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CRITICAL REVIEW

Vitamin D and Melatonin in Multiple Sclerosis

EFFECTS OF SEASONAL CHANGES

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Multiple sclerosis (MS) is the most common inflammatory-demyelinating disease of the central nervous system (CNS) and is the most frequent cause of neurologic disability in young adults. Understanding of MS was revolutionized by recent studies on immunological pathways relevant to the disease as well as the use of high field magnetic resonance imaging (MRI). Currently, therapies for the early stages of MS have been developed, however, there is still no effective treatment for progressive MS and relapse. Recent findings suggest that MS incidence is higher in geographic regions with less sunlight exposure. Both vitamin D (VD) and melatonin influence the effect of sunlight on health and can therefore be considered to play a role in MS. Several studies indicate that high levels of both VD and melatonin may decrease the extent of disease progression. This review aims to explore various studies that elucidate the effects of VD and melatonin on the pathology, management, and treatment of MS.

MULTIPLE SCLEROSIS

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.[1] 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.[1] The condition is known to affect more than 2 million people worldwide.[2] 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 inexorably worsen.[3] 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.[2]

VITAMIN D OR MELATONIN?

Recent research has shown an impressive geographical gradient with significantly higher incidence of MS in correlation to increasing latitude.[4] 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.[5] 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.[2] 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. Less sunlight in the fall and winter increases melatonin, whereas more sunlight during spring and summer decreases it.[6] Therefore, both melatonin and VD contribute to control MS disease activity. However, specifically with regards to seasonal changes, melatonin plays a stronger role than VD in MS.[5]

SHINING LIGHT ON THE ROLE OF VITAMIN D

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.[6] VD exerts its effect on immune cells by regulating the production of cytokines, a group of small proteins that drive inflammation by attracting immune cells. In MS patients, the pro-inflammatory action of cytokines tends to worsen the disease by producing inflammation, tissue destruction, and in some cases, shock and death. In MS patients, inflammation in the brain causes loss of neurological function.[7] In 2012, a randomized, double-blind study conducted by Pennsylvania State University explored the effects of 10-week high-dose

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.[8]

It is interesting to note that MS prevalence increases as one approaches the geographic poles.[9] Furthermore, a strong inverse relationship has been observed between amount of sun exposure and subsequent MS development within the same geographical area.[4] 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.[10] 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.[11] 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.[12] 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.[12]

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.[13] Melatonin is a natural hormone secreted by the pineal gland in response to sensory input from the retina.[14] It is also known for having antioxidant and anti-inflammatory effects and is involved in regulating circadian and seasonal rhythms.[15] There is a known correlation between melatonin levels and seasonality: melatonin production decreases in spring and summer, and increases in the fall and winter.[12]

Melatonin modulates immune responses by suppressing pro-inflammatory cytokine production.[17] 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.[18] 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.[15] These studies showed that melatonin is vital in MS disease progression by its effects on two cell types: pathogenic effector and regulatory T cells. T regulatory (T_{reg}) 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_h) cells. Conventional T_h 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.[19] Two subtypes of T_h cells, T_h1 and T_h17, divide rapidly when activated and secrete various cytokines to facilitate immune responses, such as recruiting white blood cells to sites of infection or damage.[20,21] Interleukin-17 (IL-17) is a cytokine produced by T_h17 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_h1 and T_h17 cells are implicated as the main T_h cell populations in MS. Hence, studies investigated the effects of melatonin on T_h1, T_h17, and T_{reg} cells in the lymph nodes and the CNS of EAE mice.[21] Evidence shows that T_h17 produces pro-inflammatory IL-17 in MS patients.[22] Conversely, T_{reg} cells oppose the activity of T_h1 and T_h17 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.[23] In particular, melatonin reduces T_h1 response and instead enhances the activity of type 1 regulatory cells ($T_{reg}1$), which suppress immune responses through IL-10 production.[23] Results indicated that melatonin down-regulates the T_h1 and T_h17 pro-inflammatory immune responses in MS patients and shifts the response towards immunosuppressive $T_{reg}1$ cells.[21,22,23] Thus, through regulating effector and regulatory T cells, seasonal changes in melatonin levels may contribute to decreased MS activity during autumn and winter.[23]

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.[24] However, a study by Quintana et al. has warned against the use of melatonin supplements in MS patients, citing drawbacks such as unwanted drowsiness.[25] 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.[26] 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.[15] 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.[24,25] 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.[14]

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. ■

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