond as understanding this relationship will allows us to allocate resources and provide effective management for chronic sleep disorders which are important public health liabilities.

CONCLUSION

This research review explores a close and complex bond between sleep and immunity, sleep disturbances can weaken our immune system and increase risk for infections and chronic diseases. On the other hand, immune activation by infection or autoimmune conditions can create a cycle of poor sleep patterns. neural and endocrine mechanisms involved in this tells us about the complexity of this bond.

In conclusion, recognising sleep as an essential component of immune function is important for overall well-being and disease prevention. Various therapeutic interventions must be explored to target this intricate relationship.

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CONCLUSION

This research review explores a close and complex bond between sleep and immunity, sleep disturbances can weaken our immune system and increase risk for infections and chronic diseases. On the other hand, immune activation by infection or autoimmune conditions can create a cycle of poor sleep patterns. neural and endocrine mechanisms involved in this tells us about the complexity of this bond. SM, Ravdin L, Hilton E. Sleep quality in Lyme disease. Sleep. 1995;18(10):912–6.

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