Vitamin D and Melatonin in Multiple Sclerosis

EFFECTS OF SEASONAL CHANGES
Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS). It involves abnormal immune responses attacking myelin, the fatty tissue that forms an insulating layer around nerve fibers and allows for efficient transmission of nerve impulses. The resulting degradation of the myelin sheath is a key part of MS pathogenesis since it disrupts cell-to-cell connections within the brain and slows signalling to the rest of the body. This clinically manifests itself through difficulties with vision, balance, and muscle coordination, as well as weakened cognitive functions. The condition is known to affect more than 2 million people worldwide. Most individuals affected with MS undergo a relapsing–remitting period where the symptoms alternate between flaring up and disappearing. The majority of people with relapsing–remitting MS (RRMS) eventually develop secondary progressive MS, in which their symptoms inexcorably worsen. The cause of the disease is still unknown, although researchers have identified risk factors such as viral infections, specific levels of gene expression, and the lack of white blood cells in the bloodstream.

**VITAMIN D OR MELATONIN?**

Recent research has shown an impressive geographical gradient with significantly higher incidence of MS in correlation to increasing latitude. Previous literature has advocated varying exposure to sunlight based on seasonal patterns and the resulting alteration in vitamin D (VD) production as the explanation for this gradient. During spring and summer, the increased exposure to sunlight results in increased production of VD in our body, and this is hypothesized to allow efficient modulation of immune responses in reducing MS relapses. On the other hand, researchers have now discovered a seasonal paradox - MS relapses continue to increase in the spring and summer when levels of sunlight are high. This directed the researchers’ attention towards melatonin, a sunlight-dependent hormone that is an additional regulator of immune responses and promoter of anti-inflammatory processes. VD is a nutrient that is known to help our bodies use calcium and phosphorus to build and maintain strong bones and teeth. However, VD affects numerous aspects of health beyond bone strength. In fact, its anti-inflammatory, immunomodulatory, and antiproliferative effects have recently become a research focus.
VD supplementation on MS patients. The results demonstrated that VD lowers the production of inflammatory cytokines. This further promotes the notion that VD is a modulator of physiological immune responses. It is interesting to note that MS prevalence increases as one approaches the geographic poles. Furthermore, a strong inverse relationship has been observed between amount of sun exposure and subsequent MS development within the same geographical area. Validating these observations, a study conducted in Norway, where the northerly latitude only allows minimal sunlight, demonstrated that an increase in summer activities during early life significantly reduced the risk of MS. Based on the strong correlation between latitude, sun exposure, and intrinsic VD production, VD can be interpreted to have a substantial effect on the incidence of MS. This is important from a public health perspective, as VD deficiency is common, especially in northern countries like Canada where exposure to sunlight is decreased during the winter.

Supplementation of VD could be beneficial for inhabitants of countries with cold climates. A large prospective cohort study was conducted to evaluate the effect of VD supplementation on MS incidence in North American women. Results showed that those who took VD supplements were 45 percent less likely to develop MS than those who did not. Relationships between the risk of MS and intake of VD only during the subject’s teenage years were analyzed. Consuming more than 450 International Units (IU)/day of VD during one’s teenage years did not significantly decrease the risk of developing MS. Thus, research suggests that it may be more effective to consume VD supplementation throughout an entire lifetime to decrease MS incidence.

THE REGULATORY ROLE OF MELATONIN

While VD has been shown to play a beneficial role in lowering MS incidence, researchers recently discovered a stronger relationship between melatonin and MS symptoms. Melatonin is a natural hormone secreted by the pineal gland in response to sensory input from the retina. It is also known for having antioxidant and anti-inflammatory effects and is involved in regulating circadian and seasonal rhythms. There is a known correlation between melatonin levels and seasonality: melatonin production decreases in spring and summer, and increases in the fall and winter.

Melatonin modulates immune responses by suppressing pro-inflammatory cytokine production. A study conducted by Farhadi et al. measured serum levels of melatonin and tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine associated with most MS lesions, in both MS patients and a control group. Serum melatonin was lower in MS patients compared to healthy controls, while TNF-α levels were higher in MS patients. Other studies have observed relationships between melatonin and MS through studying the effects of exogenous melatonin on the pathogenesis of experimental autoimmune encephalomyelitis (EAE), the most frequently used animal model of MS. These studies showed that melatonin is vital in MS disease progression by its effects on two cell types: pathogenic effector and regulatory T cells. Regulatory (T<sub>reg</sub>) cells regulate the immune system and maintain tolerance to self-antigens. They are characterized by the production of interleukin-10 (IL-10), an anti-inflammatory cytokine involved in immunoregulation and antibody production. They also suppress the production of autoreactive effector T cells, such as T helper (T<sub>h</sub>) cells. Conventional T<sub>h</sub> cells modulate immune response by activating other effector immune cells such as B cells and macrophages in an antigen-specific manner, but they have also been implicated in deleterious activities. Two subtypes of T<sub>h</sub> cells, T<sub>h</sub>1 and T<sub>h</sub>17, divide rapidly when activated and secrete various cytokines to facilitate immune responses, such as recruiting white blood cells to sites of infection or damage. Interleukin-17 (IL-17) is a cytokine produced by T<sub>h</sub>17 cells that has been linked to pro-inflammatory responses, including the production of TNF-α, and has often been implicated in diseases such as MS.

T<sub>h</sub>1 and T<sub>h</sub>17 cells are implicated as the main T<sub>h</sub> cell populations in MS. Hence, studies investigated the effects of melatonin on T<sub>h</sub>1, T<sub>h</sub>17, and T<sub>reg</sub> cells in the lymph nodes and the CNS of EAE mice. Evidence shows that T<sub>h</sub>17 produces pro-inflammatory IL-17 in MS patients. Conversely, T<sub>reg</sub> cells oppose the activity of T<sub>h</sub>1 and T<sub>h</sub>17 cells, accumulating in the CNS of EAE animals and protecting the animals from EAE in an IL-10-dependent manner. Unlike IL-17, IL-10 is an anti-inflammatory cytokine and is
positively correlated with serum melatonin levels. In particular, melatonin reduces T<sub>n</sub>-1 response and instead enhances the activity of type 1 regulatory cells (T<sub>reg</sub>), which suppress immune responses through IL-10 production. Results indicated that melatonin downregulates the T<sub>n</sub>-1 and T<sub>17</sub> pro-inflammatory immune responses in MS patients and shifts the response towards immunosuppressive T<sub>reg</sub> cells. Thus, through regulating effector and regulatory T cells, seasonal changes in melatonin levels may contribute to decreased MS activity during autumn and winter.

Research has shown a correlation between melatonin supplementation and the quality of life of MS patients, many of whom suffer from sleep disturbances, depression, and fatigue. Studies have suggested that melatonin’s antioxidant properties can improve quality of life by reducing oxidative stress and potentially improve sleeping patterns. However, a study by Quintana et al. has warned against the use of melatonin supplements in MS patients, citing drawbacks such as unwanted drowsiness. Thus, further research is necessary to determine the optimal dose of melatonin supplements to maintain balanced sleeping habits in MS patients.

**CONCLUSION**

While previous studies focused on genetic factors involved in the development of autoimmune disorders, the rise in MS in the past 50 years and the correlation of its symptoms or incidence with seasonal changes has shifted greater attention towards environmental factors. Through epidemiological observation, a relationship between sunlight exposure and subsequent MS development was noted. Through its immunomodulatory processes, VD is able to alleviate MS symptoms during the summer. Based on experimental and clinical reports, supplementary VD can also be used to alleviate inflammation and attenuate neuronal damage in MS. However, future research should focus on developing a multi-center, randomized, placebo-controlled, double-blind clinical trial to effectively evaluate the therapeutic value of VD supplementation.

Although VD operates as a protective factor, recent research is focused on melatonin, which is considered to play a greater role in suppressing MS symptoms. Melatonin is a hormone involved in regulating the sleep-wake cycle and influences MS disease activity and relapse seasonality by impacting immune response and T cell activation. Research is currently exploring the molecular mechanisms that underlie melatonin’s role in MS in order to develop pharmaceuticals and identify additional mechanisms of action.

The contrasting patterns of melatonin and VD give rise to a paradox in the seasonal regulation of MS. While VD is known to increase during spring and summer, melatonin levels increase during winter. However, research has not yet focused on establishing a connection between the two factors that evidently attenuate MS symptoms. As such, future research should identify mechanisms through which melatonin and VD can operate synergistically to develop a clearer understanding of their relative effects on MS progression.