

Clinical Understanding of the Sleep-Immune Connection

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Abstract

The science of sleep is becoming better understood all the time, and here is a fact that has only recently been revealed: sleep and immune system function have a bidirectional relationship. The disturbance of sleep can create an alteration in immune function. The opposite is also true, in that activation of the immune system can create a disturbance in sleep cycling. This dynamic can ultimately create a feed-forward loop of increasing immune dysfunction and sleep disruption. These systems are intimately intertwined. The clinical

approach should be to intervene upstream in the regulation of the fundamental systems that control both sleep and immune function. Through the implementation of this approach, the treatment will focus on the cause of the epigenetic modulation of the sleep-immune system imbalance, and not just its effects and symptomatology.

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“Recent discoveries demonstrate a critical role for circadian rhythms and sleep in immune homeostasis. Both innate and adaptive immune responses—ranging from leukocyte mobilization, trafficking, and chemotaxis to cytokine release and T cell differentiation—are mediated in a time of day-dependent manner.”¹

“Perfect Timing: Circadian Rhythms, Sleep, and Immunity—An NIH Workshop Summary”

Over the last 20 years, the number of research studies abstracted in the archives of the National Library of Medicine that explore the complex relationship between sleep and immunity has grown exponentially. There is an important cross-talk between physiological systems controlling sleep and those controlling immune function.² This association was first recognized in studies being conducted on the health impact of sleep deprivation, which revealed the influence that altered signaling molecules can have on immune cell function, including melatonin, reactive oxygen species, cortisol, epinephrine, norepinephrine, growth hormone, metabolites from altered gut microbiome, and adipokines from body fat.³

Sales trends for melatonin supplements have been closely watched for years, including before and during the COVID-19 pandemic. Many people now recognize the role melatonin can play in managing not only sleep, but also chronic pain and immunometabolic functions.^{4,5} Structurally, the suprachiasmatic nucleus (SCN) in the hypothalamus activates specific immune cells and triggers an inflammatory response, and stress—which we know can impact sleep quality in significant ways—influences this function.⁶

The science of sleep is becoming better understood all the time, and here is a fact that has only recently been revealed: sleep and immune system function have a bidirectional relationship. The disturbance of sleep can create an alteration in immune function. The opposite is also true, in that activation of the immune system can create a disturbance in sleep cycling. This dynamic can ultimately create a feed-forward loop of increasing immune dysfunction and sleep disruption.⁷ Sleep deficiency and amplified alterations in immune function are factors that are associated with the etiology of cardiovascular, metabolic, autoimmune, and neurodegenerative diseases. When considered as a whole, systems biology mechanistically ties stress to the networked activity of the SCN with the pineal gland, thymus, adrenal system, and innate immune system.⁸ Cortisol, epinephrine, and norepinephrine all play central roles in modulation of the sleep-immune connection under conditions of stress.⁹

Lifestyle Factors that Influence the Sleep-Immune Connection

It is well known that sleep disturbances increase with age. This has recently been found to be associated with alteration in the hyperexcitability of the hypocretin-

responsive neurons.¹⁰ Research reveals that hypocretin levels and activity are also associated with obesity and chronic inflammation, a finding that once again links sleep to immune and metabolic function.¹¹ Central obesity factors into the release of inflammatory signaling molecules from both adipocytes and macrophages of the innate immune system, which in turn adversely affect sleep duration and quality.¹² The microbiome (with its connection to the gut-associated lymphatic system) also plays an important role in establishing systemic immune tone and influencing the suprachiasmatic nucleus.¹³ Pattern recognition receptors on the surface of the gastrointestinal mucosa receive signals that can trigger an inflammatory cascade that in turn influences regulation of the SCN and sleep; a key example of this is bacterial lipopolysaccharides (LPS) from the cell wall debris of specific intestinal bacteria.¹⁴ Significantly, children who are gluten sensitive experience a reduction in regional and systemic inflammation when put on a gluten-free diet, and studies have documented an improvement in sleep and a reduction in apnea symptoms.¹⁵

Adequate duration and quality of sleep have been found to be very important for reducing neuroinflammation because these factors can activate what is known as the glymphatic system. Maiken Nedergaard, a Danish neuroscientist, first described the glymphatic system in 2013. The name is a reference to the glial cells, which are vital to the body's clearance of metabolic debris. The cerebral spinal fluid that surrounds the central nervous system is a part of the glymphatic system and helps to flush immune-active substances from the brain.¹⁶ Altered function of the glymphatic system results in increased neuroinflammation, which in turn influences SCN function and affects the restorative function of sleep.

Efficacy of Dietary Supplements and Nutrition on the Sleep-Immune Connection

A systematic review and meta-analysis of the efficacy of various dietary supplements on alterations of the sleep-immune connection was recently published.¹⁷ Amino acids (such as tryptophan), melatonin, and vitamin D were shown to be significantly beneficial in improving sleep quality, although individual variation indicates the need for personalized dosing and management. It was suggested that magnesium, zinc, omega-3 oils, and phytochemicals such as resveratrol may also be efficacious. A different systematic review of the association between vitamin D deficiency and sleep disorders indicated that serum levels of 25-hydroxyvitamin D2 below 20 ng/ml of blood is strongly associated with sleep disorders.¹⁸ It has also been shown that specific pro-resolving mediators (PRMs) derived from the omega-3 fatty acid docosahexaenoic acid (DHA) may play an important role in resolving neuroinflammation and improving sleep quality.^{19,20} There is advancing evidence that specific dietary polyphenols/flavonoids are associated with sleep

quality. A study done in Italy demonstrated that the dietary intake of a portfolio of polyphenols found in the Mediterranean diet had a beneficial influence on sleep duration and quality.²¹

What has emerged from these recent studies is that improvement in immune function, and—by association—sleep quality, can be supported with three nutraceutical interventions. These pillars include specific polyphenols/flavonoids, pre- and probiotics, and omega-3 fatty acids.²² These three interventions work synergistically to improve immune system function while reducing chronic immune activation and inflammation, leading to immuno-rejuvenation. This nutritional orchestration approach results in a reduction of immune aging (i.e., immune senescence or “inflammaging”) and improved resilience of the innate and adaptive immune systems. Foundationally, this sets the stage for positive potential benefits for neuroinflammation, a rebalancing of SCN function, and ultimately improved sleep cycling, quality, and duration.

A Diet, Supplement, and Lifestyle Program to Support the Sleep-Immune Connection

Both a time-restricted feeding schedule and a fasting-mimicking diet have been studied and found to have a beneficial influence on immune resilience, a reduction in inflammation, and a positive impact on sleep.²³ This is an approach that calls for a gap of at least 12 hours between the last meal of the day and the re-introduction of food the next day. It has been documented that shifting the body into fasting physiology helps to regulate the SCN and the sleep-wake cycle.

Diets that have a low glycemic response are also beneficial in establishing proper sleep cycling and reducing neuroinflammation.²⁴ This approach should restrict the consumption of fructose, which is found principally in sweetened beverages and foods, because intake has been found to increase chronic inflammation. The diet should contain high levels of polyphenols/flavonoids from fruits and vegetables of various colors, which is an accessible concept that is now widely referred to as “eating the rainbow.”²⁵

Regular daily activity that includes walking 30 or more minutes helps improve both immune and sleep function.²⁶ Massage or physical therapy is also important in supporting proper lymphatic function, which helps eliminate immune-activating toxins and improve sleep cycling (remember the importance of the glymphatic system and how it relates to the immune-sleep connection).

Lastly, consider including foods that are high in immune-active flavonoids such as quercetin. High levels of this important nutrient are found in onions, apples, and Tartary buckwheat. Supplementing with 2000 mg per day of omega-3 oil, 5000 IU of vitamin D3, and a prebiotic-probiotic combination also helps to support the sleep-immune connection. Don't forget the important role that stress has in determining the status of the sleep-immune

system. High levels of stress correlate with increased levels of cortisol and epinephrine, which work together to increase neuroinflammation and disturbed sleep.

The important takeaway from this recent advance in understanding of the sleep-immune connection is that there is a bidirectional influence of one process on the other. Many people are locked in a cycle where sleep disturbance feeds forward into immune dysfunction and vice versa. These systems are intimately intertwined. The clinical approach should be to intervene upstream in the regulation of the fundamental systems that control both sleep and immune function. Through the implementation of this approach, the treatment will focus on the cause of the epigenetic modulation of the sleep-immune system imbalance, and not just its effects and symptomatology.²⁷

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